

ISSN 0206-4766



TARTU STATE UNIVERSITY

# ORGANIC REACTIVITY

Vol. XXV  
ISSUE 3(91) - 4(92)  
September - December  
1988

TARTU

TARTU STATE UNIVERSITY

# ORGANIC REACTIVITY

Vol. XXV

ISSUE 3(91) - 4(92)

September - December 1988

TARTU

The Editorial Board:

V. Palm, Editor-in-Chief

V.I. Minkin

A.F. Popov

I.A. Koppel

M.M. Karelson

Title of original:

Реакционная способность органических соединений.  
Том XXV, вып. 3(91)-4(92), Сентябрь-Декабрь 1988.  
Тартуский государственный университет

*Am.*  
Tartu Ülikooli  
Raamatukogu

10182

PHOTOELECTRON SPECTRA OF MOLECULES

10. AMIDES

U.H. Mölder, I.A. Koppel, R.J. Pikver,  
and J.J. Tapfer

Departments of Geophysics and Analytical Chemistry, Laboratory of Chemical Kinetics and Catalysis, the Computing Center of Tartu State University, Tartu; Institute of Chemical and Biological Physics, Academy of Sciences of the Estonian SSR; Tallinn, Estonia

Received September 15, 1988

Photoelectron spectra (PES) of  $\text{CF}_3\text{CONH}_2$ ,  $\text{FCH}_2\text{CONH}_2$  and  $(\text{Me}_2\text{N})_2\text{CO}$  have been measured. They were studied by means of semiempirical (HAM/3 and CNDO/2) and nonempirical (Gaussian 80 program system, STO-3G and 3-21G basis sets) calculations.

It has been established that in case of  $\text{CF}_3\text{CONH}_2$  and  $\text{FCH}_2\text{CONH}_2$ , in PES, the first band corresponds to  $n_{\text{O}}$ -orbital, while in  $(\text{Me}_2\text{N})_2\text{CO}$  to the latter corresponds the 3rd band. In  $\text{CF}_3\text{CONH}_2$  spectrum, the 2nd band corresponds to  $\pi_{\text{CO}}$  orbital, and in  $(\text{Me}_2\text{N})_2\text{CO}$  spectrum - the 4th band.

We have also observed some cases of violation of Koopman's theorem in PES of amides in case of higher occupied MO.

In the previous work<sup>1</sup> of this series we studied the structure and PES of various alkyl derivatives of hydroxylamine. These compounds are a matter of interest, since they actually contain the oxygen atom with two lone electron pairs, and a nitrogen atom with one lone electron pair. Ac-

ording to the quantum chemical calculation with a full optimization of geometry, the conformation in which the lone pairs are turned relative to each other as much as possible is the most stable one in such compounds. In the PES of hydroxylamines the bands corresponding to the ionization of nitrogen and oxygen lone pairs have been rather well separated between each other. The nitrogen atom has been found to function as a protonation center.

In the present work, an attempt has been made to solve similar problems concerning certain amines, in the case of which the situation is a bit different, since they are situated near the amino-group of the double CO-bond of the carbonyl group. The PES of some amides have also been recorded, but in order to interpret the latter, quantum chemical calculations at different theoretical levels were involved.

### Experimental

The equipment and the technique of determining ionization potentials (IP) from PES were described in the first paper of this series<sup>2</sup>. The PES of molecules presented in Fig. 1 are the mean of repeated spectrum scanning.

The reagents produced by "Aldrich" were used.

Semiempirical CNDO/2 calculations were conducted with original parametrization<sup>3</sup>, using Pople's standard program. The following "optimum" bond length and valence angle values<sup>4</sup> have been accepted: CO = 0.121Å, CN = 0.135Å, CC = 0.155Å, NC = 0.147Å, CF = 0.138Å, NH = 0.102Å, CH = 0.109Å,  $\angle$ HNH = 107°,  $\angle$ CCF = 108.5°, carbon in carbonyl group is in the sp<sup>2</sup>-hybridization, in either methyl or CF<sub>3</sub>-group in the sp<sup>3</sup>-hybridization state.

The program<sup>5</sup> adapted for a EC-1060 computer was used in semiempirical HAM/3 calculations. As a rule, experimental geometry was used in these calculations. In the case of the absence of the latter, the geometry established by a full optimization of the bond lengths and valence angles using nonempirical calculation (the 3-21G basis set was

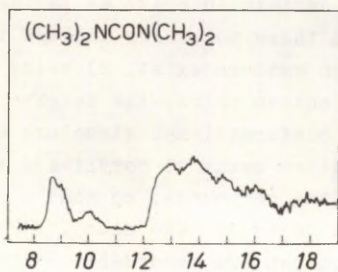
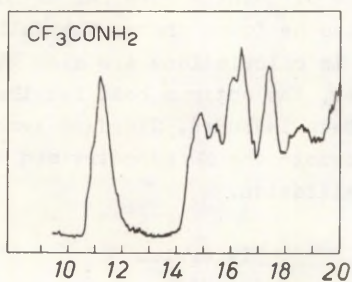
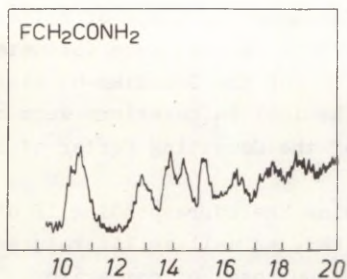


Fig. 1. Photoelectron spectra of some amides.

applied). In good approximation, the geometry corresponds<sup>6</sup> to the experimental one.

Nonempirical calculations of molecules with a full optimization of the geometry by means of either the gradient or the Sargent-Murtagh methods were conducted using the standard programs<sup>6,7</sup> of the Gaussian-80 system.

All quantum chemical calculations were conducted on a EC-1060 computer of the Computing Center of Tartu University.

Table 1 contains the corresponding IP of molecules, determined from the PES, as well as literature data, used in this report for the purposes of comparison. The IP values, calculated by means of quantum chemical methods according to Koopmans can also be found there. The full energies of molecules reached in calculations are also given. As for the 3-21G basis set, the optimum bond lengths and valence angles have also been included. Standard symbols have been used in order to denote the MO symmetry and the approximate nature of its localization.

## Discussion

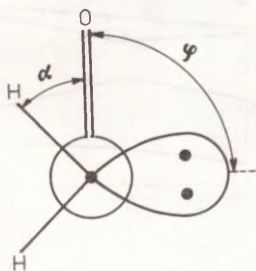
Amides are of certain interest as to the interpretation of PES : 1) in these molecules the two interacting and competing ionization centers exist, 2) owing to the participation of lone electron pairs, the neighboring groups tackle the problems of conformational structure of those molecules. The former matter seems to complicate the interpretation of the PES of the compounds, so that a substantial mixing of the orbitals tends to take place. At the same time, competing ionization centers remarkably differ from each other both in the energies of lone pair orbitals and in the number of electron pairs. The matter of conformation is of special importance also when interpreting PES, because this determines the sequence and the energies of MO-s.

The authors of papers<sup>13,14</sup> come to the conclusion that the semiempirical CNDO/2 method cannot sufficiently and adequately enough describe the system including the n-n and

$n-\pi$  interactions. When comparing the pyramidal structure of the  $\text{NR}_1\text{R}_2$  group (like in amines) with the planar structure of the  $\text{R}_1(\text{CO})\text{NR}_2\text{R}_3$ -framework, it turned out that in the case of II alkylsubstituted amides, calculated by means of this method the planar structure was more stable. The difference in their energies is diminishing parallel with the gain of the volume of the substituents at the nitrogen atom (in kcal/mol):  $\text{HCONH}_2$  - 29,  $\text{MeCONH}_2$  - 25,  $\text{Me}(\text{CO})\text{NHMe}$  - 17,  $\text{MeCONMe}_2$  - 9,  $(\text{NH}_2)_2\text{CO}$  - 9,  $(\text{NHMe})_2\text{CO}$  - 7.

Our nonempirical calculations of the acetamide using the 3-21G basis set refers to the finding that the planar structure is more stable in excellent agreement with experimental results<sup>15</sup>. The planar conformation of monofluoroacetamide is, according to the results of semiempirical CNDO/2 calculations by 7 kcal/mol more stable than the pyramidal one, while according to nonempirical calculation using the STO-3G basis set, the difference is 8.5 kcal/mol.

We have carried out a more detailed study of the structure of trifluoroacetamide. Let us mark the deflection angle between the direction of the nitrogen lone pair and C = O group as  $\psi$ , and the angle between C = O and NH-bond (the pyramidal level) in a simplified Newman projection of the molecule as  $\alpha$  (see the Scheme):



It can be stated on the basis of nonempirical calculations in the minimal STO-3G basis set that the most stable structure can be traced when the nitrogen lone pair is perpendicular to the CO-bond ( $\psi = 90^\circ$ ) and the hydrogen atoms of

NH-group have been turned out from the carbonyl group plane by  $\alpha = 27.2^\circ$  (pyramidal nitrogen). The valence angle  $\angle \text{HNC} = 113.0^\circ$ . The conformation with  $\varphi = 0^\circ$  ( $\alpha = 59.42^\circ$ ) is by 8.4 kcal/mol and the one with  $\varphi = 180^\circ$  ( $\alpha = 55.88^\circ$ ) is by 7.3 kcal/mol more stable in comparison with the above-mentioned conformation.

For this molecule the Walsh diagram (Fig. 2) shows that a rather firm stability of the corresponding perpendicular orientation of the nitrogen lone pair relative to the C = O bond can be reached via a sharp stabilization of the  $\pi_{\text{CO}}$  orbital.

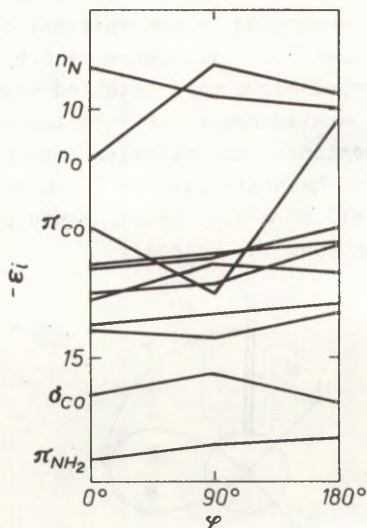


Fig. 2. The Walsh diagram for  $\text{CF}_3\text{CONH}_2$ . STO-3G calculation (all conformations have been totally optimized).

Table 1

Ionization Potentials of Some Amides, Determined from PES and Orbital Energies  
 ( $-\epsilon_i$ ), in eV Calculated According to Various Methods

1. MeCONH<sub>2</sub>

IP <sub>v</sub> <sup>a</sup>	CNDO/2 <sup>b</sup>		HAM/3 <sup>c</sup>		3-21G <sup>d</sup>				
	$-\epsilon_i$	MO	$-\epsilon_i$	MO	$-\epsilon_i$	MO			
10.0	13.05	3a''	$\pi(0,N)$	10.07	13a'	n <sub>O</sub>	10.75	3a''	$\pi(N,O)$
10.4	13.30	9a'	n <sub>O</sub>	10.12	3a''	n <sub>N</sub>	11.04	13a'	n <sub>O</sub>
13.0	16.27	8a	$\sigma_{CO}, \sigma_{NH}$	12.84	2a''	$\pi_{CO}$	14.17	2a''	$\pi_{CO}, n_N, \pi_{CH_3}$
14.1	17.31	2a''	n <sub>N</sub> , $\pi_{CH_3}$	13.72	12a'		15.22	12a'	$\sigma_{CH}$
14.5	18.13	7a'	$\sigma_{CH}, \sigma_{NH}$	13.96	11a'		15.49	11a'	$\sigma_{CO}$
15.4	22.43	6a'	n <sub>O</sub> , $\pi_{CH_3}$	14.99	10a'		16.82	1a''	$\pi_{CH_3}, \pi_{CO}, n_N$
16.0	23.04	5a'		14.99	1a''		17.86	10a'	$\bar{n}_O$
18.0	23.78	1a''		18.23	9a'		19.58	9a'	
19.4	24.82	4a'		18.92	8a'		21.53	8a'	
23.9	36.26	3a'		23.22	7a'		27.37	7a'	

a - see<sup>8</sup>, also<sup>9-11</sup>; b -  $E_{tot} = -48.0418$  a.u., this work; c - see<sup>8</sup>; d -  $E_{tot} = -206.8156$  a.u., this work; optimum geometry: CO = 1.2154Å, CC = 1.5167Å, CH1 = 1.0782Å, CH = 1.0845Å, CN = 1.3597Å, NH = 0.9958Å, ∠CCO = 123.30°, ∠HCC = 108.68°, ∠HCH = 108.60°, ∠NCO = 123.01°, ∠HNC = 120.74°

2. FCH<sub>2</sub>CONH<sub>2</sub>

Table 1 continued

I <sub>p</sub> <sup>a</sup> <sub>v</sub>	CNDO/2 <sup>b</sup>		HAM/3 <sup>c</sup>		STO-3G <sup>d</sup>		3-21G <sup>e</sup>	
	- ε <sub>i</sub>	MO	- ε <sub>i</sub>	MO	- ε <sub>i</sub>	MO	- ε <sub>i</sub>	MO
10.38	13.44	4a" $\overline{\text{N}}(0, \text{N})$	9.98	11a' n <sub>O</sub>	8.38	4a" $\overline{\text{N}}(\text{N}, 0)$	11.23	4a" $\overline{\text{N}}(\text{N}, 0)$
10.68	13.56	11a' n <sub>O</sub>	10.45	4a" $\overline{\text{N}}(\text{N}, 0)$	8.68	16a' n <sub>O</sub>	11.50	16a' n <sub>O</sub>
12.99	16.63	10a' $\overline{\text{C}}_{\text{CO}}, \overline{\text{N}}_{\text{CH}_3}$	12.28	3a" n <sub>F</sub> , $\overline{\text{N}}_{\text{CH}_2}$	11.66	3a" n <sub>F</sub> , $\overline{\text{N}}_{\text{CH}_2}$	14.18	3a" n <sub>F</sub> , $\overline{\text{N}}_{\text{CH}_2}$
13.91	16.77	3a" n <sub>N</sub> , n <sub>F</sub>	13.20	10a' n <sub>F</sub>	12.52	15a' n <sub>F</sub> , n <sub>O</sub>	15.09	15a' n <sub>F</sub>
14.47	19.22	9a' n <sub>F</sub>	13.92	2a" $\overline{\text{N}}_{\text{CO}}, n_{\text{F}}$	13.33	2a" $\overline{\text{N}}_{\text{CO}}, n_{\text{N}}$	16.00	2a" n <sub>F</sub> , $\overline{\text{N}}_{\text{CO}}$
15.18	20.02	8a' n <sub>F</sub>	14.70	9a' n <sub>O</sub>	13.64	14a' n <sub>O</sub> , n <sub>F</sub>	16.77	14a' n <sub>O</sub> , n <sub>F</sub>
16.39	20.47	2a" n <sub>F</sub> , n <sub>N</sub>	16.34	8a' $\overline{\text{N}}_{\text{NC}, \text{CC}, \text{CF}}$	15.26	13a' n <sub>F</sub>	17.56	13a' n <sub>F</sub>

a - IP<sub>a</sub><sup>(1)</sup> = 10.19 eV, IP<sub>a</sub><sup>(2)</sup> = 12.62 eV; this work;

b - E<sub>tot</sub> = - 75.0158 a.u., this work;

c - optimum 3-21G geometry; this work;

d - E<sub>tot</sub> = -302.7231 a.u., this work;

e - E<sub>tot</sub> = - 305.1199 a.u., this work, optimum geometry: CO = 1.2089Å, CC = 1.5197Å, CF = 1.3897Å, CH = 1.0808Å, CN = 1.3569Å, NH = 0.9965Å, ∠CCO = 123.69°, ∠FCC = 109.17°, ∠HCH = 109.28°, ∠NCO = 124.45°, ∠HNC = 121.04°.

Table 1 continued

3.  $\text{CF}_3\text{CONH}_2$ 

$\text{IP}_v^a$	HAM/3 <sup>b</sup>		STO-3G <sup>c</sup>		3-21G <sup>d</sup>	
	$-\mathcal{E}_i$	MO	$-\mathcal{E}_i$	MO	$-\mathcal{E}_i$	MO
11.23	10.72	13a' $n_{\text{O}}$	9.17	$n_{\text{O}}, n_{\text{N}}$	11.89	8a" $\overline{\text{H}}(\text{N}, \text{O})$
	11.04	8a" $\overline{\text{H}}(\text{N}, \text{O})$	9.73	$\overline{\text{H}}(\text{N}, \text{O})$	12.58	20a' $n_{\text{O}}$
14.81	14.57	7a" $\overline{\text{H}}_{\text{CO}}$	12.91	$n_{\text{F}}$	16.51	7a" $\overline{\text{H}}_{\text{CO}}$
	14.71	12a' $\bar{n}_{\text{O}}, n_{\text{F}}$	12.93	$n_{\text{F}}$		
15.42	15.26	6a" $n_{\text{F}}$	13.11	$n_{\text{O}}, n_{\text{F}}$	16.58	19a' $\bar{n}_{\text{O}}$
	15.48	11a' $n_{\text{F}}$				
16.02	15.88	10a' $n_{\text{F}}, \bar{n}_{\text{O}}$	13.49	$n_{\text{F}}$	17.76	6a" $n_{\text{F}}$
	15.92	5a" $n_{\text{F}}$				
16.37	16.50	4a" $n_{\text{F}}$	13.68	$\overline{\text{H}}_{\text{CO}}, n_{\text{F}}$	17.98	5a" $n_{\text{F}}$
					18.01	18a' $n_{\text{F}}$
17.30	16.76	9a' $n_{\text{F}}$	14.15	$n_{\text{F}}$	18.30	17a' $\bar{n}_{\text{O}}, n_{\text{F}}$
18.1 <sup>e</sup>	18.03	8a' $\sigma_{\text{NH}}$	14.60	$n_{\text{F}}$	19.25	16a' $n_{\text{F}}$
					19.27	4a" $n_{\text{F}}$
18.4 <sup>e</sup>	19.29	3a" $\sigma_{\text{NH}}$	15.32	$\bar{n}_{\text{O}}$	20.08	15a' $\sigma_{\text{NH}}$
20.7 <sup>e</sup>	20.12	2a" $n_{\text{F}}$	16.76	$\overline{\text{H}}_{\text{NH}_2}$	22.04	14a' $\sigma_{\text{NH}}$
	20.14	1a"			22.40	3a" $n_{\text{F}}$
21.8 <sup>e</sup>	21.29	7a'	18.09		22.53	13a' $\sigma_{\text{NF}}$
			18.18		24.22	12a'
			18.68			
			20.41			
24.7 <sup>e</sup>	24.32	6a'	20.41		27.89	11a'

a -  $\text{IP}_a^{(1)} = 10.77$  eV,  $\text{IP}_a^{(2)} = 14.16$  eV; this work, see also<sup>8</sup>;

b - optimum 3-21G geometry; this work, see also<sup>8</sup>;

c -  $E_{\text{tot}} = -497.6553$  a.u., this work.

d -  $E_{\text{tot}} = -501.7883$  a.u., this work; optimum geometry:

CO = 1.2063Å, CC = 1.5191Å, CF1 = 1.3517Å, CF = 1.3316Å,

CN = 1.3408Å, NH = 0.9969Å,  $\angle\text{CCO} = 121.51^\circ$ ,  $\angle\text{FCC} = 111.78^\circ$ ,

$\angle\text{FCF} = 106.44^\circ$ ,  $\angle\text{NCO} = 126.99^\circ$ ,  $\angle\text{HNC} = 120.75^\circ$

e - see<sup>8</sup>.

Table 1 continued

4. (Me<sub>2</sub>N)<sub>2</sub>CO

IP <sup>a</sup>	CNDO/2 <sup>b</sup>		HAM/3 <sup>c</sup>		STO-3G <sup>d</sup>		3-21G <sup>e</sup>		
	- $\epsilon_i$	MO	- $\epsilon_i$	MO	- $\epsilon_i$	MO	- $\epsilon_i$	MO	
8.72	12.69	8a <sub>1</sub> n <sub>N</sub>	8.15	n <sub>N</sub>	7.05	4b <sub>1</sub> $\overline{\pi}(N,O)$	9.94	17a' n <sub>N</sub>	
8.99	12.94	7b <sub>2</sub> n <sub>O</sub>	8.69	$\overline{\pi}(O,N)$	7.58	3a <sub>2</sub> n <sub>N</sub>	9.98	15a" $\overline{\pi}(N,O)$	
9.98	13.42	6b <sub>1</sub> $\overline{\pi}_{CO}$	9.27	n <sub>O</sub>	8.37	11b <sub>2</sub> n <sub>O</sub>	11.31	14a" n <sub>O</sub>	
12.98	13.92	6b <sub>2</sub> n <sub>N</sub>	12.08	$\overline{\pi}_{CO}$	12.23	3b <sub>1</sub> $\overline{\pi}_{CO}$	IV {	13.66	13a"
13.76	16.36	3a <sub>2</sub> $\overline{\sigma}_{CH}$	12.62	$\overline{\sigma}_{CH}$	12.29	14a <sub>1</sub> $\overline{\sigma}_{CO}$		13.74	16a' $\overline{\sigma}_{NC}$
14.77	16.76	5b <sub>2</sub> n <sub>O</sub>	12.82	$\overline{\sigma}_{CO}$	12.70	10b <sub>2</sub>	V {	13.82	12a" $\overline{\pi}_{CO}$
15.96	17.41	5b <sub>1</sub> $\overline{\sigma}_{CH}$	13.30		13.34	9b <sub>2</sub>	VI {	14.67	11a"
17.22	18.49	7a <sub>2</sub> $\overline{\sigma}_{CH}$	13.36		13.80	13a <sub>1</sub>		14.98	15a' a'
					14.17	2a <sub>2</sub>	VII {	15.34	a'
					14.65	2b <sub>1</sub>		15.38	a"
							VIII {	15.80	a'
								16.01	a"
								16.88	a'

a - IP<sub>a</sub><sup>(I)</sup> = 8.46 eV, this work; see also<sup>12</sup>; b - E<sub>tot</sub> = - 86.5672 a.u.;

c - STO-3G-optimum geometry;

d - E<sub>tot</sub> = - 375.3131 a.u., e - E<sub>tot</sub> = - 377.9521 a.u., incomplete optimization: CO = 1.232 Å, NC(=O) = 1.422 Å, CN1 = 1.505 Å, CN2 = 1.495 Å, HC = 1.079 Å,  $\angle$ NCO = 121.3°,  $\angle$ CNC1 = 113.2°,  $\angle$ CNC = 125.0°,  $\angle$ HNCN = 111.9°

The calculations with a split-valence 3-21G basis set which usually leads to a more adequate geometry of molecules, also show that in the case of the most stable conformation  $\psi = 90^\circ$ . In contrast to the minimal STO-3G basis set, the split-valence 3-21G basis set foretells that the  $\text{NH}_2$ -group cannot be a pyramidal but a strictly planar one ( $\alpha = 0^\circ$ ).

A sharp drop in the energy of CO-bond in the case of perpendicular ( $\psi = 90^\circ$ ) orientation of the lone pair orbital of nitrogen relative to the C = O bond axis is in keeping with the classical chemical viewpoint about resonance interaction of these groups namely in this structure. A maximum delocalization of the  $\pi$ -electron charge is reached.

The molecule of tetramethyl urea has been calculated using the nonempirical method in the minimal STO-3G basis set, this yields the structure with planar  $\text{NR}_2\text{R}'_2$ -framework ( $\psi = 90^\circ$ ,  $\alpha = 0$ ), which can also be confirmed by the calculations in the split-valence 3-21G basis set.

In order to avoid the mistakes connected with the use of the Koopmans' theorem, the authors of<sup>16</sup> have calculated the corresponding cation-radicals of acetamide on the bases of an extended "double zeta" basis set. The calculations' results and the analysis of the vibrational structure of the PES bands showed that the highest occupied MO in the molecule is  $n_o(10a')$ , the next one being  $\pi_2(2a'')$ , while the application of the Koopmans' theorem leads to the reversed sequence of orbitals. In the case comparison of vibrational band structures, for methyl-substituted amides  $\text{HCONHMe}$  and  $\text{HCONMe}_2$  the sequence  $\pi_2, n_o$  has been obtained. This can be explained with the destabilization of the  $\pi_2$ -orbital at methyl substitution. The comparison of the vibrational structure of the bands of the basic state and cation-radical accepts some MO mixing in amides.

The analysis of the vibrational structure of PES bands with a simultaneous consideration of the induction effect has in<sup>17</sup> led to the conclusion that the character of the highest occupied orbitals in acetamide is  $n_o, n_N(\pi_2)$ , in<sup>18</sup>-

$n_o$ ,  $\pi_{CO}$ ,  $n_N$ ; and in<sup>19</sup> the 4th band has been taken for  $\pi_{CO}$ .

The results of semiempirical calculations using HAM/3 method which is the density matrix method not having the drawbacks of the Koopmans' theorem, show that prerequisites for the theorem have been violated, as concerns the highest occupied orbitals of amides in nonempirical calculations. Both our results and those of the calculations by other authors<sup>B</sup> refer to the  $n_o$ ,  $n_N$ ,  $\pi_{CO}$  sequence of orbitals in the PES of the acetamide molecule. We have also found<sup>20,21</sup> on the basis of the linear dependence between  $IP(n_o)$  and  $(IP(\pi_{CO}))$  for various carbonyl-containing compounds that the  $\pi_{CO}$ -orbitals correspond to the 4th band (12.98 eV) in PES.

Calculation of monofluoroacetamide and trifluoroacetamide by means of semiempirical CNDO/2 method and nonempirical calculations in the STO-3G and 3-21G basis sets in the framework of the Koopmans' theorem refer to the mixed character of the highest occupied orbital, the next orbital belongs to the lone oxygen pair. We can conclude on the basis of the similarity with the acetamide spectrum and taking into account the results of our HAM/3 calculations leading to the reversed sequence of the highest occupied orbitals that in the molecules mentioned, the Koopmans' theorem is also violated for those orbitals. Evidently, the highest seems to be the orbital localized at the oxygen atom and having a  $n_o$ -character.

It should be said that in work<sup>B</sup> the localization character for  $CF_3CONH_2$  differs from ours and the sequence of the first three orbitals is as follows:  $n_N$ ,  $n_o$ ,  $\pi_{CO}$ .

All our calculations lead to the conclusion that in monofluoroacetamide the  $\pi_{CO}$ -orbitals significantly get mixed with the  $n_F$ -orbital of fluorine, while no such mixing was observed in trifluoroacetamide spectrum. The assignment of bands at 14.81 eV in the  $CF_3CONH_2$  spectrum to the  $\pi_{CO}$  orbital seems to be a rather unambiguous phenomenon. Such a conclusion can be drawn both from the analysis of our (see Table 1) calculations and from those of the HAM/3 cal-

culations given in Ref. 8, as well as on the basis of the results of nonempirical calculations in the 3-21G basis set. The comparison of the  $IP(n_0)$  and  $IP(\bar{\pi}_{CO})$  values for a number of carbonyl-containing compounds from different classes has yielded the same statement<sup>20,21</sup>.

The PES of tetramethyl urea has been measured by the authors of<sup>12,22</sup>. Our spectrum quite well agrees with the published results. Our CNDO/2 calculations have been conducted for the pyramidal  $sp^3$ -hybridization of nitrogen ( $C_{2V}$  symmetry,  $\psi = 180^\circ$ ). The MO sequence coincides with the results of CNDO/S<sup>12,22</sup> calculations, parametrized on the basis of molecular spectra.

Nonempirical calculation in the STO-3G basis set has been carried out for a planar conformation of the  $C_{2V}$  symmetry, the nitrogen lone pair orbital orientated perpendicularly relative to the C = O bond axis ( $\psi = 90^\circ$ ). In this case the appearance of the mixed  $4b_1$  orbital higher than those of the lone pairs seems also to evidence the drawbacks of the Koopmans' theorem. This statement is even more valid if we consider the MO sequence in the HAM/3 calculation:  $n_N, \bar{\pi}_{(O,N)}, n_O$ .

The regression analysis of the spectra of the eigenvalues in the framework of the Koopmans' theorem (Table 2) according to equation

$$IP_i = \alpha \epsilon_i + \beta, \quad (1)$$

where  $\epsilon_i$  denotes the consecutive MO energy values taken with an opposite sign, and  $\alpha$  and  $\beta$  are constants for separate molecules.

refers to good statistical indicators  $\alpha \approx 1$  and  $\beta \approx 0$  especially in the case of a semiempirical HAM/3 calculation method. Roughly the same results have also been obtained nonempirically in using nonempirical methods, e.g. split-valence 3-21G basis set. However one should keep in mind the statements concerning the violations of the Koopmans' theorem mentioned in the text (vide supra).

Table 2

Regression Treatment of Calculated Spectra of Eigenvalues According to Eq. (1)

No	Molecule	Method	$\alpha$	$\beta$	r	s	n
1.	CH <sub>3</sub> CONH <sub>2</sub>	CNDO/2	0.592 (0.046)	3.112 (0.961)	0.977	0.95	10
		HAM/3	1.926 (0.030)	-0.033 (0.463)	0.997	0.36	10
		3-21G	0.838 (0.015)	1.222 (0.264)	0.999	0.23	10
2.	FCH <sub>2</sub> CONH <sub>2</sub>	CNDO/2	0.755 (0.071)	0.47 (1.23)	0.978	0.51	7
		HAM/3	0.980 (0.047)	0.704 (0.611)	0.994	0.26	7
		STO-3G	0.871 (0.027)	3.04 (0.33)	0.997	0.18	7
		3-21G	0.863 (0.017)	0.732 (0.243)	0.999	0.09	7
3.	CF <sub>3</sub> CONH <sub>2</sub>	CNDO/2	1.023 (0.94)	-3.86 (1.97)	0.975	0.94	12
		HAM/3	1.007 (0.038)	0.025 (0.663)	0.994	0.44	11
		STO-3G	1.247 (0.043)	-0.675 (0.635)	0.995	0.40	11
		3-21G	0.869 (0.029)	0.866 (0.572)	0.995	0.40	11
4.	[(CH <sub>3</sub> ) <sub>2</sub> N] <sub>2</sub> CO	CNDO/2	1.260 (0.014)	-7.32 (0.23)	0.999	0.07	8
		STO-3G	0.962 (0.048)	1.70 (0.56)	0.993	0.43	8
		HAM/3	1.127 (0.023)	-0.56 (0.28)	0.999	0.17	8

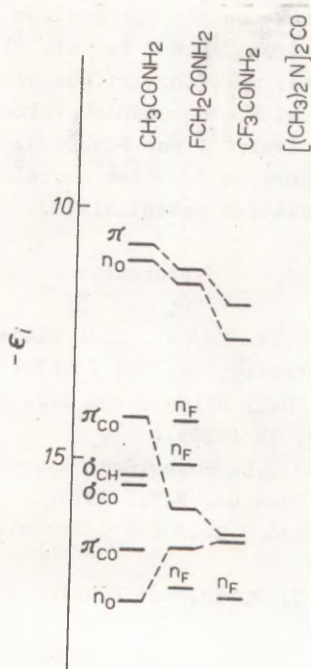


Fig. 3. Correlation diagram of eigenvalues, calculated according to nonempirical method of 3-21G basis set for some amides.

Fig. 3 presents the diagram of MO energies calculated nonempirically in the 3-21G basis set for the amides studied.

Acetamide is protonated to the oxygen atom of carboxylic group, while the calculation in the 3-21G basis set yields the proton affinity value 219.9 kcal/mol. Analogous calculation in the case of trifluoroacetamide gives 192.1 kcal/mol. The structures protonated to the nitrogen atom have turned out to be far less stable for those atoms. If we take into consideration the corrections from regression analysis (see Eq. 8 from Table 2 in Ref.<sup>23</sup>), for acetamide we get PA = 212.0 kcal/mol, for trifluoroacetamide PA = 189.1, which well agree with experimental values 210.4 and 192.4 kcal/mol, respectively<sup>21</sup>. For  $\text{FCH}_2\text{CONH}_2$ , value PA = 205 kcal/mol can be derived from the correlation of proton affinities and ionization potentials<sup>21</sup>.

#### References

1. U.H. Mölder, I.A. Koppel, R.J. Pikver, and J.J. Tapfer, *Organic Reactivity*, 24, 314 (1987).
2. I.A. Koppel, U.H. Mölder, and R.J. Pikver, *Organic Reactivity*, 20, 45 (1983).
3. I.A. Pople and D.L. Beveridge, *Approximate MO Theory*, McGraw-Hill Book Co, N.Y., 1970.
4. I.A. Koppel and U.H. Mölder, *Organic Reactivity*, 18, 42 (1981).
5. L. Åsbrink, C. Fridh, and E. Lindholm, *QCPE*, 12, 393, (1980).
6. W. Hehre, L. Radom, P.v.R. Schleyer, and J.A. Pople, *Ab Initio Molecular Orbital Theory*, Interscience, N.Y., 1986.
7. I.S. Binkley, R.A. Whiteside, R. Krishnan, et al., *QCPE*, N 437, 446, 500.
8. L. Åsbrink, A. Svensson, W.v.Niessen, and G. Bieri, *J. Electron Spectrosc. Relat. Phenom.*, 24, 293 (1981).
9. D.A. Sweigart and D.W. Turner, *J. Am. Chem. Soc.*, 94, 5592 (1972).

10. J.L. Meeks, J.F. Arnett, and S.P. McGlynn, *J. Am. Chem. Soc.*, 97, 3905 (1975).
11. S.P. McGlynn, and J.L. Meeks, *J. Electron Spectrosc. Relat. Phenom.*, 6, 269 (1975).
12. D. Dougherty, K. Wittel, J. Meeks, and S.P. McGlynn, *J. Am. Chem. Soc.*, 98, 3815 (1976).
13. A. Veillard, *Chem. Phys. Letters*, 33, 15 (1975).
14. C. Giessner-Prette and A. Pullmann, *Theor. Chim. Acta*, 37, 335 (1975).
15. Landolt-Börnstein, New Series. Vol. 7. Hellwege K.-H., Hellwege A.M., Eds., Berlin, Springer, 1976.
16. C.R. Brundle, D.W. Turner, M.B. Robin, and H. Basch, *Chem. Phys. Letters*, 3, 292 (1969).
17. D.A. Sweigart and D.W. Turner, *J. Am. Chem. Soc.*, 94, 5592 (1972).
18. S.P. McGlynn, and J.L. Meeks, *J. Electr. Spectrosc. Relat. Phenom.*, 6, 269 (1975).
19. J.L. Meeks, J.F. Arnett, D.B. Larson, and S.P. McGlynn, *J. Am. Chem. Soc.*, 97, 3905 (1975).
20. U.H. Mölder, I.A. Koppel, and R.J. Pikver, *Organic Reactivity*, 24, 218 (1987).
21. I.A. Koppel, D. Sc. Thesis (in Russian), Moscow, 1986.
22. G.W. Mines and H.W. Thompson, *Spectrochimica Acta*, 31A, 137 (1975).
23. I.A. Koppel, U.H. Mölder, and V.A. Palm, *Organic Reactivity*, 22, 3 (1985).

ACIDITY OF SOME SUBSTITUTED BICYCLO [2.2.2]  
OCTANE-1-, BICYCLO [2.2.2]OCT-2-ENE-1-, AND  
CUBANE-1- CARBOXYLIC ACIDS IN DMSO

I.A.Koppel, J.B.Koppel, A.O.Kõrgesaar, and  
V.O.Pihl

Department of Analytical Chemistry and Laboratory  
of Chemical Kinetics and Catalysis, Tartu State Uni-  
versity, 202400 Tartu, Estonia, U.S.S.R.

Received December 20, 1988

The potentiometric titration was used for the determination of the acidic dissociation constants of some derivatives of bicyclo [2.2.2]octane-1-, bicyclo [2.2.2]oct-2-ene-1-, and cubane-1-carboxylic acids in dimethylsulfoxide. The present results and literature data for the other solvents were compared with the corresponding information about the acidity of these alicyclic acids in the gas phase. It was established that the transfer from the aqueous organic solvent into DMSO influences rather modestly the sensitivity of the reaction series towards the substituent effects whereas the substitution of the both above-mentioned solvents for the gas phase increases very significantly the latter characteristic of the reaction series. It was also found that the conductivity of the 4 - substituted bicyclo [2.2.2]octane ring exceeds that quantity in the case of a 3-substituted derivati-

ve whereas the substituent attenuation factors of the 4-substituted bicyclo[2.2.2]octane, bicyclo[2.2.2]oct-2-ene and cubane rings are approximately equal.

The acidity of substituted bicyclo[2.2.2]octane-1-, bicyclo[2.2.2]oct-2-ene-1-, and cubane-1- carboxylic acids was studied<sup>1-8</sup> during a rather long time period mostly only in the aqueous organic and aqueous solutions. In the case of the first of those reaction series in Ref. 4b also the acidity of some 4-substituted derivatives was measured in anhydrous methanol whereas the relative acidities for the same series of acids were determined<sup>4a</sup> in aqueous ethanol, methanol, and DMSO as well as in anhydrous ethanol, methanol, acetone, and DMSO.

However, as mentioned in literature<sup>3</sup> and also accepted by the authors<sup>4a</sup>, one cannot have full confidence that all quantities measured in the latter work can serve as an adequate quantitative measure of the relative acidity of these acids in a given solvent, especially in aqueous organic mixtures with a relatively high content of water (vide infra).

In Ref. 9 the  $pK_a$  values only for three representatives of bicyclo[2.2.2]octane-1- carboxylic acids were measured in DMSO, methanol, n-butanol, and 1,2 -ethanediol. Recently<sup>10</sup>, the acidity of a wide range of derivatives belonging to the above-mentioned three classes of alicyclic acids was also measured in the gas phase\*.

Unfortunately, the information about the acidities of 4-substituted bicyclo[2.2.2]oct-2-ene-1- carboxylic acids and 4-substituted cubane-1- carboxylic acids refers only to the aqueous ethanol solution<sup>6,8</sup> and to the gas phase<sup>10-14</sup>.

From the analysis of this complex of sometimes contradictory data up to now emerges only one unambiguous inference: the transfer of the above-mentioned series of alicyclic acids from aqueous-organic solvents into the gas

---

\* The preliminary information about some results of this work could be found also in Refs. 9, 11 - 14.

phase enhances very significantly the sensitivity of those reactions series towards the substituent effects. However, the comparison of the influence of nonaqueous, e.g. dipolar aprotic solvents (DMSO, acetonitrile, etc.) with the influence of the aqueous-organic mixtures on the acidity in the above-mentioned series of alicyclic acids still remains to be performed. In that sense somewhat more information is available in the case of substituted adamantane-1- carboxylic acids, whose acidity was measured in the aqueous ethanol<sup>15-19</sup> as well as in DMSO<sup>20</sup>. Also some very first data<sup>10, 12, 14, 21</sup> about the acidity of the substituted adamantane carboxylic acids in the gas phase has become available. These data evidence that in the case of this alicyclic reaction series the transfer from the aqueous-organic solvent into the DMSO increases the sensitivity of this process towards the substituent effect. At the same time, as in the case of the substituted bicyclo[2.2.2]octane-1-, bicyclo[2.2.2]oct-2-ene-1-, and cubane-1- carboxylic acids, the substitution of the aqueous-organic or dipolar aprotic solvent for the gas phase again very significantly increases the range of influence of the structure on the acidity of the substituted adamantane-1- carboxylic acids.

In the present work an attempt has been made to measure the  $pK_a$  values of the acidic dissociation of some 2-, 3-, and 4-substituted bicyclo[2.2.2]octane-1-, 4-substituted bicyclo[2.2.2]oct-2-ene-1, and 4-substituted cubane-1- carboxylic acids in DMSO.

### Experimental

The technique for the potentiometric measurement of  $pK_a$  values of acidic dissociation of bicyclic acids in DMSO via the potentiometric titration of the acidic substance with the solution of tetrabutylammonium hydroxide in the mixture (1:4) of *i*-PrOH and benzene was used as described elsewhere<sup>20</sup>.

The calibration of the glass electrode (Radiometer A 2222B or HCT) filled up with mercury was made using the  $pK_a$

value of benzoic acid ( $pK_a = 11.0^1$ ) as the reference compound.

The purification of DMSO is also described in our earlier publication<sup>20</sup>.

The synthesis and purification of 2-CN and 3-CN substituted bicyclo[2.2.2]octane-1-carboxylic acids was thoroughly described by one of us<sup>22</sup>. The synthesis of 4-COOH, 4-COOEt, and 4-CN-derivates of the same type of acids was performed in the present work according to the method used by Roberts<sup>23</sup>. 3-Cl, 3-Br, 3-OH, 3-COOH and 3-O= substituted bicyclo[2.2.2]octane-1-carboxylic acids were synthesized by us using the techniques described by other authors<sup>7,24</sup>.

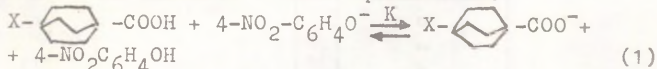
The unsubstituted bicyclo[2.2.2]octane-1-carboxylic acid and bicyclo[2.2.2]oct-2-ene-1-carboxylic acid were made using the method of Grob<sup>25,26</sup>.

4-Cl, 4-CN and 4-CF<sub>3</sub>-substituted bicyclo[2.2.2]oct-2-ene-1-carboxylic acids were delivered by Prof. R. W. Taft (University of California, Irvine), as well as 4-H and 4-Br substituted cubane-1-carboxylic acids (the same samples, used in works<sup>6,8</sup> of L.M. Stock, were used).

The titration of the acids was repeated 3-5 times, from the mean arithmetic values  $pK_a$  of the individual runs the arithmetic mean  $pK_a$  values were calculated. The latter values are listed in the 3-rd column of Table 1 (the reliability intervals are given in the parenthesis under the  $pK_a$  values) alongside a few available literature data.

For the sake of comparison, Table 1 also includes some literature  $pK_a$  values for a few aqueous-organic solvents as well as the  $\delta\Delta G^\circ$  (kcal/mol) values for the gas phase<sup>10-14</sup>.

The 3rd column of Table 1 also includes some absolute  $pK_a$  values for DMSO solution calculated from the data of Ritchie and Lewis<sup>4a</sup> concerning the relative equilibrium constants  $K$  of the acid - base equilibrium.



for some 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids (for the paranitrophenol the  $pK_a = 11.0^1$  was used).

One can see that in those cases when the comparison is

Table 1

Acidity of Some Alicyclic Carboxylic Acids in DMSO, Aqueous Ethanol,  
Aqueous Methylcellosolve, Water and Gas Phase

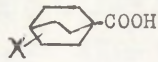
A c i d		pK <sub>a</sub> (298 K)				-ΔG° (kcal/mol), 373 K	Gas Phase <sup>10-12</sup>
		DMSO, this work	50 % (weight) EtOH - H <sub>2</sub> O	H <sub>2</sub> O <sup>5b</sup>	80 % (weight) methylcellosolve H <sub>2</sub> O <sup>9</sup>		
1	2	3	4	5	6	7	
							
1.	X = H	12.90 (0.06) 12.80 <sup>9</sup> 12.95 <sup>**</sup>	6.83 <sup>9</sup> , 6.87 <sup>3</sup> , 6.79 <sup>2*</sup>	5.08	7.81	0 <sup>a</sup>	
2.	2-CN	12.03 (0.04)	5.70 <sup>9*</sup>		6.61	7.9	
3.	3-Cl	12.15 (0.03)	6.33 <sup>9*</sup>		7.25	3.9	
4.	4-Br	12.07 (0.04) 12.30 <sup>9</sup>	6.29 <sup>9*</sup>		7.19	-	

Table 1 continued

1.	2.	3	4	5	6	7
5.	3-I	-	6.49 <sup>9*</sup>		7.39	-
6.	3-OH	12.85 (0.04)	6.47 <sup>9*</sup>		7.63	-
7.	3-OMe	-	6.48 <sup>9*</sup>		7.59	0.9
8.	3-COOH	12.55 (0.03)	-		-	-
9.	3=O	12.15 (0.03)	5.85 <sup>9*</sup>		6.83	7.6
10.	3-CN	12.00 (0.05) 12.03 <sup>9</sup>	6.05 <sup>9*</sup>		7.01	6.4
11.	4-CN	12.15 (0.04) 12.08**	5.94 <sup>2</sup>	4.55	-	8.4
12.	4-Cl	-	6.15 <sup>3</sup>	-	-	6.5
13.	4-OH	12.88**	6.50 <sup>3</sup>	-	-	-
14.	4-MeO	-	6.40 <sup>3</sup>	-	-	2.6
15.	4-Me	-	6.89 <sup>3</sup>	-	-	0.9
16.	4-Et	-	6.89 <sup>3</sup>	-	-	-
17.	4-CH <sub>2</sub> OH	-	6.80 <sup>3</sup>	-	-	-

Table 1 continued

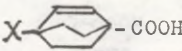
1	2	3	4	5	6	7
18.	4-COOH	12.20 (0.05) 12.16**	6.10 <sup>3</sup>	4.47	-	-
19.	4-COOEt	12.47 (0.05) 12.22**	6.40 <sup>3</sup>	4.76	-	-
20.	4-Br	12.04**	6.14 <sup>3</sup>	4.62	-	6.4
21.	4-CF <sub>3</sub>	-	6.24 <sup>6</sup>	-	-	6.4
22.	4-NO <sub>2</sub>	-	5.82 <sup>3</sup>	-	-	-
23.	4-CO <sub>2</sub>	14.71**	7.47 <sup>6</sup>	5.46	-	8.5
24.	4-NMe <sub>3</sub> <sup>+</sup>	11.74**	5.37 <sup>5a</sup>	4.08	-	-
25.	4-NH <sub>3</sub> <sup>+</sup>	-	5.64 <sup>5a*</sup>	-	-	-
26.	4-F	-	-	-	-	5.6
	 -COOH					
1.	X = H	12.40 (0.05)	6.54 <sup>3</sup>	0	-	0 <sup>b</sup>
2.	4-Cl	11.50 (0.05)	5.71 <sup>3</sup>	-	-	6.2
3.	4-CF <sub>3</sub>	11.55 (0.06)	5.78 <sup>3</sup>	-	-	6.3

Table 1 continued


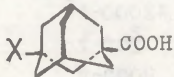
1	2	3	4	5	6	7
4.	4-CN	11.30 (0.02)	5.49 <sup>3</sup>	-	-	8.4
5.	4-COOEt	-	6.00 <sup>3</sup>	-	-	3.2
6.	4-Me	-	6.50 <sup>3</sup>	-	-	-
7.	4-CONH <sub>2</sub>	-	5.96 <sup>3</sup>	-	-	-
8.	4-COOH	-	5.67 <sup>3</sup>	-	-	-
9.	4-CO <sub>2</sub> <sup>-</sup>	-	7.11 <sup>3</sup>	-	-	-
10.	4-NMe <sub>3</sub> <sup>+</sup>	-	4.83 <sup>3</sup>	-	-	-
						
1.	X = H	12.20 (0.05)	5.94 <sup>8</sup> , 5.95 <sup>6</sup>	-	-	0 <sup>9</sup>
2.	4-Br	11.40 (0.07)	5.32 <sup>8</sup>	-	-	5.7
3.	4-COOH	-	5.13 <sup>8</sup>	-	-	-
4.	4-CO <sub>2</sub> <sup>-</sup>	-	6.53 <sup>8</sup>	-	-	-
5.	4-COOEt	-	5.40 <sup>8</sup>	-	-	-
6.	4-COOMe	-	5.40 <sup>8</sup>	-	-	4.3
7.	4-CN	-	5.14 <sup>8</sup>	-	-	-

Table 1 continued

1	2	3	4	5	6	7
						
1.	X = H	13.09 <sup>20</sup>				0 <sup>d</sup>
2.	3-Cl	-				5.1
3.	3-Br	12.11 <sup>20</sup>				-

\* - 50 % (volume) EtOH - H<sub>2</sub>O

\*\* - Calculated from data<sup>4a</sup> for the equilibrium (1), taking pK<sub>a</sub> = 11.0 for the 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OH in DMSO (see the text).

a - The relative  $\sigma^{\Delta} G^{\circ}$  values are given. For this reference compound the absolute  $\Delta G^{\circ} = 337.2$  kcal/mol ( $-\Delta H = PA = 344.2$  kcal/mol).

b - See the previous footnote: for this reference compound  $\Delta G^{\circ} = 335.3$  kcal/mol, PA = 342.4 kcal/mol.

c - See the previous footnotes; for this reference compound  $\Delta G^{\circ} = 334.1$  kcal/mol, PA = 341.2 kcal/mol.

d - See the previous footnotes: for this reference compound  $\Delta G^{\circ} = 336.6$  kcal/mol, PA = 343.8 kcal/mol.

possible (excluding probably the 4-COOEt derivative) a satisfactory agreement between the  $pK_a$  values measured in this work and those quantities calculated from the data of Ref. 4a is observed (see also the "Discussion").

### Discussion

The statistical analysis of the influence of solvent-solute interactions on the sensitivity of some of the above-mentioned reaction series towards the substituent effects could be performed by the direct comparison of the  $pK_a$  values for the different solvents  $i$  and  $j$ , in terms of the linear equation:

$$pK_{a(i)} = \alpha pK_{a(j)} + \beta, \quad (2)$$

where  $\alpha$  and  $\beta$  are constants, the subscripts  $i$  and  $j$  refer to the solvents compared. In terms of the same equation, the verification of the compatibility of literature data on the  $pK_a$  values for the acidic dissociation of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids measured either by the different authors or by the same group of authors at different times or using the different experimental techniques was also performed.

Some results of the statistical analysis of the data in terms of Eq.(2) are listed in Table 2 (see also Fig.1) From Table 2, e.g., one can see (see series A 17) that in the case of the reaction series of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids in 50 % (weight) aqueous alcohol the results of the measurements of Ritchie and Lewis<sup>4a</sup> of the equilibrium (1) by the indicator method on the one hand, and the results of the other authors<sup>2,3,5,6</sup>, on the other hand, are clearly incompatible. Due to some peculiarities of the experimental techniques used in Ref. 4a the majority of the data concerning Eq.(1) should be considered in the further analysis with due caution. However, according to the above-said (see also Table 2, series A6) a satisfactory agreement between the results of the present work and those of Ritchie and Lewis<sup>4a</sup> was noticed for the series of

substituted bicyclo [2.2.2]octane-1- carboxylic acids in anhydrous DMSO solution. At the same time one should admit that the results of two works<sup>4a,b</sup> by Ritchie et al. on the determination of the  $pK_a$  values of 4-substituted bicyclo[2.2.2]octane-1- carboxylic acids in anhydrous methanol are incompatible with each other (see Table 2, series A18).

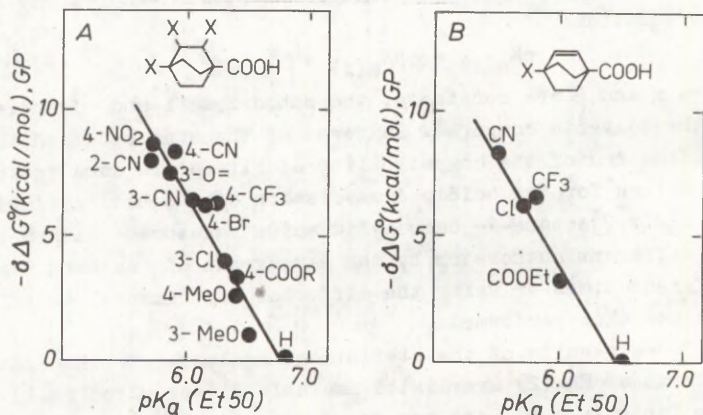


Fig. 1. The comparison of the acidities of substituted bicyclo[2.2.2]octane-1-COOH (A) and substituted bicyclo[2.2.2]oct-2-ene-1-COOH (B) in the gas phase ( $\delta\Delta G^\circ$ ) and in 50 % (weight) aqueous ethanol.

Table 2

The Comparison of Acidities of Some Series of Alicyclic Acids  
in Terms of Eq. (2) From the Text <sup>a, b</sup>

The reaction series, solvents		$\alpha$	$\beta$	r	s	n
1	2	3	4	5	6	7
A. Substituted bicyclo[2.2.2]octane- 1- Carboxylic Acids						
1.	DMSO and 50 % (w) H <sub>2</sub> O - EtOH	0.859 (0.223)	6.7 (1.4)	0.789	0.23	11
2.	DMSO and H <sub>2</sub> O	1.41 (0.05)	5.74 (0.24)	0.999	0.02	3
3.	DMSO and 80 % (w) H <sub>2</sub> O - methyl cellosolve(MCS)	0.805 (0.203)	6.5 (1.5)	0.871	0.21	7
4.	DMSO and Gas Phase (GP)	-0.0908 (0.0247)	12.7 (0.2)	0.855	0.18	7
5.	DMSO and MeOH <sup>4b</sup>	1.300 (0.356)	-0.3 (3.5)	0.903	0.16	5
6.	DMSO (this work) and DMSO <sup>4a</sup>	-0.929 (0.045)	11.1 (0.01)	0.996	0.04	5
7.	GP and DMSO	8.28 (2.45)	-10.7 (30.0)	0.860	1.8	6
8.	GP and 50% (w) H <sub>2</sub> O-EtOH	8.50 (0.87)	-58.1 (5.4)	0.951	0.9	12

Table 2 continued

1	2	3	4	5	6	7
9.	GP and MeOH <sup>4b</sup>	13.6 (0.4)	-139.6 (3.5)	0.999	0.2	3
10.	GP and 50% (v) H <sub>2</sub> O-MeOH <sup>5b</sup>	12.0 (0.9)	-75.0 (5.5)	0.997	0.5	3
11.	GP and 80% (w) H <sub>2</sub> O-MCS	7.36 (0.63)	-57.3 (4.6)	0.985	0.6	6
12.	GP and H <sub>2</sub> O	15.2 (2.6)	-76.8 (12.6)	0.971	1.1	4
13.	80% (w) H <sub>2</sub> O-MCS and 50% (w) H <sub>2</sub> O-EtOH (see Table 1)	1.11 (0.10)	0.21 (0.63)	0.976	0.10	8
14.	H <sub>2</sub> O and 30% (w) H <sub>2</sub> O-EtOH	0.737 (0.072)	0.11 (0.46)	0.981	0.10	6
15.	MeOH <sup>4b</sup> and "	0.536 (0.029)	6.45 (0.18)	0.991	0.04	8
16.	50% (v) H <sub>2</sub> O → MeOH and "	0.674 (0.234)	5.50 (1.50)	0.855	0.17	5
17.	50% (w) H <sub>2</sub> O-EtOH <sup>4a</sup> and "	0.637 (0.173)	5.37 (1.10)	0.878	0.13	6
18.	MeOH <sup>4b</sup> and MeOH <sup>4a</sup>	0.838 (0.099)	10.9 (0.1)	0.973	0.05	6

Table 2 continued

1	2	3	4	5	6	7
B. 4-Substituted Bicyclo [2.2.2]oct-2-ene-1- Carboxylic Acids						
1. GP and 50% (w) H <sub>2</sub> O-EtOH		3.08 (0.77)	-52.5 (4.6)	0.987	0.6	5
2. GP and DMSO		7.42 (0.43)	-91.9 (5.1)	0.997	0.4	4
3. DMSO and 50% (w) H <sub>2</sub> O-EtOH		1.06 (0.04)	5.43 (0.23)	0.999	0.03	4
C. 4-Substituted Cubane-1- Carboxylic Acids						
1. GP and 50% (w) H <sub>2</sub> O-EtOH		8.75 (1.05)	-51.9 (5.8)	0.993	0.5	3
D. Comparison of Series of Acidic Dissociation of 4-Substituted Bicyclo [2.2.2]octane-1-COOH and 4-Substituted Bicyclo [2.2.2]oct-2-ene-1-COOH						
1. GP		1.01 (0.03)	0.05 (0.16)	0.999	0.17	4
2. 50% (w) H <sub>2</sub> O-EtOH		0.877 (0.030)	1.15 (0.19)	0.996	0.04	8

Table 2 continued

1	2	3	4	5	6	7
E. Comparison of Series of Acidic Dissociation of 4-Substituted Bicyclo 2.2.2 octane-1-COOH and 4-Substituted Cubane-1-COOH						
1. GP		1.03 (0.30)	-0.3 (1.3)	0.960	1.3	3
2. 50 % (w) H <sub>2</sub> O-EtOH		1.01 (0.11)	0.81 (0.62)	0.977	0.10	6
F. Comparison of Series of Acidic Dissociation of 4- and 3-Substituted Bicyclo 2.2.2 octane-1-COOH						
1. GP		1.27 (0.20)	0.8 (0.7)	0.978	1.0	4
2. 50 % (w) H <sub>2</sub> O-EtOH		1.30 (0.14)	-2.08 (0.14)	0.979	0.08	6

### Footnotes

- a - If not indicated otherwise, the comparable quantities ( $pK_a$  and/or  $\delta\Delta G^\circ$ ) are taken from Table 1. In columns 3 and 4 under the regression coefficients their reliability intervals are given. For the quantities  $\delta\Delta G^\circ$  for the gas phase the kcal/mol units were used. Therefore, in the case of comparison of  $\delta\Delta G^\circ$  values with  $pK_a$  values (A4, A7, A11, B1, B2, C1) for the conversion of  $\alpha$ -coefficients into the common scale the latter should be multiplied or divided by the factor  $2.3 RT$ , i.e. 1.705.
- r - correlation coefficient. s - standard deviation. n - the number of points.
- b - In the case of substituted bicyclo[2.2.2]octane-1-COOH the  $pK_a$  values for the 50 % (volume) aqueous ethanol (see Table 1) were recalculated into the corresponding quantities for the 50 % (weight) aqueous ethanol by correcting the former values by the increment + 0.07 units of  $pK_a$ .

At the same time it seems hard to give preference to any series of those results (see also further discussion in this paper).

The problem about the independent or self - consistent verification of the results of Ritchie and Lewis<sup>4a</sup> for the anhydrous ethanol and most of the aqueous-organic mixtures ( $H_2O$ -MeOH\*, water-EtOH (except the 50% aqueous ethanol, vide supra), aqueous DMSO) still remains to be resolved.

One can see from Table 2 that the influence of the nature and composition of the solvent on the substituent effects in the case of the series of acidic dissociation of substituted bicyclo 2.2.2 octane-1- carboxylic acids has

---

\* For the 50 % aqueous methanol the results of work <sup>4a</sup> are probably also incompatible with the results from the other laboratory <sup>5b</sup> (the difference amounts to 15-20 %).

rather complicated and even somewhat undetermined features. Naturally, there is no doubt that the substitution of any aqueous-organic or anhydrous solvent (methanol, DMSO, ethanol) for the gas phase increases very significantly (from 4 to 8 times) by the analogy with many other reaction series,<sup>1,4</sup> the sensitivity of these alicyclic reaction series towards the structural effects (Fig. 1, Table 2).

Unfortunately, much more complicated is the situation in the case of transitions between different binary aqueous-organic mixtures or individual hydroxylic or dipolar aprotic (DMSO) solvents. So, the transfer from H<sub>2</sub>O into aqueous ethanol (Table 2, A14) as well as into aqueous methanol<sup>5b</sup> or aqueous DMSO<sup>4a</sup> enhances rather moderately (by ca 20-30%) the sensitivity of the given reaction series towards substituent effects. As far as one can judge on the basis of rather limited data (Table 2, A2) the similar transfer from water into DMSO increases the same characteristics of the reaction series up to 50 per cent. At the same time, the transitions from 50 % aqueous ethanol into 50 % aqueous methanol or into 80 % aqueous methyl cellosolve practically does not change the relative reactivity in the given series of substituted alicyclic acids.

However, somewhat suprising seems to be the decrease of the sensitivity of this reaction series towards substituent effects due to the transfer from aqueous-organic solvent (50 % aqueous ethanol, 80 % aqueous methyl cellosolve, 50 % aqueous methanol) into anhydrous methanol and possibly also into anhydrous ethanol (respectively ~1.7 (Table 2, A15)\* and 1.2 (data from<sup>4a</sup>) times). Somewhat unexpected is also relatively slight change (increase) of the sensitivity of this reaction series towards structural effects due to substitution of the aqueous (vide supra) or aqueous-organic solvent for the dipolar aprotic solvent - DMSO, which differs

---

\* In connection with the above-mentioned incompatibility of two different acidity scales for 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids reported in Refs.4a,b for methanol this figure should be taken with great caution.

from the usual behaviour<sup>11,14,27-29</sup>, which is characteristic to the reactions of acidic dissociation of aliphatic and aromatic carboxylic acids, aliphatic alcohols and phenols. One can remind that in the latter cases the transfer from the electrophilic solvent into the dipolar aprotic solvent is always accompanied with the significant increase of the range of the substituent effects.

As far as one can judge on the basis of much more scarce data base for the reaction series of 4-substituted bicyclo [2.2.2]oct-2-ene-1- carboxylic acids and 4-substituted cubane-1- carboxylic acids here the situation is rather analogous with the above - described one in the case of 4-substituted bicyclo 2.2.2 octane-1- carboxylic acids (see Table 2 and Fig. 1). Indeed the transfer from the aqueous ethanol into the gas phase in both cases leads to the almost five-fold increase of the gross-sensitivity characteristics ( $\alpha$ ) of the reaction series towards the substituent effects, whereas the substitution of aqueous ethanol for the DMSO is hardly ever accompanied by any rather noticeable solvent effect on the relative reactivity of these two classes of alicyclic acids.

On the other hand, one recalls that for the other series of the alicyclic acids, 2-3- or 4-substituted adamantane-1- carboxylic acids<sup>20</sup> the transfer from the 50 % aqueous ethanol into DMSO results in a 1.5-2-fold increase of the sensitivity of this reaction series towards substituent effects whereas based on the extremely scarce (two points) data from Table 1 for 3-substituted acids the substitution of 50 % aqueous ethanol for the gas phase enhances the total range of the substituent effects ca 5 times.

The results of the direct comparison for the fixed solvent of the acidity constants in the case of all three alicyclic series (see Table 2, C1 and C2, D1 and D2)\* de-

\* In this case the subscripts i and j in Eq. (2) refer (the fixed solvent) to two different reaction series to be compared (4-substituted bicyclo [2.2.2]octane-1-COOH and 4-substituted bicyclo [2.2.2]oct-2-ene-1-COOH or 4-substituted bicyclo [2.2.2]octane-1-COOH and 4-substituted cubane-1-COOH).

monstrate that the attenuation factors of substituent effects via different 4-substituted alicyclic systems (bicyclo[2.2.2]octane, bicyclo[2.2.2]oct-2-ene and cubane rings) are roughly equal in the gas phase as well as in 50 % (w) aqueous ethanol. The close comparability of the attenuation factors for the different alicycles evidently does not agree with the considerations about the transfer of the substituent inductive effect through the bonds only because in the latter case, e.g., the inductive attenuation factor of the cubane cycle  $Z^* = 6(Z_C^*)^4$  (where  $Z_C^*$  is the attenuation factor for one carbon atom) should be twice higher than the same quantity for the 4-substituted bicyclo[2.2.2]octane cycle ( $Z_{(4)}^* = 3(Z_C^*)^4$  (see also further discussion). It is possible that these circumstances evidence that the substituent effects in the case of at least some 4-substituted cycles are transmitted through the space by the electrostatic mechanism (field effects)<sup>3,5-9,11,20,21</sup>. For the reaction series studied in this work the direct comparison of the attenuation factors of the effects of substituents which are located in the different positions of the alicyclic ring is possible only in two cases (see Table 2, F1 and F2). It turns out that in the gas phase as well as in 50 % (w) aqueous ethanol the attenuation factors for the 4-substituted bicyclo[2.2.2]octane ring is approximately by 30 % higher than the attenuation factor for corresponding 3-substituted cycle. The comparison based only on two points (H and CN) indicates that the attenuation factors of 4- and 2-substituted bicyclo[2.2.2]octane rings in the gas phase are roughly equal, whereas (also based only on two points) in the aqueous ethanol the transmittance of the 2-substituted bicyclo[2.2.2]octane cycle is by 40-45 per cent higher than the quantity for the 4-substituted cycle (see Tables 1 and 2).

It follows from the hypothesis about the through-bond only transmission of  $\sigma$ -inductive effect of substituents (see Refs. 30,31 for the references) that the following or-

der of the attenuation factors of the inductive effect  $Z_{(i)}^*$  via the differently substituted bicyclo[2.2.2]octane cycles should hold:  $Z_{(2)}^* > Z_{(3)}^* \geq Z_{(4)}^*$ , where depending on the accepted value of the attenuation factor  $Z_C^*$  for the carbon atom (0.35  $\geq Z_C^* \geq 0.5$ )<sup>30</sup> the ratio  $Z_{(2)}^*/Z_{(3)}^*$  can range from 1.4 to 2.3 whereas the ratio  $Z_{(3)}^*/Z_{(4)}^*$  could vary between 1.0 and 1.2<sup>+</sup> (see also 7,9,20). Therefore it is evident that at least qualitatively the experimentally found inversion of the ratio of the attenuation factors for the 3- and 4- positions speaks clearly against the transfer of the inductive effect via the bonds. Most probably that in this case the condition  $Z_{(4)}^*/Z_{(3)}^* > 1$  agrees much better with the field-effect-based through-space model of the inductive effect<sup>+</sup>.

Concluding this section of the Discussion it seems interesting to mention that judging by the minimum data (X=H and Cl) from Table 1, that the transmittance of the 3-substituted adamantane ring exceeds that of the 3-substituted bicyclo[2.2.2]octane ring also  $5.1/3.9=1.3$  times, whereas according to the through-bond model of the inductive effect those quantities should be approximately equal (in case of 3-substituted adamantane ring  $Z_{(3)}^* = (Z_C^*)^3 + 2(Z_C^*)^5 + 2(Z_C^*)^7$ ).

It is evident that alongside with the above-used direct comparison of the experimental quantities  $pK_a$  and  $\delta\Delta G^\ddagger$  for the different reaction series and/or solvents, the analysis of the substituent effects on the acidity of these alicyclic acids can be performed also in terms of special variants of the correlation equations<sup>11,13,14,27-29</sup> recently suggested for the quantitative evaluation of the structural effects on the chemical reactivity of the reagents.

To achieve this goal, in this work the statistical analysis of the data was also made in terms of Eqns. (3)<sup>20,28,29</sup> and (4)<sup>11,13</sup>:  $A = a_0 + a_1 \sigma_x^* + a_2 AR$ , (3)

---

+  $Z_{(4)}^* = 3(Z_C^*)^4$ ;  $Z_{(3)}^* = (Z_C^*)^3 + 2(Z_C^*)^5$ ;  $Z_{(2)}^* = (Z_C^*)^2 + 2(Z_C^*)^6$ , the subscripts in the parenthesis at  $Z_{(i)}^*$  refer to the 4, 3 or 2-position of the substituent in the bicyclo[2.2.2] octane-ring.

+<sup>+</sup>See also 3,5-9,11,20,30,31

where A in the present case is  $pK_a$  or  $\delta\Delta G^\circ$ ,  $\sigma_X^*$  - Taft's inductive constant,  $\Delta R = MR - MR(CH_3)$  - the measure of the polarizability of the substituent as expressed by its molecular refraction,  $a_0$ ,  $a_1$  and  $a_2$  - constants of the reaction series, and

$$A = a_0' + a_1'\sigma_F + a_2'\sigma_\alpha \quad (4),$$

where  $A = pK_a$  or  $\delta\Delta G$ ,  $\sigma_F$  and  $\sigma_\alpha$  are measures of substituent field and polarizability effects,  $a_0'$ ,  $a_1'$  and  $a_2'$  - are constants of the reaction series,

which are partial variants from more general relationships which include, in addition to the above-said, also some additional characteristics of the substituents.

As shows the preliminary statistical analysis the respective scales of substituent constants ( $\sigma_X^*$  and  $\sigma_F$ ,  $\sigma_\alpha$  and  $\Delta R$ ) in Eqns. (3) and (4) are connected with each other by rather approximate linear relationships. So, for 10 substituents (H, CN, COOMe, Br, Cl, F, MeO, CF<sub>3</sub>, NO<sub>2</sub>, Me):

$$\sigma_X^* = (5.43 \pm 0.37)\sigma_F + (0.38 \pm 0.16) \quad (5)$$

$$r = 0.982, s = 0.26, n = 10,$$

and for 22 substituents

$$\sigma_\alpha = (0.034 \pm 0.0046)\Delta R - (0.240 \pm 0.034) \quad (6)$$

$$r = 0.858, s = 0.13, n = 22.$$

As regards the scale of  $\sigma_F$  constants<sup>13</sup> when the latter are related to the  $\sigma_I$  constants by the equation:

$$\sigma_F = (0.943 \pm 0.049)\sigma_I + (0.006 \pm 0.002) \quad (7)$$

$$r = 0.970, s = 0.05, n = 25.$$

Therefore one can expect that both approaches in terms of Eqns (5) and (4) should lead, at least formally, to rather close results.

The results of the statistical treatment of data on the acidities of the above-mentioned alicyclic acids in the gas phase and solution according to Eqns (3) and (4) (see Tables 3 and 4) as a rule, do not contradict these expectations as well as the conclusions drawn from the analysis of experimental results in terms of Eqn. (2) (see Table 2).

One can see (Tables 3 and 4) that in case of both equations, for the gas phase and solution the contribution of the polarizational effect into the gross substituent effect

Table 3

The Results of Statistical Treatment of Data on Acidic Dissociation of Alicyclic Acids in Gas Phase (GP) and Solution in Terms of Eq. (3)<sup>a</sup>

Reaction Series, Solvent	$a_0$	$-a_1$	$-a_2$	R	s	n	
1	2	3	4	5	6	7	8
A. 3-Substituted Bicyclo[2.2.2]octane-1-COOH							
1. DMSO	13.2 (0.2)	0.339 (0.066)	-	0.948	0.16	5	
2. "	12.8 (0.0)	0.238 (0.002)	0.036 (0.001)	0.999	0.003	4	
3. 50 % (w) H <sub>2</sub> O-EtOH	6.96 (0.06)	0.223 (0.026)	-	0.973	0.07	6	
4. "	6.97 (0.10)	0.226 (0.041)	0	0.973	0.08	6	
5. 80 % (w) H <sub>2</sub> O-MCS	8.00 (0.06)	0.270 (0.025)	-	0.984	0.06	6	
6. "	8.02 (0.09)	0.278 (0.037)	0	0.984	0.07	6	
7. GP	1.70 (1.11)	2.06 (0.44)	-	0.955	1.1	4	

Table 3 continued

1	2	3	4	5	6	7	8
B. 4-Substituted bicyclo[2.2.2]octane-1-COOH							
1. DMSO		13.05 (0.14)	0.254 (0.068)	-	0.907	0.15	5
2. "		13.03 (0.12)	0.235 (0.076)	0	0.930	0.16	5
3. 50 % (w) H <sub>2</sub> O-EtOH		6.90 (0.02)	0.269 (0.01)	0	0.997	0.03	10
4. GP		0.36 (0.65)	2.24 (0.25)	0	0.954	0.95	10
5. H <sub>2</sub> O		5.15 (0.05)	0.175 (0.020)	0	0.987	0.05	4
6. MeOH <sup>4b</sup>		10.28 (0.06)	0.190 (0.027)	0	0.974	0.06	6
C. 4-Substituted bicyclo[2.2.2]oct-2-ene-1-COOH							
1. DMSO		12.56 (0.07)	0.361 (0.025)	-	0.995	0.06	4
2. "		12.34 (0.05)	0.289 (0.018)	0.044 (0.010)	0.999	0.02	4
3. 50 % (w) H <sub>2</sub> O-EtOH		6.50 (0.03)	0.276 (0.011)	-	0.998	0.04	7
4. "		6.50 (0.01)	0.278 (0.006)	-0.005 (0.002)	0.999	0.02	5

Table 3 continued

1	2	3	4	5	6	7	8
5. GP		1.55 (0.68)	2.74 (0.27)	-	0.986	0.63	5
6. "		1.60 (0.59)	2.81 (0.24)	0.068 (0.048)	0.993	0.54	5
D. 4-Substituted Cubane- -1-COOH							
1. DMSO		12.40	0.348	-	-	-	2
2. 50 % (w) H <sub>2</sub> O-EtOH		5.99 (0.04)	0.235 (0.017)	0.013 (0.003)	0.996	0.04	5
3. GP		1.1 (0.6)	2.52 (0.27)	-	0.994	0.5	3

a - Experimental data are, as a rule, taken from Table 1 (see also footnotes a and b to Table 2). Under the regression coefficients  $a_0$ ,  $a_1$  and  $a_2$  are given their reliability intervals. The dash in column 5 means that with the contribution of the  $a_2 \Delta R$  was neglected from the very beginning, the zero means that the contribution of this term is statistically negligible. In order to convert into the same scale the coefficients  $a_1$  and  $a_2$  for the solution and gas phase the quantities for the latter medium should be divided by the factor  $2,3RT=1.7$ . R - correlation coefficient, s - standard deviation (in  $pK_a$  units for solution, in kcal/mol units for the gas phase), n - the number of points.

Tabel 4

The Results of Statistical Treatment of Data on Acidities of Substituted Alicyclic Acids in the Gas Phase (GP) and in Solution in Terms of Eqn(4)<sup>a</sup>

Reaction Series, Solvent		$a'_0$	$-a'_1$	$-a'_2$	R	s	n
1	2	3	4	5	6	7	8
A. 3-Substituted Bicyclo[2.2.2] octane-1-COOH							
1.	DMSO	13.00 (0.16)	1.68 (0.37)	0	0.933	0.18	5
2.	50 % (w) H <sub>2</sub> O-EtOH	6.91 (0.04)	1.25 (0.08)	-	0.993	0.04	5
3.	"	6.91 (0.05)	1.42 (0.21)	0.234 (0.222)	0.992	0.05	6
4.	80 % (w) H <sub>2</sub> O-MCS	7.89 (0.07)	1.35 (0.17)	-	0.972	0.08	6
5.	"	7.84 (0.08)	0.863 (0.365)	-0.621 (0.359)	0.983	0.08	5
6.	GP	0.76 (1.13)	(10.2) (2.7)	0	0.938	1.2	4
B. 4-Substituted Bicyclo[2.2.2] octane-1-COOH							
1.	DMSO	12.83 (0.06)	1.22 (0.20)	-	0.978	0.08	4
2.	50 % (w) H <sub>2</sub> O-EtOH	6.84 (0.02)	1.43 (0.04)	-	0.997	0.04	13

Table 4 continued

1	2	3	4	5	6	7	8
3.	50 % (w) H <sub>2</sub> O-EtOH	6.90 (0.05)	1.55 (0.11)	-0.141 (0.134)	0.988	0.07	9
4.	GP	-0.2 (0.3)	13.10 (0.73)	-	0.988	0.5	10
5.	"	-0.05 (0.30)	12.86 (0.67)	1.49 (0.73)	0.993	0.4	9
C. 4-Substituted Bicyclo[2.2.2] oct-2-ene-1-COOH							
1.	DMSO	12.36 (0.08)	1.80 (0.19)	-	0.989	0.09	4
2.	"	12.39 (0.05)	1.74 (0.38)	0	0.998	0.06	4
3.	50 % (w) H <sub>2</sub> O-EtOH	6.49 (0.02)	1.59 (0.04)	-	0.998	0.04	9
4.	"	6.55 (0.03)	1.61 (0.07)	-0.254 (0.102)	0.998	0.04	6
5.	GP	-0.16 (0.74)	13.68 (1.77)	-	0.976	0.8	5
6.	"	0.02 (0.06)	14.52 (0.20)	-0.697 (0.230)	0.999	0.1	5
D. 4-Substituted Cubane-1-COOH							
1.	DMSO	12.20	1.78	-	-	-	2
2.	50 % (w) H <sub>2</sub> O-EtOH	5.91 (0.04)	1.37 (0.12)	-	0.983	0.08	7

Table 4 continued

1	2	3	4	5	6	7	8
3. GP		-0.4 (0.9)	12.80 (3.2)	-	0.951	1.0	3

a - see Footnote to Table 3

is either statistically negligible or very close to that (see also Refs. 11,13,20).

In several cases the statistical verification of two - parameter constraints of Eqns. (3) and (4) was impossible due to the insufficient set of experimental data.

As expected, the numerical values of regression coefficients of  $a_1$  and  $a_1'$  from Tables 3 and 4 also do not contradict the above-drawn conclusion that the transmission of the substituent effects for the 4-substituted bicyclo[2.2.2]octane cycle exceeds that in case of 3-substituted cycle. The earlier made inference about the closeness of the attenuation factors of the 4-substituted bicyclo[2.2.2]octane-, 4-substituted bicyclo[2.2.2]oct-2-ene- and 4-substituted cubane cycles as well as the previous conclusions on the basis of the data from Table 2 about the regulations of the solvent effects in the case of these reaction series have also found additional support.

In conclusion it is necessary to recall that some of the above-mentioned results and conclusions, especially those drawn on the basis of not very representative data sets for aqueous-organic mixtures (with the exception of 50 % (w) of aqueous ethanol) and anhydrous solvents should be considered with some caution. Evidently, new, additional data for the gas phase and solvents is badly needed. Also, the further verification of some of the existing experimental data (e.g. concerning acidic dissociation of 4-substituted bicyclo [2.2.2]octane-1-COOH in MeOH, aqueous DMSO, etc. is an urgent task.

Several aspects of the problem tackled in the present work have been dealt with in some other publications<sup>9,11,13,14,20,27-29,33,34</sup>.

## References

1. Tables of Rate and Equilibrium Constants of Heterolytic Organic Reactions, V.A.Palm (Ed), Vol. I (1), Suppl.Vol. I(1-2), VINITI- Tartu State University Publ. House, Moscow - Tartu, 1975, 1984.
2. J.D. Roberts and W.T.Moreland, J. Am. Chem. Soc., 75, 2167 (1953).
3. H.D.Holtz and L.M.Stock, *ibid.*, 86, 5188 (1964).
4. a. C.D.Ritchie and E.S.Lewis, *ibid.*, 84, 591 (1962).  
b. C.D.Ritchie and G.H.Megerle, *ibid.*, 89, 1447, 1452 (1967).
5. a. C.F.Wilcox and J.S.McIntyre, J.Org. Chem., 30, 777 (1965).  
b. C.F. Wilcox and C.Leung, J. Am. Chem. Soc., 90, 336 (1968).
6. F.W.Baker, R.C.Parish, and L.M.Stock, J. Am. Chem. Soc., 89, 5677 (1967).
7. Z.Friedl, J.Hapala and O.Exner, Coll.Czech.Chem.Comm., 44, 2928 (1979).
8. T.W.Cole, C.J.Mayers and L.M.Stock, J. Am. Chem. Soc., 96, 4555 (1974).
9. K.Kalfus, Z.Friedl and O.Exner, Coll. Czech. Chem. Comm. 49, 179 (1984).
10. I.A.Koppel, M.Mishima, L.M.Stock, R.D.Topsom and R.W. Taft, University of California, Irvine, 1982.
11. R.W.Taft and R.D.Topsom, Progr. Phys. Org. Chem., 16, 1 (1987).
12. J.W.Bartmess, The 1987 Gas Phase Acidity Scale, Dept. of Chemistry, Univ. of Tennessee, Knoxville TN 37996-1600.
13. R.W.Taft, J.L.M.Abboud, F.Anvia, M.Berthelot, M.Puzio, J.-F.Gal, A.D.Headley, W.G.Henderson, I.A.Koppel, J.H. Qian, M.Mishima, M.Taagepera and S.Ueji, J. Am. Chem.Soc. 109, 1797 (1988).
14. a) I.A.Koppel, D.Sc. Dissertation, Moscow 1986.  
b) I.A.Koppel, J.B.Koppel, and V.O.Pihl, Organic Reactivity, 25, 77 (1988).
15. H.Stetter and J.Mayer, Chem. Ber., 95, 667 (1962).

16. M.M.Krayuschkin, V.V.Sevastyanova and G.I.Danilenko, *Izv. AN SSSR, Khimiya*, 1969, 2884.
17. M.L.Bagal and V.I.Lantvoyev, *Zh.Or.Kh.*, 9, 291 (1973).
18. V.I.Lantvoyev, *ibid.*, 12, 2516 (1975).
19. V.I.Lantvoyev, *ibid.*, 13, 81 (1977).
20. I.A.Koppel, L.A.Moretskaya, V.I.Lantvoyev, J.B.Koppel, and V.O.Pihl, *Organic Reactivity*, 20, 508 (1983).
21. C.Jinfeng, R.D.Topsom, A.D.Headley, I.A.Koppel, M.Mishima and R.W.Taft, *J. Mol. Struct. (Theochem.)*, 168, 141 (1988).
22. A.O.Körgesaar, T.L.Tensing and M.B.Netschayeva, *Organic Reactivity*, 21, 473 (1984).
23. J.D.Roberts, W.T.Moreland and W.Frazer, *J. Am. Chem.Soc.* 75, 637 (1953).
24. W.R.Vaughan, R.Caple, J.Csapilla and P.Scheiner, *J. Am. Chem. Soc.*, 87, 2204 (1965).
25. C.A.Grob, M.Ohta, E.Renk and A.Weiss, *Helv. Chim. Acta*, 41, 1191 (1958).
26. F.W. Baker and L.M.Stock, *J.Org. Chem.*, 32, 3344 (1967).
27. I.A.Koppel, *Organic Reactivity*, 24, 263 (1987).
28. I.A.Koppel and M.M.Karelson, *ibid.*, 11, 985 (1975).
29. I.A.Koppel and U.H.Mölder, *ibid.*, 20, 2 (1983).
30. V.A.Palm, *Foundations of Quantitative Theory of Organic Reactions*, Leningrad, Khimiya, 1977.
31. O.Exner and P.Fiedler, *Coll. Czech. Chem. Comm.*, 45, 1251 (1980).
32. M.Charton, *Progr. Phys. Org. Chem.*, 13, 119 (1981).
33. I.A.Koppel, M.Mishima, L.M.Stock, R.D.Topsom and R.W. Taft, *J. Am. Chem. Soc.*, in press.
34. N.Inamoto, S.Masuda, and J.Niwa, *Bull. Chem. Soc. Japan*, 58, 158 (1985).

KINETICS OF HEXACHLOROCYCLOPHOSPHAZOTRIENE PHE-  
NOLYSIS UNDER CONDITIONS OF INTERPHASE TRANSFER

A.F. Popov, A.E. Shumeiko, A.A. Afonkin, and  
Zh.P. Piskunova

Institute of Physicoorganic Chemistry and Coal  
Chemistry, Academy of Sciences of the Ukrainian  
SSR, Donetsk

Received October 27, 1988

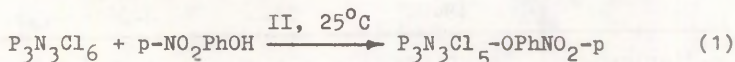
Kinetics of hexachlorocyclophosphazotriene reaction with p-nitrophenol under conditions of interphase transfer in system of 0.01 normal buffer (pH = 9.18) - organic solvent (hexane, chloroform, o-dichlorobenzene, symmetetrachloroethane) in presence of triethylbenzylammonium chloride has been studied. Levels of p-nitrophenolate ion transfer from water into organic phase at varied catalyst concentrations are determined. It is shown that reaction rate is affected by organic solvent polarity and its ability to extract the p-nitrophenolate ion. The scheme of the process is suggested.

Studies of the reactivity of cyclic phosphonitrilechlorides have proved to be one of the most significant tasks in the chemistry of phosphorus compounds, as they enable to solve a series of problems aimed at a purposeful synthesis of organophosphazenes. In this respect, the reactions of phenolysis are of special interest, since the yield products can be used as essential components in producing glues, modified additives for polymers and powder composites<sup>1</sup>. The number of papers on this field is rather limited and they are mainly of preparatory nature<sup>2</sup>. In the media of organic solvents

phenols react with hexachlorocyclophosphazotriene (I) extremely slowly, thus differing from the phenolates of alkali metals. At the same time, these salts have poor solubility in low-polarity organic media, but the use of solvents having high dielectric permittivity values (DMFA, DMSO) is complicated due to their rapid interaction reaction with (I)<sup>2</sup>. Therefore it would be more reasonable to carry out the phenolysis (I) in apolar media during continuous generation of anionic nucleophile. Such conditions can be realized when using interphase catalysis.

The present work is aimed at studying the kinetic regularities of the phenolysis of phosphonitrilechloride trimer under the conditions of interphase transfer in order to establish the scheme of the process and its topology.

To fulfil the task, we have studied kinetics of reaction (1) in a two-phase medium of water-organic solvent (1:1) in the presence of triethylbenzylammonium chloride (II) at  $[P_3N_3Cl_6] > [p-NO_2-PhOH]$ .



0.01 normal borate buffer, pH = 9.18, where p-nitrophenol ( $pK_a = 6.99$ ) is prevailingly in its ionic form, was used as the aqueous phase. Test experiments have demonstrated that without the interphase transfer catalyst (II), both the neutral form of p-nitrophenol and the aryate-ion cannot be extracted into the organic phase. Under similar conditions, the extraction of (I) into aqueous phase is negligible. Consequently, in the case of the absence of (II), no phenolysis (I) can actually take place. After the introduction of the interphase transfer catalyst into a two-phase system there appears p-nitrophenolate ion in the organic phase, but the solubility of (I) in the aqueous phase will not be increased. It has also been established that during kinetic measurements, the substrate is resistant to hydrolysis.

The kinetics of the present reaction was studied at the 4-10-time excess of (I) in the organic phase as compared to

Table 1

Rate Constants ( $k_{\text{obs}}^{\text{IP}}$ ) of p-Nitrophenol Interaction with (I) in Two-Phase System Borate Buffer-Organic Solvent, 25°C

Organic solvent	$[\text{II}]_0 \cdot 10^3$ mol $\cdot$ l $^{-1}$	$[\text{I}]_{\text{OP}} \cdot 10^3$ mol $\cdot$ l $^{-1}$	$k_{\text{obs}}^{\text{IP}} \cdot 10^4, \text{s}^{-1}$
1	2	4	5
hexane	6.40	99.5	$0.78 \pm 0.06$
	14.05	99.5	$1.63 \pm 0.11$
	19.5	99.5	$1.95 \pm 0.10$
	25.25	99.5	$2.39 \pm 0.06$
	25.25	31.9	$0.98 \pm 0.05$
	25.25	75.0	$1.70 \pm 0.15$
	25.25	159.0	$3.29 \pm 0.09$
	25.25	213.0	$4.08 \pm 0.04$
	49.00	99.5	$2.36 \pm 0.13$
o-dichloro- benzene	0.635	1.01	$3.65 \pm 0.36$
	1.265	1.01	$7.16 \pm 0.60$
	6.35	1.01	$13.40 \pm 0.30$
	6.35	0.76	$9.32 \pm 0.87$
	6.35	1.26	$14.90 \pm 0.40$
	6.35	1.65	$20.00 \pm 0.40$
	12.65	1.01	$13.40 \pm 1.30$
	19.00	1.01	$18.90 \pm 1.00$
25.30	1.01	$18.40 \pm 0.40$	
chloroform	0.323	2.25	$0.98 \pm 0.07$
	0.645	2.25	$1.48 \pm 0.10$
	1.27	2.25	$2.53 \pm 0.09$
	3.00	2.25	$6.50 \pm 0.50$
	4.90	2.25	$9.42 \pm 0.86$
	6.25	2.25	$9.30 \pm 0.71$
	12.75	2.25	$14.80 \pm 0.20$
	25.00	2.25	$21.90 \pm 1.80$

Table 1 continued

1	2	3	4
	37.50	2.25	29.00 $\pm$ 1.20
	50.00	2.25	29.50 $\pm$ 2.50
	89.50	2.25	33.00 $\pm$ 1.10
	189.50	2.25	36.20 $\pm$ 1.40
symm-tetrachloro- ethane	0.063	0.99	5.87 $\pm$ 0.31
	0.063	1.50	9.25 $\pm$ 0.63
	0.063	1.98	12.30 $\pm$ 1.00
	0.127	0.99	9.85 $\pm$ 0.76
	0.253	0.99	17.20 $\pm$ 1.53
	0.505	0.99	23.70 $\pm$ 1.98
	0.750	0.99	27.80 $\pm$ 2.03
	1.000	0.99	30.00 $\pm$ 2.75
	1.265	0.99	34.80 $\pm$ 2.78

Note. The concentration of (II) is considered for the total volume of two-phase system.

the p-nitrophenol concentration in the aqueous phase<sup>x</sup>, which made it possible in all cases to guarantee the holding of the pseudomonomolecularity conditions of the process. The pseudofirst order rate constants  $k_{obs}^{IP}$ , obtained when varying the concentrations of (I) and (II) are given in Table 1. They show that the reaction rate tends to grow if the concentrations of the substrate and the catalyst increase. At that, the  $k_{obs}^{IP}$  dependence on the concentration of (I) can be depicted as a straight line, proceeding from the origin. The dependence of  $k_{obs}^{IP}$  on the concentration of (II) happened to be of still more complicated character. The

<sup>x</sup> When studying the reaction in hexane, the ratio of these concentrations was 140-900.

$k_{obs}^{IP}$  values are in linear dependence on the catalyst concentration at a low concentration of (II) in the system only. When salt concentration starts growing, this dependence takes a curvilinear shape and tries to exceed its normal limits.

The analysis of the rate constants of the phenolysis of (I) permits us to suggest that the ability of the organic phase to extract p-nitrophenolate ion significantly affects the reaction rate. In order to estimate the value of the factor we determined the level of arylate ion transfer from the aqueous to the organic phase to be  $\alpha_{PhO} = [QPhO_{OP}] / [PhO_{AP}]^x$  in case of varying (II) concentration (see Table 2).

Table 2

p-Nitrophenolate-Ion Distribution in Two-Phase System Borate Buffer-Organic Solvent in Presence of (II)

Organic solvent	$[II]_0 \cdot 10^2$ mol $\cdot$ l $^{-1}$	$[PhO]_{AP} \cdot 10^3$ mol $\cdot$ l $^{-1}$	$[QPhO]_{OP} \cdot 10^4$ mol $\cdot$ l $^{-1}$	$\alpha_{PhO} \cdot 10^2$
1	2	3	4	5
hexane	2.70	2.15	0.20	0.93
	3.80	2.10	0.27	1.29
	6.05	2.11	0.20	0.95
	8.45	2.08	0.22	1.06
	9.95	2.05	0.20	0.98
o-dichloro- benzene	0.63	2.14	0.33	1.54
	1.25	2.14	0.35	1.64
	2.50	2.14	0.39	1.82
	4.23	2.51	0.40	1.59
	6.15	2.51	0.25	1.00
	12.30	2.50	0.25	1.00

<sup>x</sup> Q - triethylbenzylammonium cation; AP and OP denote the indices marking aqueous and organic phases, respectively.

Table 2 continued

1	2	3	4	5
chloroform	1.25	2.32	0.60	2.59
	2.50	2.25	0.94	4.18
	3.75	2.33	1.30	5.58
	5.00	2.22	1.18	5.32
	8.95	2.18	1.60	7.34
	18.95	2.18	1.65	7.57
symm-tetrachloro-ethane	0.05	2.08	1.19	5.72
	0.075	2.06	1.40	6.80
	0.10	2.05	1.54	7.51
	0.125	2.04	1.64	8.04
	1.17	1.72	4.19	24.36
	2.455	1.47	6.59	44.83
	4.70	1.28	8.23	64.30
	8.05	1.17	9.15	78.21
	8.25	1.13	9.48	83.89
	16.30	1.21	9.90	81.81

Note. The error of determining  $\alpha_{\text{PhO}^-}$  does not exceed 15%. In case  $[\text{QPhO}]_{\text{OP}} \leq 3 \cdot 10^{-5} \text{ mol} \cdot \text{l}^{-1}$  - ~ 50%.

We should also like to pay attention to the nonlinearity of the transfer level dependence on the catalyst concentration (Fig. 1). Probably, the tendency of the  $\alpha_{\text{PhO}^-}$  to exceed its limit values is connected with achieving the maximum competing solubility in the organic phase of chloride and p-nitrophenolate of triethylbenzylammonium. This tendency largely depends on the state of the both salts in the organic phase<sup>4</sup>.

The comparison of the data of Tables 1 and 2 confirms the supposition that in the organic phase the extraction of p-nitrophenolate ion substantially influences the phenolysis rate of (I) in a two-phase system. The increase of the se -

cond-order rate constant  $k_2^{IP^x}$  with the  $\alpha_{PhO^-}$ -increase in the case of any solvent studied also supports the aforesaid facts (Fig. 2). As to chloroform and symm-tetrachloroethane,

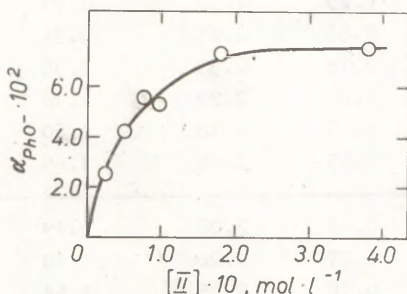


Fig. 1. Effect of (II) concentration on transfer level of p-nitrophenolate-ion ( $\alpha_{PhO^-}$ ) in two-phase system borate buffer-chloroform.

in case of which the rate constants of (I) phenolysis and of p-nitrophenolate-ion transfer level were measured in the same concentration range of (II), the dependence of  $k_2^{IP}$  on  $\alpha_{PhO^-}$  has a clearly linear character. Nevertheless, various slants of the lines in Fig. 2 mean that the ability of an organic solvent to extract salt (III) is not the only factor determining phenolysis rate under interphase conditions. The solvents used remarkably differ from each other in their polarities, whose changes seem to affect the effects observed in the organic phase. Thus, in series: hexane ( $\epsilon = 1.9$ ), chloroform ( $\epsilon = 4.7$ ), symm-tetrachloroethane ( $\epsilon = 8.2$ ), o-dichlorobenzene ( $\epsilon = 9.9$ ) at a fixed value  $\alpha_{PhO^-} \sim 1 \cdot 10^{-2}$ , the  $k_2^{IP}$  constants are increasing

<sup>x</sup> Rate constants  $k_2^{IP}$  ( $l \cdot mol^{-1} \cdot s^{-1}$ ) were calculated taking into account the concentration of (I).

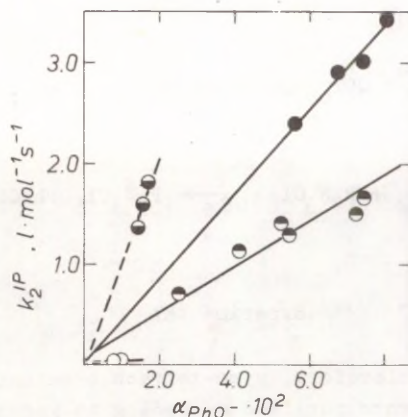


Fig. 2. Dependence of phenolysis rate of (I) on p-nitrophenolate-ion transfer level ( $\alpha_{\text{PhO}^-}$ ) in two-phase system borate buffer-organic solvent (○-hexane, ◐ - chloroform, ◑ - symm-tetrachloroethane, ● - o-dichlorobenzene).

with the increase of dielectric permittivity, equalling 0.0025, 0.25, 0.5, 1.0  $\text{l} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$ , respectively<sup>x</sup>. The fact that the rate of an interphase-catalyzed phenolysis reaction (I) is not affected by the extracting ability of an organic solvent only, but also by its polarity, evidences that the reaction proceeds either during the organic phase or in the boundary organic layer.

Thus, on the basis of the obtained and literary<sup>3</sup> data, we can suggest the following interphase and p-nitrophenol interaction scheme (I), including synchronous formation and transfer into the organic phase (Eq. (2)) of reagent (III) as well as self-phenolysis (I) with reaction products' for -

<sup>x</sup>  $k_2^{\text{IP}}$  values for chloroform, symm-tetrachloroethane, and o-dichlorobenzene have been extrapolated into the given  $\alpha_{\text{PhO}^-}$  value according to Fig. 2.



yielded such a concentration of p-nitrophenolate-ion which was rather suitable for conducting spectrophotometric measurements. The contribution of the side-reaction of p-nitrophenolate-ion with chloroform and symm-tetrachloroethane, not exceeding 7-10%, has been taken into consideration when calculating the rate constants of phenolysis (I). In the case of hexane, the phenolysis rate of (I) was measured by the reaction product accumulation in the organic phase registered at the wavelength of 320 nm. These rate constants found on the basis of the reaction product accumulation in the organic phase and of p-nitrophenolate-ion consumption in the aqueous phase coincide within the limits of experiment error.

The pseudofirst order rate constants ( $k_{\text{obs}}^{\text{IP}}, \text{s}^{-1}$ ) were calculated according to equation:

$$k_{\text{obs}}^{\text{IP}} = \frac{1}{t} \ln \frac{D_0 - D}{D_t - D},$$

where  $D_0$ ,  $D_t$ , and  $D$  denote the optical densities of aqueous solutions at the time origin, at certain time moment and at the termination of the reaction, respectively.

The kinetic conditions of carrying out the phenolysis reaction (I) (mole ratio phosphazene: p-nitrophenol 4:1, organic phase -chloroform) included the isolation of p-nitrophenoxy pentachlorocyclophosphazotriene, forming during the process. The yield was 90%, melting point 93-95°C (literature data<sup>2</sup> have given 95-97°C).

When measuring the transfer level values, the p-nitrophenolate-ion concentration in the organic phase was determined as a difference between its initial and equilibrium concentrations in the aqueous phase after a 30-min. stirring and a following 30-min. seasoning of the reaction mixture. If the  $\alpha_{\text{PhO}^-}$  values were measured in chloroform and symm-tetrachloroethane, the equilibrium values of the p-nitrophenolate-ion concentration would be extrapolated to zero time, in order to cancel out the contribution of the

reaction of this ion with solvents. The pH of the aqueous phase was determined on a pH-meter OP-211/1.

Mathematical processing of experimental results was conducted using the method of least squares.

#### References

1. L.V. Afanasev, A.N. Afanaseva, V.M. Bondarenko, and A.F. Nikolaev, Ruk. dep. VINITI, dep. No 1313/77, 1977, 29 pp.
2. G. Olyuk, Phosphorazo Compounds (in Russian), Moscow, Mir, 1976, 563 pp.
3. S.S. Yufit, The Mechanism of Interphase Catalysis, (in Russian), Moscow, Nauka, 1984, 264 pp.
4. S.S. Yufit, ZhVKhO, 31, No 2, 134-144 (1986).
5. A. Weissberger, E.S. Proscauer, J.A. Riddick, and E.E. Toops, Organic Solvents. (Russ. translation), Moscow, IL, 1958.
6. S.M. Zhivukhin, V.B. Tolstoguzov, and M.M. Levitsky, ZhNKh, 6, 2414 (1961).

MECHANISM OF INTERPHASE-CATALYZED PHE-  
NOLYSIS OF HEXACHLOROCYCLOPHOSPHAZO-  
TRIENE

A.E. Popov, A.E. Shumeiko, A.A. Afon -  
kin, and Zh.P. Piskunova

Institute of Physicoorganic Chemistry  
and Coal Chemistry, Academy of Sciences  
of the Ukrainian SSR, Donetsk

Received October 27, 1988

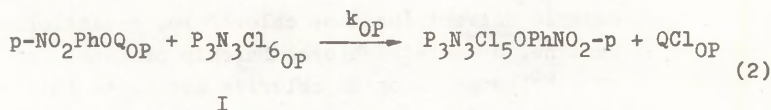
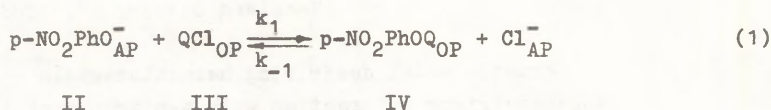
Kinetic model describing hexachlorocyclo -  
phosphazotriene interaction with p-nitrophenol in  
two-phase system of 0.01 normal borate buffer and  
organic solvent (hexane, chloroform, o-dichloro-  
benzene, symm-tetrachloroethane) in presence of  
triethylbenzylammonium chloride acting as inter-  
phase transfer catalyst is suggested. Correctness  
of the model has been proved by satisfactory cor-  
respondence between calculated constants of phe -  
nolysis rate and those measured independently in  
a definite organic phase.

It has been shown that the rate of the pro -  
cess studied is determined either by transport of  
the catalyst's active form into organic phase, or  
by reaction rate in organic solvent, depending on  
the ratio of catalyst's and substrate concentra-  
tions.

We have demonstrated<sup>1</sup> that the interaction of hexa -  
chlorocyclophosphazotriene (I) and p-nitrophenol (II) in  
the two-phase system borate buffer-organic solvent is in  
the presence of triethylbenzylammonium chloride (III) as

an interphase catalyst, determined first of all by the organic phase ability to extract the active form of the catalyst-p-nitrophenolate of triethylbenzylammonium (IV) and by the phenolysis (I) rate directly in the organic solvent. A significant polarity effect of the organic phase on the interphase-catalyzed phenolysis (I) rate was also traced. Nevertheless, we cannot still solve the problem of the contributions of any of the above-mentioned factors into the formation rate of aryloxy-substituted phosphonitrile chloride yet. In the present paper a kinetic model, taking into account not only the earlier obtained factors but also competing distribution between the phases of salts (III) and (IV) is suggested.

Phenolysis (I) proceeds according to scheme<sup>1</sup>:



Q - triethylbenzylammonium kation;  $k_{\text{OP}}$  - rate constant of phenolysis (I) in organic phase; constants  $k_1$  and  $k_{-1}$ , respectively, characterize forward and back transport (IV) between the phases and determine the ion exchange selectivity ( $K_{\text{PhO}^-/\text{Cl}^-}^{\text{sel}}$ ) according to (3).

$$K_{\text{PhO}^-/\text{Cl}^-}^{\text{sel}} = \frac{k_1}{k_{-1}} = \frac{\alpha_{\text{PhO}^-}}{\alpha_{\text{Cl}^-}} = \frac{[\text{p-NO}_2\text{PhOQ}_{\text{OP}}][\text{Cl}^-_{\text{AP}}]}{[\text{p-NO}_2\text{PhO}^-_{\text{AP}}][\text{QCl}_{\text{OP}}]}, \quad (3)$$

where  $\alpha_{\text{PhO}^-} = [\text{p-NO}_2\text{PhOQ}_{\text{OP}}] / [\text{p-NO}_2\text{PhO}^-_{\text{AP}}]$  and  $\alpha_{\text{Cl}^-} = [\text{QCl}_{\text{OP}}] / [\text{Cl}^-_{\text{AP}}]$  denote the levels of transfer of p-nitrophenolate and chloride ions from the aqueous (AP) to the organic phase.

In keeping with scheme (1), on the basis of the stationary principle for (IV) and material balance for phenolate ion, scheme (2) will change as follows for reaction rate:

$$-\frac{d[\text{p-NO}_2\text{PhO}_{\text{AP}}^-]}{dt} = \frac{k_{\text{OP}} K_{\text{PhO}^-/\text{Cl}^-}^{\text{sel}} [\text{P}_3\text{N}_3\text{Cl}_6] [\text{p-NO}_2\text{PhO}_{\text{AP}}^-] [\text{QCl}_{\text{OP}}]}{[\text{Cl}_{\text{AP}}^-] + \frac{k_{\text{OP}}}{k_{-1}} \cdot [\text{P}_3\text{N}_3\text{Cl}_6]} \quad (4)$$

After integration, if  $[\text{P}_3\text{N}_3\text{Cl}_6] \gg [\text{p-NO}_2\text{PhO}_{\text{AP}}^-]$  we can obtain the equation for rate constant  $k_{\text{H}}^{\text{IP}}$ :

$$k_{\text{obs}}^{\text{IP}} = \frac{k_{\text{OP}} K_{\text{PhO}^-/\text{Cl}^-}^{\text{sel}} [\text{QCl}_{\text{OP}}] [\text{P}_3\text{N}_3\text{Cl}_6]}{[\text{Cl}_{\text{AP}}^-] + \frac{k_{\text{OP}}}{k_{-1}} \cdot [\text{P}_3\text{N}_3\text{Cl}_6]} \quad (5)$$

Eq. (5) reflects the fact that the rate of the process can be established not only by means of phenolysis (I) in a separate organic phase ( $k_{\text{OP}}$ ) and by the organic solvents ability to selectively extract active catalyst form ( $K_{\text{PhO}^-/\text{Cl}^-}^{\text{sel}}$ ), but also via its transport from the organic to the aqueous phase ( $k_{-1}$ ). If we want to use Eq. (5) for describing the interphase-catalyzed phenolysis (I), we will have to know the  $K_{\text{PhO}^-/\text{Cl}^-}^{\text{sel}}$  values. The determination of the latter was based on the same conditions that the earlier obtained<sup>1</sup> p-nitrophenolate-ion transfer level values (both are given in Table 1).

Table 1

Ion Exchange Selectivity Constants ( $K_{\text{PhO}^-/\text{Cl}^-}^{\text{sel}}$ ) in Two-Phase System Borate Buffer-Organic Solvent (volume ratio of phases 1:1), 25°C

Organic solvent	$[\text{III}]_0 \cdot 10^2$ mol · l <sup>-1</sup>	$[\text{III}_{\text{AP}}] \cdot 10^2$ mol · l <sup>-1</sup>	$[\text{III}_{\text{OP}}] \cdot 10^3$ mol · l <sup>-1</sup>	$\alpha_{\text{PhO}^-} \cdot 10^2$	$K_{\text{PhO}^-/\text{Cl}^-}^{\text{sel}}$
Hexane	2.70	5.16	1.60	0.93	0.30
	3.80	7.42	1.60	1.29	0.59
	6.05	11.98	1.51	0.95	0.77

Table 1 continued

Organic solvent	$[\text{III}]_0 \cdot 10^2$ mol · l <sup>-1</sup>	$[\text{III}]_{\text{AP}} \cdot 10^2$ mol · l <sup>-1</sup>	$[\text{III}]_{\text{OP}} \cdot 10^3$ mol · l <sup>-1</sup>	$\alpha_{\text{PhO}^-} \cdot 10^2$	$k_{\text{PhO}^-}^{\text{sel}} / \text{Cl}^-$
	8.45	16.78	1.64	1.06	1.09
	9.95	19.70	1.82	0.98	1.05
<b>o-dichloro- benzene</b>	0.63	1.44	0.59	1.54	0.37
	1.25	2.49	0.75	1.64	0.54
	2.50	5.00	0.90	1.82	1.01
	4.23	8.34	1.09	1.59	1.22
	6.15	12.26	1.15	1.00	1.06
	12.30	24.50	1.50	1.00	1.64
<b>chloroform</b>	1.25	2.44	0.53	2.59	1.19
	2.50	5.05	1.01	4.18	2.10
	3.75	7.13	1.85	5.58	2.15
	5.00	9.99	2.18	5.32	2.48
	8.95	17.44	4.27	7.34	3.00
	18.95	37.60	9.00	7.57	3.20
<b>symm-tetra- chloroethane</b>	0.05	0.075	0.25	5.72	0.17
	0.075	0.121	0.29	6.80	0.28
	0.10	0.167	0.33	7.51	0.38
	0.125	0.214	0.36	8.04	0.48
	1.17	2.258	0.82	24.36	6.70
	2.455	4.786	1.24	44.83	17.30
	4.70	9.33	1.62	64.30	37.00
	8.05	15.96	1.90	78.21	65.66
	8.25	16.27	2.06	83.89	66.28
	16.30	32.60	2.47	81.82	110.00

<sup>x</sup> Initial concentration (III) is considered for the total volume of the two-phase system.

In reciprocal coordinates Eq. (5) can be written as follows:

$$\frac{k_{\text{PhO}^-/\text{Cl}^-}^{\text{sel}} \cdot [\text{QCl}_{\text{OP}}]}{k_{\text{obs}}^{\text{IP}}} = \frac{1}{k_{-1}} + \frac{[\text{Cl}_{\text{AP}}^-]}{k_{\text{OP}} [\text{P}_3\text{N}_3\text{Cl}_6]} \quad (6)$$

By means of this equation (its applicability is illustrated in Fig. 1) we established  $k_{\text{OP}}$  values for phenolysis (1) in the two-phase system<sup>x</sup> borate buffer-chloroform ( $21.4 \pm 1.0 \text{ l} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$ ) and symm-tetrachloroethane ( $42.6 \pm 4.1 \text{ l} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$ ).

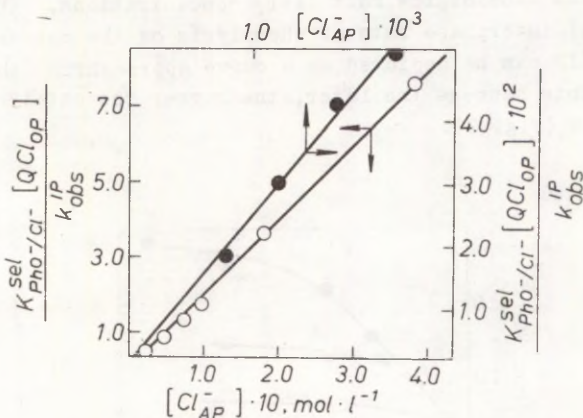


Fig. 1. Processing data of phenolysis reaction (acc. to Eq. (6)) (1) proceeding in two-phase system borate buffer-organic solvent (○ - chloroform,  $r = 0.9985$ ; ● - symm-tetrachloroethane,  $r = 0.9978$ ).

Eq. (5) becomes much simpler if  $[\text{Cl}_{\text{AP}}^-] \ll \frac{k_{\text{OP}}}{k_{-1}} [\text{P}_3\text{N}_3\text{Cl}_6]$ .

<sup>x</sup> We have chosen the systems containing chloroform and symm-tetrachloroethane as the organic phase, since, their  $k_{\text{PhO}^-/\text{Cl}^-}^{\text{sel}}$  values and the corresponding  $k_{\text{obs}}^{\text{IP}}$  were measured in a similar concentration range of the catalyst. Measuring errors do not permit us to reliably find the  $k_{-1}$  values according to Eq. (6).

This can be achieved both by reducing the catalyst content in the two-phase system and by increasing the substrate concentration. We get Eq. (7), which indicates that if the necessary condition is satisfied, the reaction rate will not depend on the substrate concentration but it will be determined by the transport of (IV) between phases:

$$k_{\text{obs}}^{\text{IP}} = k_{-1} \cdot \alpha_{\text{PhO}^-} \cdot [\text{Cl}_{\text{AP}}^-] \quad (7)$$

Really, in the case of low salt (III) concentrations, the dependence of interphase rate of phenolysis on the concentration of (I) can be depicted as a curve approaching the asymptote. This happens the later, the higher the catalyst concentration (Fig. 2).

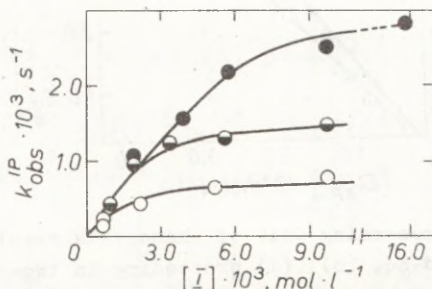


Fig. 2. Phenolysis (I) rate dependence in two-phase system borate buffer-chloroform ( $k_{\text{obs}}^{\text{IP}}$ ,  $\text{s}^{-1}$ ) on (I) concentration ( $\text{mol} \cdot \text{l}^{-1}$ ),  $25^\circ\text{C}$ :  
 ○ -  $[\text{Cl}_{\text{AP}}^-] = 3.65 \cdot 10^{-3} \text{ mol} \cdot \text{l}^{-1}$ ; ● -  $[\text{Cl}_{\text{AP}}^-] = 1.99 \cdot 10^{-2} \text{ mol} \cdot \text{l}^{-1}$ ; ● -  $[\text{Cl}_{\text{AP}}^-] = 2.92 \cdot 10^{-2} \text{ mol} \cdot \text{l}^{-1}$ )

The procession of the data given in Fig. 2 according to Eq. (5) at the fixed value  $k_{\text{OP}} = 21.4 \text{ l} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$ ,

yields the following results:

$[Cl_{AP}^-], \text{mol} \cdot \text{l}^{-1}$	$\alpha_{\text{PhO}^-}^{\text{calc}} \cdot 10^2$	$k_{-1}$	r
$3.65 \cdot 10^{-3}$	$0.85 \pm 0.11$	$71.5 \pm 9.6$	0.995
$1.99 \cdot 10^{-2}$	$2.72 \pm 1.02$	$6.66 \pm 2.03$	0.961
$2.92 \cdot 10^{-2}$	$2.79 \pm 0.34$	$5.91 \pm 0.69$	0.994

The values  $\alpha_{\text{PhO}^-}^{\text{calc}}$  quite well satisfy the earlier obtained<sup>1</sup> experimental dependences of p-nitrophenolate-ion transfer level values on the catalyst concentration. One should also pay attention to the fact that if the concentration of (III) increases, in the two-phase borate buffer-chloroform system the  $k_{-1}$  constant will accordingly decrease and strive for its constant value.

If  $[Cl_{AP}^-] \gg \frac{k_{OP}}{k_{-1}} \cdot [P_3N_3Cl_6]$ , Eq. (5) will take the following form:

$$k_{\text{Obs}}^{\text{IP}} = k_{OP} \alpha_{\text{PhO}^-} \cdot [P_3N_3Cl_6] \quad (8)$$

In this case the reaction studied can be controlled by the phenolysis rate (i) only in a separate organic phase and  $k_{\text{Obs}}^{\text{IP}}$  linearly depends on the substrate concentration<sup>1</sup>. Thus, in proportion to the increase of catalyst concentration, the interphase phenolysis reaction of (I) is less and less limited by the relationship between the forward and back transport of ions, more and more depending on the reaction rate in the organic phase. As to the systems borate buffer-hexane, o-dichlorobenzene, chloroform, the limit values of arylate ion reached  $\alpha_{\text{PhO}^-} = (1.1 \pm 0.2) \cdot 10^{-2}$ ,  $(1.36 \pm 0.3) \cdot 10^{-2}$ ,  $(7.5 \pm 1.2) \cdot 10^{-2}$ , respectively, enabling us to calculate the  $k_{OP}$  values according to Eq. (8). The values are given in Table 2 together with those calculated according to Eq. (6). Table 2 also contains  $k_{OP}$ , found from the kinetic phenolysis (I) data in a separate organic phase. They were obtained as follows. Under the conditions of interphase transfer chloroform, symm-tetrachloroethane

Table 2

Rate Constants  $k_{OP}$  ( $l \cdot mol^{-1} \cdot s^{-1}$ ) of Phenolysis Reaction (I),  $25^{\circ}C$

$k_{OP}$	Calculated		Experimental
	acc. to Eq. (6)	acc. to Eq. (8)	
Solvent			
hexane		$0.21 \pm 0.11$	$0.30 \pm 0.03$
chloroform	$21.4 \pm 1.0$	$21.9 \pm 3.3$	$15.7 \pm 0.6$
symm-tetra- chloroethane	$42.6 \pm 4.1$		$40.0 \pm 4.2$
o-dichloro- benzene		$141 \pm 71$	$166 \pm 15$

and o-dichlorobenzene were saturated with reagent (IV), phenolysis kinetics was studied at a varied concentration (I). As in the case of the system borate buffer-hexane in the organic phase, it was not possible to reach such a correlation of (IV) which would be suitable for spectrophotometric measurements, the reaction rate was changed in mixtures with chloroform<sup>x</sup> containing p-nitrophenolate ion, while rate constants  $k_{OP}$  were extrapolated to pure hexane according to the Kirkwood equation (9):

$$\log k_{OP} = (-2.84 \pm 0.30) + (11.66 \pm 1.09) \frac{\epsilon - 1}{2\epsilon + 1} \quad (9)$$

$n = 7 \quad r = 0.976$

The comparison of  $k_{OP}$  calculated according to Eqs. (6), (9) and those found experimentally confirms the correctness of the chosen model of interphase-catalyzed phenolysis reac -

x The hexane-chloroform mixture having known dielectric permittivity values was used<sup>2</sup>. The effect of water on  $\epsilon$  was neglected by virtue of its very low content in mixtures.

tion (1). Thus, Eq. (5) satisfactorily describes the studied reaction if two experimentally determinable parameters - the rate constant in a separate organic phase and the selectivity constant of ionic exchange, which both vary in a rather wide range ( $k_{OP} = 0.3 \div 166 \text{ l} \cdot \text{mol}^{-1} \cdot \text{s}^{-1}$ ,  $K_{\text{PhO}^-/\text{Cl}^-}^{\text{sel}} = 0.17 \div 3.20$ ) are used.

### Experimental

The synthesis and purification of the initial reagents and solvents was conducted as described in<sup>1</sup>.

When measuring the selectivity constants of ionic exchange, the chloride-ion concentration in aqueous and organic phases was determined by potentiometric argentometric titration.

The phenolysis (I) rate was measured during the interphase transfer, using methods<sup>1</sup>.

The phenolysis (I) rate in separate organic phase (chloroform, symm-tetrachloroethane, o-dichlorobenzene) was found as described below. Equal amounts of organic solvent and borate buffer, containing triethylbenzylammonium chloride and p-nitrophenol were mixed. After establishing equal distribution of ions, the necessary volume of the organic phase was chosen, this was put into a thermostated shell, where a certain amount of substrate (solution) was added within a corresponding solvent. The phenolysis (I) rate was monitored according to the p-nitrophenolate-ion ( $\lambda = 410 \text{ nm}$ ) absorption loss. The contribution of the side reaction of p-nitrophenolate ion with chloroform and symm-tetrachloroethane which does not exceed 7-10% has been taken into consideration when calculating the constant of phenolysis (I) rate.

### References

1. A.F. Popov, A.E. Shumeiko, A.A. Afonkin, and Zh.P. Piskunova, *Organic Reactivity*, this issue, p. 313.
2. A.Yu. Akhadov, *Dielectric Properties of Binary Solvents* (in Russian), Moscow, Nauka, 1977.

RETRIEVAL SYSTEM OF "CIS-TARTU" DATA BANK

J.K. Kiho and A.N. Jalas

Tartu University, Departments of Programm-  
ing and Organic Chemistry, 202400 Tartu,  
Estonian SSR

Received November 29, 1988

The data bank "CIS-Tartu" contains about 250.000 rate and equilibrium constants of heterolytic reactions. The contents of the bank are accessible by means of the universal retrieval system, ensuring selection of necessary information from the bank according to retrieval order. Reaction retrieval according to the given scheme as well as on the basis of its definite medium can be carried out.

Programs have been written in FORTRAN-77.

The data bank "CIS-Tartu"<sup>1</sup> was created and is being supplemented at the department of organic chemistry of Tartu University. The bank fully reflects the data of the tables of rate and equilibrium constant of heterolytic reactions<sup>2</sup>, containing  $\approx$  250.000 constants. Since collecting of the constants continues, the input of new constants and data about reactions is going on simultaneously.

The creation of the "CIS-TARTU" bank as such was not our only aim. The data of the bank will be used in theoretical studies, particularly, for prognostication of unknown reaction characteristics. Therefore, a retrieval system enabling us to use the bank data most effectively, including search for particular constants as the easiest problem, was created in parallel. Certainly, the simple inquiry-reply

form is insufficient for solving more complicated problems. The task of the retrieval system stands first of all in guaranteeing the selection of sufficiently accurate and exhaustive information for its further use as the initial data for superior systems.

The data of "CIS-TARTU" have been divided into several themes being stored in the sequence of the so called CIS-files on 6 tape volumes. Each topic has got a catalog indicating which subdivision of the topic a CIS-file belongs to.

The data bank bulk and structure indicate that there would inevitably be a preliminary step of data retrieval. A retrieval inquiry should first of all contain either the theme name or that of its subdivision within which the retrieval will take place. Using the catalog the DCISNIM program compiles the list DOO-FILELIST of the CIS-files involved. With the aid of system means, the DOO program loads these CIS-files from the magnetic tape. In the course of the preliminary step, the bank retrieval subarea will be recorded onto the disk.

The retrieval system is divided into two autonomous parts. Their operation sequence is determined by the user. As a rule, retrieval action is followed by the data selection from among the initial data set, satisfying inquiry conditions. To the obtained selection is given a standard form and its structure is similar with that of the initial one. Thus, after task specification, the retrieval system can be reused with the results of the previous step. The selection of the initial data set should precede the primary use of the both parts of the retrieval system. In the case of their either repeated or successive use as initial data, they will be given the results of the previous step.

The DOTSA program system is applied to find reactions according to the given scheme.

In reply to system prompt OUTPUT: the resultant file name should be given. There are three versions for the file name initial letter:

### 1. P (PRINT)

In this case, the process results in printing out a table containing complete information on the reaction found.

### 2. F (FILE)

The reaction is recorded in its initial form in the file analogous with the CIS-file. The former file is meant for a further retrieval.

### 3. R (RESULTS)

The data about the reaction for a further treatment by superior programs.

All 3 file types or their arbitrary pairs may be asked to be compiled simultaneously.

After the prompt SKELETT: the LINCS-code<sup>3</sup> of the scheme<sup>4</sup> of the reactions considered should be given. After input this code is transformed into a graph, where undetermined groups have been qualified as variables.

The SOURCE: prompt the system is given either the name of the file next in the DOO-FILELIST or that of F-file, resulting from the DOTSA or DPOISK systems during the previous step.

During retrieval, the graph obtained after the LINCS code system transformation is compared with each graph of the SOURCE-file. If they do not coincide, messages MISMATCH will be displayed and another graph will be taken. If the graphs coincide, message MATCH will be displayed, the groups having previously remained undetermined in the inquiry, will be defined and their numbers in the substituents list will be established. In case the substituent does not stand in the list, it will be given a negative number and the substituent will be included into the WILD-SUBSTIT list. After the termination of the system operation the list can be printed out for a visual study. Such a situation occurs if the selectivity level is low enough, i.e. if the substitution groups in the scheme have been determined loosely.

After the given F-file records or those of the last

CIS-file of the DOO-FILELIST are exhausted, the DOTSA system will wait for an answer to prompt MORE? (Y/N). The first version suggests that the functioning of the system should continue from the prompt SOURCE: and with presenting either another DOO-FILELIST or F-file. In the case of the latter version, the system stops.

It is often beneficial to specify retrieval on the basis of some additional information, i.e. to find the reactions which proceed under given conditions. The task can be performed by means of the DPOISK program system.

To the OUTPUT: prompt of this system, the reply versions coincide with those of the DOTSA. The exits of both systems are identical in their forms, thus enabling the user choose their operation order.

The DPOISK system is applied also to analyze the references to the literature used. If the first reply version is given to prompt REFERENCES? (Y/N), reference processing will start; in the case of negative answer, no respective processing will take place. In the first version autonomous references concerning each topic will be replaced by their numbers in the stored full list of literature. The user can get the listing of the references, related to the reactions chosen. If the reply to the prompt of LITERATURE? (Y/N) system is positive, the list will be compiled in the form of an output file PRINT. In this list, some titles can recur as well as references related to the reactions considered. This means is recommended to be made use of on the final stage of retrieval only, since the existing list of references is rather long. Scanning of the list takes some extra time, thus retarding the functioning of the system.

Retrieval conditions will be specified during the dialog between the user and the DPOISK system. Likewise in the DOTSA system, the package mode is possible, i.e. several different inquiries can be united in one step. If the reply to the TASK? (Y/N) prompt is positive, the system is ready for accepting another order. In case of a negative answer, the system will stop.

Prompt SOURCE: foresees passing to the next file in

the DOO-FILELIST or the name of F-file (see analogous inquiry in the DOTSA system). In reply to the REACTION TYPE prompt, the number M/N of the series undergoing retrieval, where M and N are integers, should be given.

Prompt CONDITIONS (T, LGK, ERR, PØ, SOLV) permits us to specify retrieval conditions; reply versions are given in parentheses. The necessary conditions should be presented in succession, one by one. The inquiry will be repeated until all the fixed conditions of the reaction searched during the operation of the program are satisfied, i.e. until prompt CONDITIONS gets the so called "empty" reply (by pressing the RETURN button).

We are going to discuss the behavior of the system in all cases of the reply to the prompt.

- 1) For reply T, the system suggests two successive extra prompts, in order to define the upper limits of temperature range: TEMP : T1 =  
TEMP : T2 =

The reply to the both inquiries should be some real number kk. nn. If it is necessary to establish the definite value, the T1-T2 interval will be chosen rather small: variable T1 will be given the definite value T, while T2 = T1 + 0.01, for instance.

- 2) Similarly to the aforesaid two extra prompts are suggested for reply LGK:

LGK : C1 =

LGK : C2 =

The reply should be of the analogous form as the one in the case of temperature.

- 3) As concerns reply ERR, the existence of the VT error parameters should first of all be found out by prompting SIGN VT =. If the error is not taken into account, the reply will be "- ", otherwise the "empty" reply is given. Then, analogously with T and LGK: ERR : V1 =  
ERR : V2 =

are suggested to fix the error interval.

- 4) In the case of PØ reply, similarly with ERR, the existence of the PT pressure parameters will be established.

The SIGN PT = can have a reply "-" if pressure is not taken into account, otherwise an "empty" reply is given. In the latter case, two extra prompts

PRESSURE : P1 =

PRESSURE : P2 =

can be suggested for the user in order to fix the pressure value interval. The units of pressure differing from atmosphere, are given in the Table in column 8. They can be obtained when analyzing the comments.

- 5) For reply SOLV, the system suggests inquiry SOLV : NR = to find the number of solvents in the reactions concerned. The reply should be an integer N; then N times will be prompted S(I) = in order to determine definite solvent numbers where  $I = 1..N$ . If  $N \geq 2$ , it is possible for the user to fix the solvent concentration used in the reaction. The existence of the concentration parameter will be established by prompting SIGN KT(I) = which can have one of the following replies:

- - concentration is not taken into consideration  
V - volume concentration is given (V%)  
W - weight concentration is given (W%)  
U - undetermined concentration (V%, W%)  
L - molar-weight concentration is given  
R - molar-volume concentration is given  
"empty" - normal concentration is given (M%)

In the first case, the system passes to the following prompts of CONDITIONS. In other cases, the user will be prompted N-1

times K(1, I) =

K(2, I) =

where  $I = 1..N-1$

in order to establish the interval of the concentrations to be found for any of N solvents.

When finding the intervals of the values, it is not possible to simultaneously study several such intervals. If it might, nevertheless be necessary, another inquiry package should be made repeating retrieval.

After exhausting all desirable conditions indispensable for reaction procedure, i.e. if the prompt CONDITIONS will be given an "empty" reply to, the user will be offered a possibility to analyze the information in columns 3 and 8 of the Table, (in the comments to the reaction). If the prompt COMM?(Y/N) gets a positive reply, the text of the comment will be suggested. First TEXT(3) =, then TEXT(8) =. In case the contents of one of the columns do not interest the user, an "empty" reply should be given. During retrieval, are selected the lines where the beginning of a definite comment part coincides with the suggested one.

After the whole set of retrieval conditions has been given, the DPOISK system will check whether they are satisfied in a given order for each reaction of the SOURCE-file. If the conditions are satisfied, the message MATCH will be displayed on the screen and the corresponding recordings into the P-, F- or R-file will be done. Otherwise the message MISMATCH is output. After that, the next reaction of the given CIS- or F-file will be proceeded to.

The DPOISK system stops after exhausting the whole task package.

The information exchange between the retrieval system and external storage is illustrated in the Scheme.

In Fig. 1, the auxiliary files can be considered as follows; for system DOTSA-files of direct codes, terminal labels and substituents (see<sup>1</sup>); for system DPOISK - list of references. Additional file for system DOTSA-file WILD-SUBSTIT, described above, for system DPOISK-file PRINT for the listing of the references. The contents of the P-, F-, R-files have been described above .

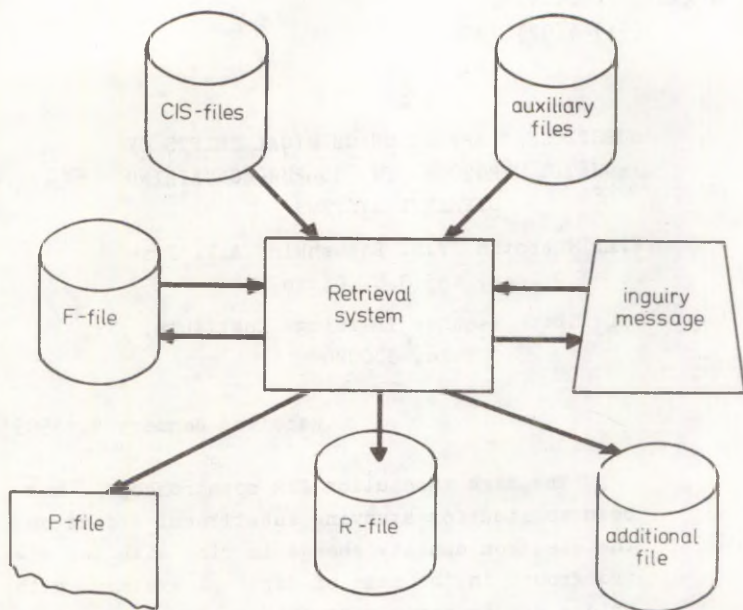


Fig. 1. Scheme of information flow in retrieval system.

#### References

1. A.N. Jalas, Information Presentation and Retrieval in Bank "CIS-TARTU", ZhOKh (in print) (in Russian).
2. Tables of Rate and Equilibrium Constants of Heterolytic Reactions (5 vols), Moscow, VINITI, 1975-1978.
3. J.K. Kiho, Input of Ographs into Computer (in Russian), Trudy VC Tart. un.-ta., No 35, 18-36 (1976).
4. J.K. Kiho, Program Means of Input, Processing, Retrieval and Designing of Molecular Graphs in "CIS-TARTU" System, (in Russian), ZhOKh (in print).

SUBSTITUENT EFFECT ON CHEMICAL SHIFTS OF  
AROMATIC PROTONS IN SULFUR-CONTAINING  
DIPHENYL SYSTEMS

V.A. Subbotin, V.N. Babushkin, A.V. Iva-  
nov, and S.S. Gitis

Tula State Teacher Training Institute,  
Tula, 300026

Received January 9, 1989

The high resolution PMR spectroscopy has been applied for studying substituent effect on the electron density change in ring with two nitro groups in the case of diphenyl systems with bridge groups containing sulfur at various oxidation levels. Correlation analysis enables us to show that in static molecular state this effect depends on interaction of substituent and free electron pairs of sulfur atoms. The following series of electronic bridge groups according to their electron conductivity:



has been obtained.

Earlier we have studied the substituent effect's nature in the alkaline hydrolysis in the 4'-substituent series of 2,4-dinitrophenyl-sulfides (I), -sulfoxides (II), and -sulfones (III) in dioxan-water medium. It was established that those processes obey general regularities of activated aromatic nucleophilic substitution<sup>1-3</sup>. A deviation from these general regularities was found when conducting the reaction of alkaline hydrolysis in water<sup>4</sup>. The deviation

was explained with the existence of solvation effects on the bridge group. The supposition was confirmed<sup>5</sup> by studying the substituent effect onto the frequencies of valence shifts of sulfur-containing bridge groups in systems (I-III) according to the IR spectrum data in the state without any solvation effects of the medium.

In order to continue this research, the effects of different substituents on the electronic conductivity of sulfur-containing bridge groups are studied in this paper, using high resolution PMR spectroscopy. The analysis of the PMR spectra of the compounds studied shows that in the case of the protons of benzene ring with two nitro groups the splitting of signals has the same nature as those of the three-spin AMX system which can be analyzed according to the regulations of the first order spectra<sup>6</sup>.

A typical spectrum for 2,4-dinitrodiphenyl sulfide with assignment of all signals is depicted in Fig. 1. The results of the effect were estimated on the basis of the chemical shift of the doublet signal of proton H<sub>6</sub>, which is situated nearest to the bridge bond and can be easily identified in the PMR spectrum. The position of the proton signal in the PMR spectrum is probably conditioned by the electron density around the atom, therefore, a change in chemical shift can be a qualitative characteristic distinguishing bridge group electronic conductivity. The results are presented in Table 1.

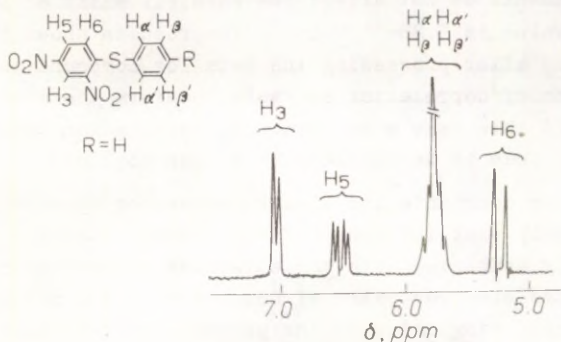


Fig. 1. PMR spectrum of 2,4-dinitrodiphenyl sulfide.

Table 1

Chemical Shifts ( $\delta$ , ppm) of  $H_6$  Proton of Benzene Ring in Dimethylacetamide

No	M		S	SO	SO <sub>2</sub>
	R				
1.	SCH <sub>3</sub>		5.30	-	-
2.	NH <sub>2</sub>		5.30	6.82	6.53
3.	OCH <sub>3</sub>		5.26	6.82	6.76
4.	CH <sub>3</sub>		5.28	6.84	6.80
5.	H		5.26	6.82	6.82
6.	Cl		5.36	6.82	6.86
7.	Br		5.38	6.82	6.85
8.	COCH <sub>3</sub>		5.40	6.86	6.87
9.	SO <sub>2</sub> CH <sub>3</sub>		5.46	6.86	6.90
10.	NO <sub>2</sub>		5.51	6.88	6.94

The analysis of these data shows that in general, introduction of electron-donor substituents leads to the  $H_6$  proton shift into the range of strong fields, and to the electron-acceptor substituents shift into the weak field region if compared with a molecule having no substituents.

As concerns compound series (I) the effects of donor substituents do not affect the chemical shift of proton  $H_6$  whose value is 5.28-5.30 ppm. The results shown in Fig. 2 obtained after processing the data for compound series (I) by means of correlation analysis, confirm the above statement. In this case a satisfactory correlation coefficient for  $\delta_{H_6}$  can be established only when combined with aromatic inductive constants for electron-acceptor substituents. A relatively weak influence of donor substituents is most probably connected with the existence of conjugation between lone electron pairs of donor groups and nitrogroups of the second ring owing to the presence of free electrons at the sulfur atom.

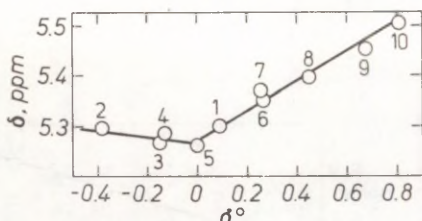


Fig. 2. Relationship  $\delta_{H_6} - \vartheta^\circ$  for series (I) ( $r = 0.984$ ,  $\rho = 0.280$ ,  $S = 0.017$ ,  $n = 7$ , numbers of compounds: 1,5-10). Compound numbers can be found in Table 1. Fig. 3 follows the same numeration.

At the same time, acceptor substituents start interacting with them. The electron density decrease near the bridge group is compensated for by withdrawal of electrons from a neighboring ring. The latter action makes the signal of the  $H_6$  proton shift to the weak field region and is reflected by correlation relation  $\delta_{H_6} - \vartheta^\circ$  (Fig. 2).

As to the compounds  $\delta_{H_6}$  of series (III), a gradual shift of the proton  $H_6$  signal into the weak fields' region takes place with the increase of electron-donor properties of the substituent (Table 1). Since in this case the sulfonic group does not contain any free electrons, the substituents interact directly with the electrons of the second ring. The latter action causes a change in the chemical shifts of the signals of all protons, and particularly in that of the  $H_6$  proton, being also reflected by the correlation analysis (Fig. 3). The data refer to a rather good proportional relationship between  $\delta_{H_6}$  and  $\vartheta^\circ$ . All substituents, including that of methylsulfonyl in 2,4-dinitro-4'-methylsul-

fonyldiphenylsulfone, having abnormally high rate of alkaline hydrolysis in both 40% dioxane<sup>2</sup> and in water<sup>4</sup>, excellently fall onto the straight line.

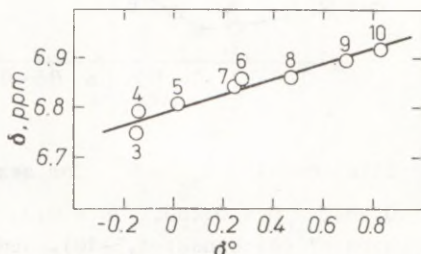


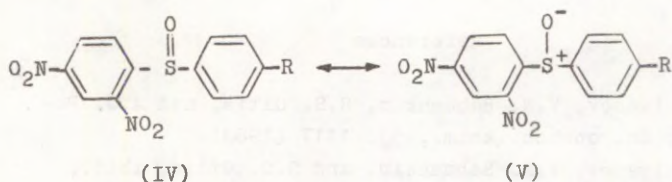
Fig. 3.  $\delta_{H_6}$  -  $\rho$  relationship for series (III) ( $r_6 = 0.970$ ,  $\rho = 0.150$ ,  $S = 0.0149$ ,  $n = 8$ , Compound numbers: 3-10).

Thus, in static molecular state, methyl-sulfonyl group has normal electronic effects, while both in water and dioxane-water media in reaction state<sup>2-4</sup> appear the specific solvation effects of the substrate's specific solvation caused by solvent molecules. A similar conclusion was drawn in the case of studying the frequencies of valence symmetric shifts of sulfonic group on the basis of the IR spectra of the compounds of series (III) in the static state<sup>5</sup>.

The same phenomenon was observed in the case of sulfides: in 2,4-dinitro-4'-methylmercaptodiphenylsulfide, the thiomethyl substituent of the molecule which does not react in the static state reveals the properties characteristic of hydrogen (Fig. 2.). In the case of alkaline hydrolysis<sup>1</sup>, an abnormally strong electron-donor effect has been traced.

Series (II) appeared to be not very sensitive to the

changes of substituent nature (Table 1). This seems to be caused by the fact that, owing to a good polarizability of the sulfur-oxygen bond, the sulfoxide group can be described by structure (V), where the lone electron pair of the sulfur atom is shifted strongly to the oxygen atom:



Depending on the substituent nature, the bridge group polarity either grows or drops, thus screening the substituent effect to the restructuring of the electron system in the activated benzene ring. Such approaches are in keeping with the data of<sup>7</sup>, according to which in sulfoxides, the sulfur-oxygen bond is strongly polarized.

Thus, the obtained data enable us to arrange according to electron conductivity the bridge groups containing sulfur at its various oxidation levels in the following succession:  $SO_2 > S > SO$ .

#### Experimental

4'-substituted 2,4-dinitrodiphenyl sulfides, synthesized by means of known methods from 2,4-dinitrochlorobenzene and from the corresponding thiophenolate (ref.<sup>1</sup> and those cited therein) were used. 2,4-dinitrophenylsulfoxide and -sulfone derivatives were obtained after oxidation either with hydrogen peroxide or with a double excess of chromic anhydride in the medium of the acidic acid of the corresponding sulfides. The purity level of the compounds was checked by means of thin-layer chromatography and by finding the melting point. The data were in keeping with those of literature.

The PMR spectra were recorded on a spectrometer "Tesla" BS-497, its operation frequency in dimethylacetamide at 25°C was 100 MHz. Weight concentration of substances was

5%. Hexamethyldisylfoxane was used as an inner standard . The accuracy of chemical shift was  $\pm 0.03$  ppm.

The accuracy of experimental data was estimated using the methods of mathematical statistics according to known formulae<sup>8</sup>.

#### References

1. A.V. Ivanov, V.N. Babushkin, S.S. Gitis, and A.G. Popova, *Zh. obshch. khim.*, 53, 1117 (1983).
2. A.V. Ivanov, V.N. Babushkin, and S.S. Gitis, *ibid.*, 55, 1570 (1985).
3. V.N. Babushkin, A.V. Ivanov, and S.S. Gitis, *ibid.*, 55, 2773 (1985).
4. A.V. Ivanov, S.S. Gitis, and V.N. Babushkin, in coll.: *Synthesis and Technology of Monomers*, Moscow, NIITEKHIM, 1988, pp. 124-132 (in Russian).
5. V.N. Babushkin, A.V. Ivanov, S.S. Gitis, V.F. Andrianov, and A.Ya. Kaminsky, *Zh. obshch. khim.*, 58, 1634 (1988).
6. B.I. Ionin, B.A. Ershov, and A.I. Koltsov, *NMR-spectroscopy in Organic Chemistry*, Leningrad, Khimiya, 1983, p. 85 (in Russian).
7. *General Organic Chemistry*, vol. 5. *Compounds of Phosphorus and Sulfur*, Moscow, Khimiya, 1983, 720 pp. (in Russian).
8. V.P. Spiridonov and A.A. Lopatkin, *Mathematical Processing of Physicoorganic Data*, Moscow: Moscow State University, 1970, 470 pp. (in Russian).

REACTIONS OF IMIDO ACID DERIVATIVES WITH  
NUCLEOPHILIC REAGENTS. ACTIVATION PARA-  
METERS OF  $S_N1$  and  $S_N2$  PROCESSES WITH  
N-SUBSTITUTED BENZIMIDOYL CHLORIDES

L.P. Drizhd, E.N. Kryuchkova, L.I. Bondarenko, and V.A. Savyolova

Institute of Physicoorganic Chemistry and  
Coal Chemistry, Academy of Sciences of  
the Ukrainian SSR, Donetsk

Received June 15, 1988

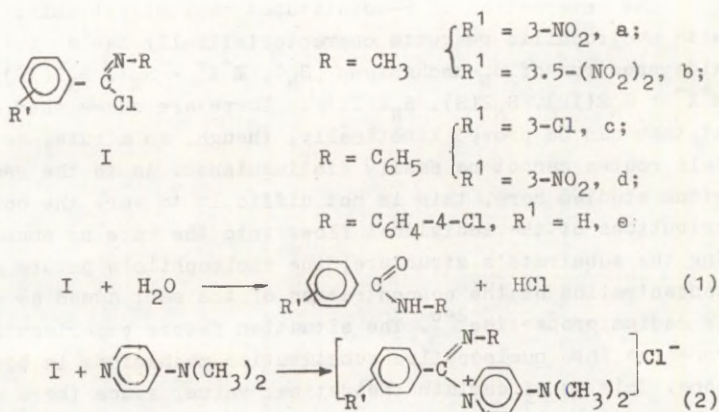
Aminolysis and hydrolysis of N-substituted benzimidoyl chlorides have been used to find the activation parameters of  $S_N1$  and  $S_N2$  processes. Thermodynamic evidence to prove the discreteness of nucleophilic substitution mechanism in border zone of their realization has been obtained.

The interaction of P-substituted benzimidoyl chlorides with nucleophilic reagents characteristically has a rather wide spectrum of  $S_N$ -mechanisms [ $S_N1$ ,  $M^+X^- \cdot S_N1$ ,  $S_N2(IP)$ ,  $M^+X^- \cdot S_N2(IP)$ ,  $S_N2(S)$ ,  $S_N2(TI)$ ]<sup>1</sup>. There are cases when any of them can be proved kinetically, though, as a rule, certain routes cannot be easily distinguished. As to the reactions studied here, this is not difficult to vary the contributions of the individual flows into the rate by changing the substrate's structure, the nucleophile's nature and concentration or the concentration of the salt added as well as medium properties<sup>2-6</sup>. The situation favors experimental research into nucleophilic substitution mechanisms in border zone. This is of certain theoretical value, since there are no common views<sup>7</sup> on the character of substitution mechanism in transition region (the mechanism might be either contin-

uous, having a steadily changing transition state structure, or discrete, i.e. being a total of individual routes with close free activation energy values).

In the present work, we have tried to concentrate our studies on certain routes in border zone by examining their activation parameters, on the examples of some reactions or series of reactions with the participation of related substrates, their mechanisms having been firmly proved kinetically. This would be easier in the case of  $S_N1$ ,  $M^+X^- \cdot S_N1$  and  $S_N2(S)$  processes. Literature data<sup>2,8N-10</sup> on the activation parameters for the substitution reactions imidoyl chlorides are extremely scarce, often obtained from a limited temperature range. Besides, this information was not discussed from the point of view of the border zone mechanisms.

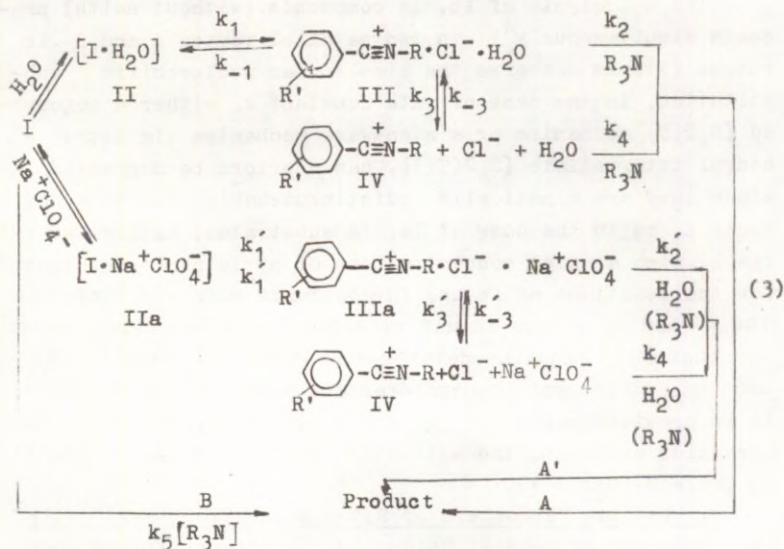
We have studied the temperature-dependence of the rates of hydrolysis and aminolysis of N-substituted benzimidoyl chlorides I with 4-N,N-dimethylaminopyridine ( $R_3N$ ) in different solvents. In the neutral hydrolysis of imidoyl chlorides I the N-substituted amides of carboxylic acids form on the basis of reaction (1). In acetonitrile, the reaction proceeds quantitatively and irreversibly according to scheme (2)<sup>11</sup>.



Kinetic measurements were carried out in pseudomonomolecular conditions at a large excess of the nucleophilic reagent in comparison with imidoyl chloride:  $[H_2O], [R_3N] > [I] \approx 5 \cdot 10^{-5} \text{ mol} \cdot \text{l}^{-1}$ . The reaction rate was monitored spectrophotometrically according to the accumulation of final products.

### Kinetics and Mechanisms of Studied Processes

The peculiarities of kinetics and the arguments showing the mechanism of aminolysis of imidoyl chlorides I in acetonitrile<sup>3-6</sup>, as well as those of their neutral hydrolysis in dioxan-water (1 : 1) mixture in the presence of sodium perchlorate<sup>12</sup> have been thoroughly studied in previous publications. Temperature variation does not affect the validity of those regularities. It has been shown in papers cited that the aminolysis of substrates I proceeds in acetonitrile according to various nucleophilic substitution mechanisms depending on the nature of the R and R' substituents:



Thus, for the interaction of the Ia, Ie compounds with pyridinic bases, we suggest a step-wise mechanism via nitrile-cationic intermediates III, IV (route A in scheme (3)). In the high concentration range of tertiary amine, the total process rate is limited by the ionization stage of imido-yl chloride ( $k_1$ ), which in accordance with<sup>6</sup> seems to proceed with electrophilic contribution of water found in the acetonitrile purified by ordinary methods. Analogous mechanism can also be suggested<sup>12</sup> for the hydrolysis reactions of Ic, Id substrates in water-dioxan (1:9) mixture, constant ionic strength of  $\text{NaClO}_4$  being 0.01 M, and for the Ie aminolysis in the presence of sodium perchlorate in acetonitrile (route A' in scheme (3)); and besides, sodium perchlorate<sup>6</sup> acts as the electrophilic catalyst in the step of imido-yl chloride ( $k_1$ ) ionization. The  $k_1$  values found from the interaction kinetics of Ia, Ie compounds with 4-N,N-dimethylaminopyridine in acetonitrile and from the hydrolysis kinetics of Ic and Id substrates in the presence of sodium perchlorate are given in Tables 1 and 2; the corresponding activation parameters are presented in Table 3 (Nos 5-9).

The aminolysis of Ib, Id compounds (without salts) proceeds simultaneously<sup>4,5</sup> in two parallel routes A and B in scheme (3). As concerns the bimolecular nucleophilic substitution, in the case of rate constant  $k_5$  either a concerted  $[\text{S}_\text{N}2(\text{S})]$  mechanism or a step-wise mechanism via tetrahedral intermediate  $[\text{S}_\text{N}2(\text{TI})]$ , can a priori be suggested, since they are kinetically indistinguishable. The rate of route A, as in the case of Ia, Ie substrates, is limited by the  $k_1$  step at high concentrations of pyridinic base. Thus, for the reactions of Ib and Id compounds with pyridinic bases the  $k_1$  and  $k_5$  values should simultaneously be calculated on the basis of kinetic data (see Scheme (3): their values at different temperatures are presented in Table 1. As in previous cases, the  $k_1$  and  $k_5$  values agree with the Arrhenius equation, the activation parameters can be found in Table 3 (Nos 1-4).

Activation Parameters of  $\text{S}_\text{N}1$  and  $\text{S}_\text{N}2$  Processes with Participation of Imido-yl Chlorides. As it was already shown

in the case of the nucleophilic substitution at the  $sp^3$ -carbon atom, activation parameters can serve for an identification criterion of the  $S_N1$  and  $S_N2$  mechanisms<sup>13</sup>. As to the analogous processes with the  $sp^2$ -unsaturated centers, any far-reaching conclusions of the matter cannot be found yet. The data set embracing both previously obtained<sup>2,8-10</sup> data and those of the present paper enable us to do this analysis, using the substitution reaction at the imidoilyc carbon atom as an example. The reactions proved to be unique, since they make it possible to determine the activation parameters of  $S_N1$  and  $S_N2$  mechanisms in the case of structurally close substrates; or even in the case of one and the same substrate, while with substitution, in the vicinity of the  $sp^3$ -carbon atom this is allowed only for the reagents having substantial structural differences or for those with varied process conditions.

Bimolecular processes ( $k_2$ ) should characteristically have much higher negative activation entropy values and much lower activation enthalpy values than ionization mechanism  $S_N1$  ( $k_1$ ). Thus, the aforesaid is valid in the case of the reactions studied (cf.  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  for Nos 1,3,5-9 and 2,4 in Table 3, more correctly - No 1 with No 2 and No 3 with No 4). This conclusion is qualitatively supported by the result given in Fig. 1, where the rate constants' logarithms of a majority of reactions from Tables 1-2 have been compared at two different temperatures (isokinetic correlation<sup>14</sup>).

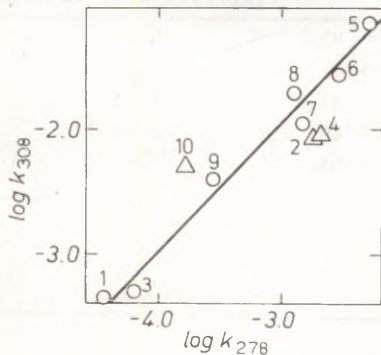


Fig. 1. Isokinetic relationship for the processes of nucleophilic substitution with participation of N-substituted benzimidoyl chlorides in different media. (Point numbers corresponds to those of Table 3).

Table 1

Pseudofirst Order Rate Constants  $k_H^I$ , ( $s^{-1}$ ) of N-Substituted Benzimidoyl Chlorides I Interaction with 4-N, N-Dimethylaminopyridine ( $R_3N$ ) in Acetonitrile, Ionization Constants  $k_1$ ,  $k_1'$  ( $s^{-1}$ ) Calculated from them, and Second Order Rate Constants  $k_5$  ( $l \cdot mol^{-1} \cdot s^{-1}$ )

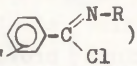
I (  )	Temperature, K	$[R_3N] \cdot 10^2$ , mol·l <sup>-1</sup>	$k_H^I \cdot 10^4$	
1	2	3	4	
Ia; R = CH <sub>3</sub> R' = 3-NO <sub>2</sub>	278	6.49	48.5	
		13.0	52.1	
		32.5	49.1	
		64.9	50.2	
	$k_1 = (5.0 \pm 0.1) \cdot 10^{-3}$			
	288	5.33	134	
		16.0	136	
		26.7	139	
		42.6	142	
		74.6	140	
$k_1 = (1.90 \pm 0.06) \cdot 10^{-2}$				
298		$k_1 = (3.4 \pm 0.3) \cdot 10^{-2}$ 5		
	308	6.34	731	
		31.7	721	
63.4		759		
$k_1 = (7.4 \pm 0.2) \cdot 10^{-2}$				
Ib; R = CH <sub>3</sub> R = 3,5-(NO <sub>2</sub> ) <sub>2</sub>	278	0.81	0.77	
		1.62	0.85	
		3.24	1.34	
		6.48	2.04	
		9.04	2.56	
		13.6	3.47	
		18.1	4.12	
$k_1 = (6.5 \pm 0.7) \cdot 10^{-5}$				
$k_5 = (2.00 \pm 0.08) \cdot 10^{-3}$				

Table 1 continued

1	2	3	4	
Ib; R = CH <sub>3</sub> R' = 3,5-(NO <sub>2</sub> ) <sub>2</sub>	288	0.84	1.75	
		2.10	2.12	
		4.20	2.61	
		8.40	3.75	
		13.9	5.90	
		16.8	6.80	
			$k_1 = (1.4 \pm 0.1) \cdot 10^{-4}$	
			$k_5 = (3.2 \pm 0.1) \cdot 10^{-3}$	
	298		$k_1 = (2.6 \pm 0.1) \cdot 10^{-4}$	5
			$k_5 = (5.5 \pm 0.1) \cdot 10^{-3}$	5
308	1.27	5.66		
	2.39	7.41		
	6.69	10.8		
	15.8	19.5		
	16.7	20.3		
		$k_1 = (4.8 \pm 0.2) \cdot 10^{-4}$		
		$k_5 = (9.2 \pm 0.2) \cdot 10^{-3}$		
Id; R = C <sub>6</sub> H <sub>5</sub> R' = 3-NO <sub>2</sub>	278	2.91	0.95	
		5.82	1.76	
		8.74	2.29	
		11.7	2.88	
			$k_1 = (3.6 \pm 0.8) \cdot 10^{-5}$	
		$k_5 = (2.2 \pm 0.1) \cdot 10^{-3}$		
	298		$k_1 = (2.34 \pm 0.06) \cdot 10^{-4}$	4
			$k_5 = (5.92 \pm 0.06) \cdot 10^{-3}$	4
	308	1.32	5.71	
		3.32	7.14	
6.63		10.1		
9.95		12.9		
13.3		15.9		
	$k_1 = (4.4 \pm 0.1) \cdot 10^{-3}$			
	$k_5 = (8.6 \pm 0.1) \cdot 10^{-3}$			

Table 1 continued

1	2	3	4
Id; R = C <sub>6</sub> H <sub>5</sub> R' = 3-NO <sub>2</sub>	323	1.31	13.6
		6.56	26.4
		9.84	29.3
		13.1	39.0
			$k_1 = (1.1 \pm 0.1) \cdot 10^{-3}$ $k_5 = (2.0 \pm 0.2) \cdot 10^{-3}$
Ie; R = C <sub>6</sub> H <sub>4</sub> -Cl-4 R' = H	277	3.29	13.3
		4.93	14.9
		6.58	14.6
			$k_1 = (1.43 \pm 0.05) \cdot 10^{-3}$
	288	1.64	28.7
		3.29	31.8
		4.93	31.2
		6.58	37.1
			$k_1 = (3.22 \pm 0.09) \cdot 10^{-3}$
	298		$k_1 = (5.18 \pm 0.09) \cdot 10^{-3}$ 6
306	1.64	124	
	4.93	115	
	6.58	114	
		$k_1 = (1.18 \pm 0.06) \cdot 10^{-2}$	
Ie; R = C <sub>6</sub> H <sub>4</sub> -Cl-4 R' = H [NaClO <sub>4</sub> ] = 1.68 · 10 <sup>-2</sup> mol · l <sup>-1</sup>	277	1.64	27.2
		3.29	28.7
		4.93	27.2
		6.58	29.1
			$k_1' = (2.81 \pm 0.09) \cdot 10^{-3}$
	288	1.64	76.8
		3.29	85.0
		4.93	85.2
		6.58	87.1
			$k_1' = (8.52 \pm 0.08) \cdot 10^{-3}$

Table 1 continued

1	2	3	4
Ie; R = C <sub>6</sub> H <sub>4</sub> -Cl-4 R' = H [NaClO <sub>4</sub> ] = 1.68 · 10 <sup>-2</sup> mol · l <sup>-1</sup>	298	1.64	148
		4.93	144
		6.58	154
			$k_1' = (1.50 \pm 0.06) \cdot 10^{-2}$
	306	1.64	281
		3.29	290
		4.93	291
		6.58	296
			$k_1' = (2.92 \pm 0.06) \cdot 10^{-2}$

Table 2

Hydrolysis Rate Constants  $k_1'$  (s<sup>-1</sup>) of N-Substituted Benzimidoyl Chlorides I (R'-C<sub>6</sub>H<sub>4</sub>-C(Cl)=NR) in Dioxan-Water (9:1) Mixture in Presence of [NaClO<sub>4</sub>] = 1.0 · 10<sup>-2</sup> mol · l<sup>-1</sup>

I	Temperature, K	$k_1' \cdot 10^3$
Id; R = C <sub>6</sub> H <sub>5</sub> R' = 3-NO <sub>2</sub>	278	0.27 ± 0.02
	288	0.68 ± 0.01
	298	1.73 ± 0.08
	308	3.98 ± 0.09
	323	12.3 ± 0.4
Ic; R = C <sub>6</sub> H <sub>5</sub> R' = 3-Cl	278	1.24 ± 0.05
	288	3.57 ± 0.04
	298	8.67 ± 0.07
	308	20.0 ± 0.1

Table 3

Activation Parameters of  $S_N$ -Reactions with Participation of N-Substituted Benzimidoyl Chlorides in Different Media

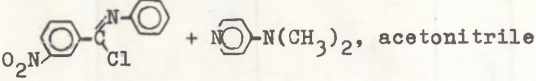
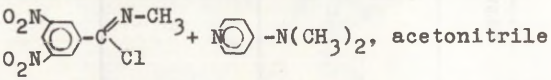
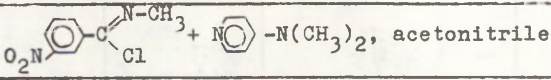
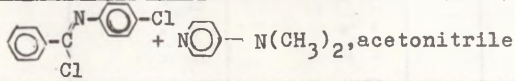
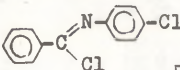
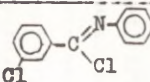
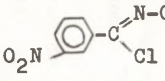
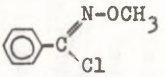
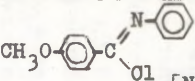
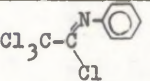
1	2	3	4	5	6
Reaction	Constant in Scheme (3)	$\Delta H^\ddagger$ , $\text{kJ}\cdot\text{mol}^{-1}$	$-\Delta S^\ddagger$ , $\text{J}\cdot\text{mol}^{-1}$ $\text{degree}^{-1}$	$\Delta G$ 298K $\text{kJ}\cdot\text{mol}^{-1}$	
1	 + $\text{N}(\text{C}_6\text{H}_5)\text{N}(\text{CH}_3)_2$ , acetonitrile	$k_1$	$54.8 \pm 0.4$	$131.3 \pm 0.4$	$94.5 \pm 0.9$
2	- " -	$k_5$	$33.9 \pm 0.4$	$173.9 \pm 0.5$	$86.1 \pm 0.9$
3	 + $\text{N}(\text{C}_6\text{H}_5)\text{N}(\text{CH}_3)_2$ , acetonitrile	$k_1$	$44.7 \pm 0.5$	$163.9 \pm 0.8$	$92.4 \pm 0.8$
4	- " -	$k_5$	$34.3 \pm 0.5$	$173.5 \pm 0.6$	$84.9 \pm 1.0$
5	 + $\text{N}(\text{C}_6\text{H}_5)\text{N}(\text{CH}_3)_2$ , acetonitrile	$k_1$	$60.2 \pm 0.4$	$70.2 \pm 0.8$	$81.1 \pm 0.7$
6	 + $\text{N}(\text{C}_6\text{H}_5)\text{N}(\text{CH}_3)_2$ , acetonitrile	$k_1$	$48.9 \pm 0.6$	$120.4 \pm 0.7$	$83.6 \pm 0.6$

Table 3 continued

1	2	3	4	5	6
7	 $+ \text{N}(\text{CH}_3)_2, \text{acetonitrile}$ $[\text{NaClO}_4] = 1.68 \cdot 10^{-2} \text{ mol} \cdot \text{l}^{-1}$	$k_1'$	$52.7 \pm 0.8$	$101.2 \pm 0.8$	$81.9 \pm 0.7$
8	 $+ \text{H}_2\text{O}, \text{dioxan-water (9:1)}$ $[\text{NaClO}_4] = 1.0 \cdot 10^{-2} \text{ mol} \cdot \text{l}^{-1}$	$k_1'$	$64.0 \pm 0.8$	$69.8 \pm 0.4$	$84.4 \pm 0.9$
9	 $+ \text{H}_2\text{O}, \text{dioxan-water (9:1)},$ $[\text{NaClO}_4] = 1.0 \cdot 10^{-2} \text{ mol} \cdot \text{l}^{-1}$	$k_1'$	$61.5 \pm 0.4$	$89.5 \pm 4.0$	$88.2 \pm 1.0$
10	 $+ \text{CH}_3\text{O}^-, \text{methanol-dimethyl-}$ $\text{sulphoxide (1:9)}$	$k_5$	74.2	41.8	86.7 <sup>10</sup>
11	 $+ \text{H}_2\text{O}, \text{dioxan-water (3:1)},$ $[\text{NaClO}_4] = 1 \cdot 10^{-1} \text{ mol} \cdot \text{l}^{-1}$	$k_1'$	129.6	-33.4	115.8 <sup>x 8</sup>
12	 $+ \text{H}_2\text{O}, \text{acetone-water (10.9% H}_2\text{O)}$	$k_1$	76.1	48.3	90.7 <sup>9</sup>

<sup>x</sup> Found at T = 393 K

The figure shows that the data of the ionization routes ( $k_1$  and  $k'_1$ ) concentrate near one and the same line:

$$\log k_{308} = (1.21 \pm 0.23) + (1.05 \pm 0.07) \log k_{298}$$

$$r = 0.989, \quad s = 0.141, \quad N = 7$$

Consequently, although there are remarkable structural differences among substrates and nucleophilic agents as well as in the reaction proceeding conditions (without salt additions or in the presence of sodium perchlorate), the isokinetic temperatures for these processes have rather close values. At the same time, as concerns reactions 2,4 and 11, their  $\log k_5$  deviate from the line. Such behavior is formally characteristic of some other isokinetic temperature value and is in keeping with essential differences between the  $S_N1(k_1, k'_1)$  and  $S_N2(k_5)$  mechanisms.

Coexistence of these mechanisms in the border zone can be explained with fairly close free activation energy values ( $\Delta G_{298}$ , cf. Nos. 1-2 and 3-4 in Table 3), although the enthalpy and entropy components of various routes differ a lot. We have already shown<sup>15</sup> that in case of the reactions having border zone mechanisms, adding salts containing not a common anion (sodium bromide or perchlorate) leads to a total "suppression" of the  $S_N2$  process owing to the acceleration of the substrate's ionization rate ( $k'_1$ ). Thus, the afore-said testifies the discreteness of the nucleophilic substitution mechanisms in the vicinity of imidoylic carbon atom in the so-called "transition" region and consequently also proves that this substrate class is inclined to react by step-wise mechanisms including unstable intermediates.

To our mind, special attention should be paid to the discussion of the  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  changes depending on the substrate's structure and those of process conducting conditions in the case of ionization mechanism.

Thus, the strengthening of the substituent's acceptor character in substrate, which must lead to the electronic destabilization of the nitrile-cationic intermediate and of

the transition state in the rate-determining step, makes activation energy drop and not increase, as might have been expected (cf. Nos 3 and 5, Nos 1 and 5 in Table 3). The fact could be adequately interpreted if we ascribed to a less stabilized transition state a considerably better solvation which is in agreement with the  $\Delta S^\ddagger$  change direction for the processes compared. The contribution of solvation effect seems to be so significant that the activation entropy in the case of the electronically destabilized transition states of the  $S_N1$  processes can have great negative values, approximating to the activation entropy of bimolecular ( $S_N2(S)$ ) routes of the same reaction.

Another interesting fact is that the electrophilic catalysis of ionization by sodium perchlorate<sup>6</sup> does not bring about any activation energy drop, which is not usually normal with catalytic processes. Moreover, during transition from a reaction without salt additions to the process with  $\text{NaClO}_4$  addition, the activation energy is even inclined to undergo a certain increase (cf.  $\Delta H^\ddagger$  for Nos 6-7 in Table 3). Here the acceleration is most probably connected with a more positive activation entropy for the  $M^+X^- \cdot S_N1$  process (No 7) in comparison with the  $\text{H}_2\text{O} \cdot S_N1$  process (No 6). The latter situation is connected with a better expressed solvation in the initial state compared with the transition one in the former case (substrate +  $\text{NaClO}_4$ ) than in the second version (initial state - substrate +  $\text{H}_2\text{O}$ ). Thus, we can state that the solvation effect of the solvent significantly contributes to the absolute value of the activation parameters of the imidoyl chlorides ionization. In some cases this contribution is evidently so substantial that this leads to the apparent inversion of the direction of either the effect of structural factors or that of the catalyst onto free energy components  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ .

The synthesis and purification of solvents, and reagents, and the methods of kinetic measurements have been described earlier<sup>4,5,12,15</sup>. The characteristics of the used compounds correspond to literature data.

The error of finding constants from a separate experi-

ment did not exceed 2%. Thermodynamic activation parameters were calculated according to known formulae, linear equations were treated by the least squares' method.

#### References

1. L.P. Drizhd and V.A. Savyolova, in: "Structure of Organic Compounds and Reaction Mechanisms", (in Russian), Kiev, "Naukova dumka", 1986, pp. 3-28.
2. R. Ta-Shma and Z. Rappoport, J. Am. Chem. Soc., 98, 8460 (1976).
3. L.P. Drizhd, L.M. Litvinenko, E.N. Kryuchkova, A.P. Prudchenko, and V.A. Savyolova, DAN SSR, 274, 1388 (1984).
4. L.M. Litvinenko, L.P. Drizhd, E.N. Kryuchkova, and V.A. Savyolova, Ukr. khim. zhurn., 51, 965 (1985).
5. E.N. Kryuchkova, L.P. Drizhd, and V.A. Savyolova, Ukr. khim. zhurn., 53, 79 (1987).
6. L.P. Drizhd, E.N. Kryuchkova, V.A. Savyolova, and A.G. Gershikov, Ukr. khim. zhurn., 54, 415 (1988).
7. J. March, Organic Chemistry (Russian translation), vol. 2, Moscow, "Mir", 1987, pp. 25-28.
8. J.E. Johnson and S.C. Cornell, J. Org. Chem., 45, 4144 (1980).
9. J. Ugi, F. Beck, and U. Fetzer, Chem. Ber., 1,126 (1962).
10. J.E. Johnson, E.H. Nalley, C. Weiding, and M. Arfan, J. Org. Chem., 46, 3623 (1981).
11. L.P. Drizhd, E.N. Kryuchkova, L.M. Litvinenko, V.A. Savyolova, and K.Yu. Chotij, Ukr. khim. zhurn., 50, 1194 (1984).
12. L.P. Drizhd, L.I. Bondarenko, M.D. Vdovichenko, and V.A. Savyolova, Organic Reactivity, 24, 179 (1987).
13. K. Ingold, "Theoretical Bases of Organic Chemistry" (in Russian), Moscow, "Mir", 1973.
14. V.A. Palm, "Foundations of Quantitative Theory of Organic Reactions" (in Russian), Leningrad, "Khimiya", 1977.
15. L.P. Drizhd, E.N. Kryuchkova, and V.A. Savyolova, Ukr. khim. zhurn. (in print).

REACTIONS OF IMIDO ACID DERIVATIVES WITH  
NUCLEOPHILIC REAGENTS. SELECTIVITY OF MO-  
LECULAR AND IONIC FORMS OF IMIDOYL CHLO-  
RIDES IN REACTIONS WITH AMINES IN ACETO-  
NITRILE

L.P. Drizhd, N.A. Taran, V.A. Savyolova,  
and A.G. Gershikov

Institute of Physicoorganic Chemistry  
and Coal Chemistry, Academy of Sciences  
of the Ukrainian SSR, Donetsk

Received January 26, 1989

Kinetics of N-arylbenzimidoyl chlorides' in-  
teraction with substituted pyridines in acetonit-  
rile, as well as tetraethyl-ammonium chloride ef-  
fect on reaction rate have been studied. It has  
been shown that the effect of this salt cannot be  
confined to action of similar ions in keeping with  
the Mass law only, as it has usually been stated  
in literature. Alongside with this the mentioned  
effect, tetraethyl-ammonium chloride affects the  
thermodynamic state of ion-pair intermediate and  
its reactivity towards amine. Selectivities of mo-  
lecular ( $S_N2$  processes) and ion-pair ( $S_N2(IP)$   
processes) forms of imidoyl chlorides in aminoly-  
sis have been compared.

The interaction of imidoylhalogenides  $ArC(X) = NR$  ( $X =$   
Cl; Br) with nucleophilic agents can be characterized<sup>1</sup> by  
various substitution mechanisms ( $S_N1$ ,  $S_N2(IP)$ ,  $S_N2$ ). The ki-  
netic regularities of these routes and the influence of  
substrate structure on their rate have been discussed rather

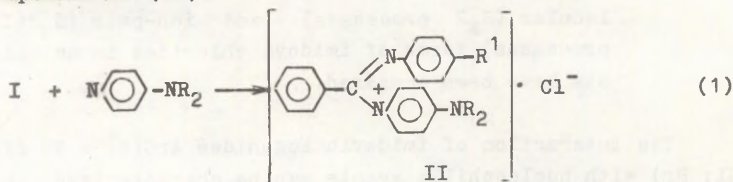
thoroughly in literature<sup>1-5</sup>. At the same time, the information on the selectivity of molecular and nitrilic ionic forms of imidoyl halogenides is comparatively limited yet<sup>2-4,6</sup>.

In order to determine the selectivity of different forms of N-arylbenzimidoyl chlorides  $C_6H_5(Cl) = NC_6H_4R^1$  (I,  $R^1 = 4-CH_3, a; 4-Cl, b; 4-NO_2, c$ ) we have studied the kinetics of their interaction with pyridine bases (4-N-morfolinopyridine, 4-N,N-dimethylaminopyridine, 4-N-piperidinopyridine) in acetonitrile as well as the effect of tetraethylammonium chloride (TEAC) on the rate of those processes.

#### Stoichiometry and Equilibrium of Process

As it was shown in<sup>4,7</sup>, the interaction of N-arylbenzimidoyl chlorides (I) with tertiary heterocyclic amines leads to the formation of imidoyl-ammonium salts. In the case of the pyridines having low basicities (pyridine, 4-phenoxy-pyridine), a reverse process can be traced, while for stronger basic amines (N-methylimidazole, 4-N,N-dimethylaminopyridine), equilibrium will be fully shifted towards the final products of II. Some of them were obtained with quantitative yields.<sup>8</sup>

In low-polarity aprotic solvents (benzene, toluene), the reaction of imidoyl chlorides (I) with 4-N-dialkyl-substituted pyridines leads to the quantitative formation of such products which cannot actually be dissolved in these products' media, whose elemental content corresponds to the compounds of (II):



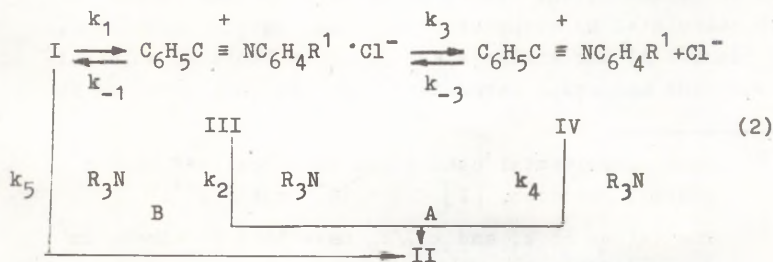
Since in acetonitrile the salts of II do not precipitate, the UV-spectra of reaction mixtures in the solvent were

analyzed to check the reversibility of the process (1). Adding pyridine bases to the imidoyl chloride Ia solution in acetonitrile (concentration ratio 1:1) brings about a total disappearance of the substrate's absorption band, there appears another band of product II, which is in comparison with the initial reagents shifted to a visible region. The spectra of previously synthesized salts II in nonpolar medium and those obtained in situ in acetonitrile are identical. The UV-characteristics of II products do not change when adding tetraethyl-ammonium chloride into their solutions in acetonitrile.

Consequently, the interaction of imidoyl chlorides I with 4-dialkylaminopyridines in the solvent mentioned proceeds quantitatively and irreversibly, as a result form the corresponding imidoylpyridinic salts II.

#### Kinetics of Reactions of Ia,b Compounds with Pyridine Compounds

The peculiarities of the interaction kinetics of pyridinic bases with N-arylbenzimidoyl chlorides in acetonitrile have been thoroughly discussed in papers<sup>4,9,10</sup>. In case of substrates 1 containing substituents R<sup>1</sup>, whose induction characteristics are  $\sigma_{R^1} < 0.5$ , the nucleophilic substitution mechanism via nitrilic-cationic intermediates as a free cation and ion pairs can be observed (route A in scheme (2)). This route is most probably valid for the interaction of imidoyl chlorides Ia,b with pyridine amines:



If  $[R_3N] > [I]^x$ , the pseudofirst order rate constant  $k_{obs}^I$  ( $s^{-1}$ ) can be expressed as<sup>2,4</sup>:

$$k_{obs}^I = \frac{k_1[R_3N]\{k_2(k_{-3}[Cl^-] + k_4[R_3N]) + k_3k_4\}}{(k_{-1} + k_2[R_3N])(k_{-3}[Cl^-] + k_4[R_3N]) + k_3k_4[R_3N]} \quad (3)$$

As to the aminolysis kinetics of substrates Ia and Ib, the following regularities can be found. The  $k_{obs}^I$  value remains constant during the process within the whole concentration range of the amine used. Thus, at low concentrations of chloride-ion, the rate of transformation of cation IV into final products exceeds that of its return into ion pair III ( $k_4[R_3N] > k_{-3}[Cl^-]$ ). As a result, Eq. (3) turns into (4):

$$k_{obs}^I = \frac{k_1(k_2[R_3N] + k_3)}{k_{-1} + k_2[R_3N] + k_3} \quad (4)$$

In the case of the processes studied, the dependence of  $k_{obs}^I$  on the amine concentration (Table 1) has a curvilinear form approaching the asymptote, as suggests Eq. (4).

In order to determine the optimum  $k_1$  values, as well as the ratios of rate constants  $k_{-1}/k_2$  and  $k_3/k_2$ , the experimental relationships  $k_{obs}^I(R_3N)$  were approximated with Eq. (4), using the least squares method. The mean-root-square deviations of both calculated and experimental  $k_{obs}^I$  values were minimized by means of the optimization algorithm of Hook and Jives<sup>11</sup>, the errors of determining the parameters were calculated by means of covariation matrix formation. The results of the analysis are given in Table 2, which also contains analogous parameters<sup>xx</sup> for imidoyl chloride Ib

<sup>x</sup> Such experimental conditions were realized in the present research,  $[I] \approx 5 \cdot 10^{-5} \text{ mol} \cdot \text{l}^{-1}$ .

<sup>xx</sup> The values of  $k_1$  and  $k_{-1}/k_2$  have been obtained in<sup>2</sup> on condition that  $k_2[R_3N] > k_3$ .

reaction with aliphatic amines taken from<sup>2</sup>.

The inhibiting action of tetraethyl-ammonium chloride on the aminolysis rate of substrates Ia and Ib agrees with the suggested scheme. The comparison of the data of Tables 1 and 3 shows that adding TEAC brings about a rather drastic drop in the reaction rate, while the salts with other anions (e.g., bromide and tetraethyl-ammonium perchlorate) accelerate the process<sup>10</sup>.

It has usually been considered<sup>2,12</sup> that the salts having similar anions inhibit the processes with substrate ionization according to the law of mass action, owing to realization of the inequality  $k_{-3}[\text{Cl}^-] > k_4[\text{R}_3\text{N}]$  with route A in scheme (2). On such a condition the expression for  $k_{\text{obs}}^{\text{I}}$  would transfer into (5) under the conditions of high TEAC concentrations. This can also be easily proved when applying Eq. (3) for the above-mentioned inequality if we assume that the members, containing  $k_3k_4$  can also be neglected. Consequently, in the case of the TEAC effect, only according to the Mass law " $k_{\text{obs}}^{\text{I}} - [\text{R}_3\text{N}]$ " should be nonlinear, and the  $k_1$  and  $k_{-1}/k_2$  calculated from the relationship, should coincide with those calculated from the experimental conditions, without tetraethyl-ammonium chloride presence.

$$k_{\text{obs}}^{\text{I}} = \frac{k_1 \cdot k_2 [\text{R}_3\text{N}]}{k_{-1} + k_2 [\text{R}_3\text{N}]} \quad (5)$$

Actually, in the presence of tetraethyl-ammonium chloride, not all the aforesaid assumptions hold in the case of the aminolysis of Ia and Ib imidoyl chlorides. It has already been shown in<sup>10</sup> that in the region of small salt additions the reaction rate drastically drops, at high concentrations tending to reach its threshold values. The latter fact is illustrated by the examples from Table 3. This effect, according to the Mass law qualitatively agrees with that of chloride-ion, being realized in TEAC high concentration region, on condition that  $k_{-3}[\text{Cl}^-] > k_4[\text{R}_3\text{N}]$ . Neverthe-

Table 1

Pseudofirst Order Rate Constants for N-4-Chlorophenylbenzimidoyl Chloride with Pyridine Bases in Acetonitrile at 25°C

Amine ( $R_3N$ )	$[R_3N] \cdot 10^4$ mol $\cdot$ l $^{-1}$	$k_{obs}^I \cdot 10^3, s^{-1}$
1	2	3
4-N-piperidino- pyridine	1.01	2.35
	2.03	2.86
	3.04	3.51
	4.06	3.60
	5.05	3.99
	10.1	4.71
	11.7	5.33
	15.2	5.45
18.2	5.51	
4-N,N-dimethyl- aminopyridine	2.95	2.33
	3.93	2.73
	5.90	2.99 <sup>x</sup>
	8.40	3.36 <sup>x</sup>
	9.82	3.84
	19.6	4.33
	29.5	4.50
	39.3	4.57
	56.6	4.71
	73.6	4.85
	74.3	4.89
	98.2	4.95
	107	4.97
	196	5.06
	295	5.40
393	5.53 <sup>x</sup>	
423	5.60 <sup>x</sup>	

Table 1 continued

1	2	3
4-N-morpholino- pyridine	1.00	2.09
	2.00	2.68
	3.00	3.12
	4.00	3.43
	10.0	5.47
	20.0	5.76
	30.0	6.97
	49.8	7.76
	80.0	8.27

<sup>x</sup> The data obtained in the present work, the rest of the results for 4-N,N-dimethylaminopyridine have been taken from <sup>10</sup>.

less, the dependence of these pseudofirst order rate constants (in the case of such experiment conditions, the constants are marked by  $k_s^I(\text{s}^{-1})$  and not by  $k_{\text{obs}}^I$  if there is no tetraethyl-ammonium chloride present) on the amine concentration is linear, preserving this character in the amine concentration region, remarkably exceeding those approaching the asymptote in the case of tetraethyl-ammonium chloride absence.

Supposedly, a strictly bimolecular rate law in the case of high tetraethyl-ammonium chloride concentrations is explained with the fact that the ionization mechanism's contribution to these conditions is negligible and the reaction mainly proceeds either via the concerted  $S_N2$ -substitution or according to a kinetically similar addition-detachment mechanism via tetrahedral intermediate (route B in Scheme (2)).

But the comparison of second order rate constants  $k_s^{II}$  (Table 3), calculated from a linear relationship " $k_s^I - [R_3N]$ " for reactions of imidoyl chlorides Ia and Ib with 4-N,N-dimethylaminopyridine, whose second order rate constants ( $k_5$

Table 2

Results of Kinetic Data Processing according to Eqs. (4), (7) for Reactions of N-Arylbenzimidoyl Chlorides  $C_6H_5C(Cl) = NC_6H_4R^1$  with Amines in Acetonitrile

R <sub>1</sub>	Amine	Reaction conditions	Rate constants and their ratios			
			$k_1 \cdot 10^3, s^{-1}$	$k_{-1}/k_2 \cdot 10^4, mol \cdot l^{-1}$	$k_3/k_2 \cdot 10^4, mol \cdot l^{-1}$	$k'_{-1}/k'_1 k'_2, mol \cdot s \cdot l^{-1}$
	4-N-piperidinopyridine	without TEAC, 25°C	7.4±0.3	6.0±1.0	1.9±0.5	-
	4-N,N-dimethylamino-pyridine	without TEAC, 25°C	5.4±0.1	6.2±1.0	2.1±1.0	-
		with TEAC, 25°C	-	-	-	50±2.5
	4-N-morpholinopyridine	without TEAC, 25°C	9.1±0.4	10.0±2.3	2.1±0.8	-
4-Cl		with TEAC, 25°C	-	-	-	114±8
	morpholine	without TEAC, 30°C <sup>x</sup>	10.2±0.3	33.3±1.1	-	-
	piperidine	without TEAC, 30°C <sup>x</sup>	11.2±0.4	13.5±0.5	-	-
	4-N,N-dimethylamino-pyridine	with TEAC, 25°C	-	-	-	3.7±0.1
4-CH <sub>3</sub>	4-N-morpholinopyridine	with TEAC, 25°C	-	-	-	7.7±0.2

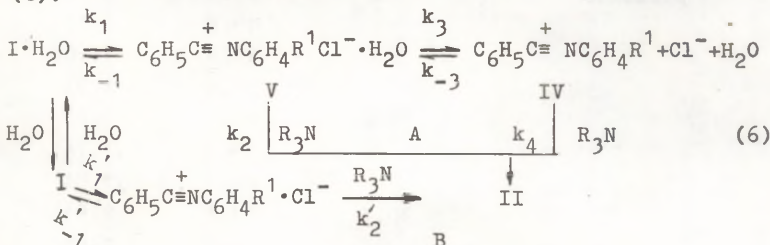
<sup>x</sup> The data were taken from<sup>3</sup>.

in Scheme (2)) were found from the Hammett relationship according to the data of<sup>4</sup> (in the case of more clearly expressed acceptor substituents R<sup>1</sup> in I than 4-Cl (Ib) shows that the contribution of mechanism B into the rate cannot be more than 11% or 0.2%, respectively.

Thus, the kinetic regularities of the aminolysis of compounds Ia, Ib studied, cannot be either in the absence or in the presence of tetraethyl-ammonium chloride be explained from the viewpoint of a common route A in Scheme (2) on condition that the action of tetraethyl-ammonium chloride leads only to the effect of a similar ion.

This enables us to say that in the presence of large TEAC additions these reactions are normally carried out according to the ionization mechanism. As an ion-pair intermediate, another particle, differing from III both in its thermodynamic state and in its reactivity to amines will be chosen.

Previously<sup>10</sup> it has been suggested that the imidoylha-genide Ia ionization in acetonitrile by means of ordinary methods, can be accomplished because of the participation of the residual water molecules in an organic solvent. Consequently, in the case of the absence of tetraethyl-ammonium chloride additions we can assume that the processes studied proceed according to ion-pair mechanism, water molecules showing electrophilic assistance promotion. This mechanism can in general be described by route A in Scheme (6):



Adding TEAC leads the process to a new route, whose reaction coordinate contains a less reactive ion pair than

Table 3

Pseudofirst Order  $k_s^I$  ( $s^{-1}$ ) and Second Order  $k_s^{II}$  Rate Constants ( $l \cdot mol^{-1} \cdot s^{-1}$ ) for Reactions of N-Arylbenzimidoyl Chlorides  $C_6H_5C(Cl) = NC_6H_4R^1$  with Pyridine Bases in Acetonitrile with Tetraethylammonium Chloride (TEAC)

$R^1$	Amine ( $R_3N$ )	$[R_3N] \cdot 10^3$ mol $\cdot$ l $^{-1}$	$[TEAC] \cdot 10^2$ mol $\cdot$ l $^{-1}$	$k_s^I \cdot 10^4$ s $^{-1}$
1	2	3	4	5
4-Cl	4-N,N-dimethyl-aminopyridines	8.07	14.8	2.23
			40.3	2.25
		12.1	8.15	3.45
			12.3	3.13
			25.6	3.15
		21.1	13.3	4.69
			34.3	4.62
		34.3	12.8	7.07
			42.1	7.02
		45.3	12.1	10.1
	45.1	9.98		
$k_s^{II} = (2.0 \pm 0.1) \cdot 10^{-2}$				
4-Cl	4-N-morpholino-pyridine	4.50	22.6	0.48
			33.9	0.48
			45.2	0.49
		9.90	24.9	1.10
			31.6	1.03
		19.2	22.6	1.99
			33.9	1.74
			45.2	1.84
		30.7	27.1	2.61
			38.4	2.55
38.4	11.6	3.89		
	22.6	3.46		

Table 3 continued

1	2	3	4	5
			27.1	3.83
			33.9	3.44
			45.2	3.70
			$k_{\text{B}}^{\text{II}} = (8.8 \pm 0.6) \cdot 10^{-3}$	
4-CH <sub>3</sub>	4-N,N-dimethyl-aminopyridine	0.505	31.4	1.76
			51.4	1.74
		2.02	49.6	6.23
			70.9	6.28
		3.02	49.6	8.10
			67.3	7.92
		4.03	49.6	11.3
			74.4	11.1
		5.04	49.6	14.4
			70.9	14.1
			$k_{\text{B}}^{\text{II}} = (2.7 \pm 0.1) \cdot 10^{-1}$	
4-CH <sub>3</sub>	4-N-morpholino-pyridine	0.500	30.2	1.12
			46.3	1.11
		2.00	54.0	3.11
		3.00	54.0	4.18
		4.00	46.3	5.79
			54.0	5.72
		5.00	49.6	7.02
			70.9	6.92
			$k_{\text{B}}^{\text{II}} = (1.30 \pm 0.04) \cdot 10^{-1}$	

that in the case of nitrile-cationic intermediates in route A. For the purposes of simplicity, the mechanism is presented by route B in scheme (6) with intermediate III and rate constants of different stages  $k'_1$ ,  $k'_{-1}$ ,  $k'_2$  differing from

$k_1, k_{-1}, k_2$ .

Linear dependence " $k_s^I - [R_3N]$ " proceeds from expression (7), which is obtained when adding in Scheme (6) a stationarity condition to route B. At the same time, non-linearity  $k_2'[R_3N] < k_{-1}'$  is once again considered in the whole used concentration range of amine. The holding of this nonlinearity in the TEAC presence even in the region of amines very high concentration makes us suppose that TEAC should remarkably decrease  $k_2'$  and increase  $k_{-1}'$  in comparison with the corresponding  $k_2$  and  $k_{-1}$  constants in the absence of salt. This is in good agreement with much lower  $k_1'k_2'/k_{-1}'$  values, if compared with similar  $k_1k_2/k_{-1}$  calculated on the basis of the experiments without salt additions. The data were taken from Table 2.

$$k_s^I = \frac{k_1' \cdot k_2'[R_3N]}{k_{-1}'} \quad (7)$$

The comparison of the  $k_s^{II}$  values for the reactions of substrates Ia and Ib (Table 3) shows that the introduction of an electron-donor substituent brings about an increase in the reaction rate. The  $\rho$ -parameter of Hammett that was estimated on the basis of those two points, equals  $\rho = -2.8$  for the reaction with 4-N,N-dimethylaminopyridine. The value is quite close to the analogous ( $\rho = -2.3$ ) one for the reactions of imidoyl chlorides I ( $R^1 = 3-CH_3, H, 3-Br, 3-CF_3$ ) with the same amine in methylene chloride<sup>5</sup>. In the latter case, mechanism  $S_N2(IP)$  is postulated. This fact once again confirms that in the presence of large TEAC additions the aminolysis of substrates Ia and Ib proceeds according to ionization mechanism.

Thus, it proceeds from the analysis of the regularities of the TEAC influence on the rate of the reactions observed that the salt has a retarding effect both owing to the mass action law via the  $V \rightleftharpoons IV + Cl^-$  equilibrium shift to the left, and to the transfer of intermediate of type V



of the ion-pair intermediate Va-Vc act as reactive particles towards a nucleophile (particularly, in the case of a tertiary amine). As a result, the  $k_2$  value will represent the total ( $k_2^a + k_2^b + k_2^c$ ). As to the heterolysis of saturated substrates, SDIP, i.e.  $k_2 = k_2^c$  acts as a reactive particle<sup>13</sup>. Thus, we can also assume that in the case of the TEAC absence at the expense of the water molecule participation, in the solvation of Va-Vc particles, ionization includes SDIP Vc and cation  $R^+$  as the most reactive particles. Already at very small amine concentrations, the return of  $R^+$  into Vc is not kinetically significant (i.e.,  $k_4[R_3N] > k_{-3}[Cl^-]$ ), since there is no retarding action of chloride-ion during the process. In proportion to the increase of amine concentration, it will be quite easy to realize the nonlinearity  $k_2^c[R_3N] > k_{-1}$ , in the result of which maximal rate can be achieved (in the present paper, this is marked by  $k_1$ ), on condition that the contributions of the  $k_2^a$  and  $k_2^b$  routes are insignificant. We cannot say whether maximal rate belongs to the rate determining stage of contact ion pair ( $k_1^a$ ) or of the sterically divided ion pair ( $k_1^b$ ) formation. Adding TEAC favors, first of all, the  $R^+$  return into the solvate-divided ion pair Vc, as a result, the rate decreases. Nevertheless, as it was already mentioned, the functions of salt are broader. Owing to the competing interaction of TEAC with water or Va-b complexes, the process will be transferred to route B via the contact ion pair IIIa, which is not evidently liable to undergo the following transformations up to the formation of intermediates of either the sterically-divided IIIb or solvate-divided IIIc type. Now route B with the contact ion pair participation becomes the basic route of aminolysis. This ion pair should be much less reactive than the solvate-divided one of the Vc type, which is considered the essential ion-pair reactant in route A. In addition to that, since in IIIa both  $X^-$  are similar, acting also as the substrate's leaving group, the step of the return of intermediate IIIa into the initial substrate can be accelerated somewhat ( $k_{-1}' > k_{-1}$ ). Therefore, in the case of large TEAC additions the nonlinearity  $k_2[R_3N] >$

$k_{-1}$  cannot be achieved even in the high concentration region of amine.

### Kinetics of Imidoyl Chloride Ic Interaction with Pyridine Bases

The rate of the processes studied was monitored conductometrically according to the imidoylpyridine salt accumulation in the solution. In case of kinetic measurements yielding  $[R_3N] > [Ic] \approx 10^{-5} \text{ mol} \cdot \text{l}^{-1}$ , pseudofirst order rate constants  $k_{\text{obs}}^I$  have similar values in the course of the reaction (for their values, see Table 4). The rate constant of the parallel hydrolysis of imidoyl chloride Ic with traces of water in solvent was estimated to equal  $8.8 \cdot 10^{-5} \text{ s}^{-1}$ .

Table 4

Pseudofirst Order  $k_{\text{obs}}^I (\text{s}^{-1})$  and Second Order  $k_5 (1 \cdot \text{mol}^{-1} \cdot \text{s}^{-1})$  Rate Constants for N-4-Nitrophenylbenzimidoyl Chloride Interaction with Pyridine Bases in Acetonitrile at 25°C

Amine ( $R_3N$ )	$R_3N \cdot 10^2$ mol $\cdot$ l $^{-1}$	$k_{\text{obs}}^I \cdot 10^4$ , s $^{-1}$
4-N,N-diethylaminopyridine	0.50	6.90
	1.04	9.76
	2.04	16.1
	3.06	20.4
	5.10	36.9
	9.30	63.3
$k_5 = (6.5 \pm 0.2) \cdot 10^{-2}$		
4-N-morpholinopyridine	0.53	2.36
	1.03	3.70
	2.06	4.73
	4.05	9.01

Table 4 continued

Amine ( $R_3N$ )	$R_3N \cdot 10^2$ mol $\cdot$ l $^{-1}$	$k_H^I \cdot 10^4$ , s $^{-1}$
	5.00	9.85
	6.10	10.9
$k_5 = (1.6 \pm 0.1) \cdot 10^{-2}$		

In the case of the aminolysis studied the relationship " $k_{obs}^I [R_3N]$ " is strictly linear. We can assume, on the basis of similarity with  $c^4$  that in the present case, operates the  $S_N2$  mechanism (route B in scheme (2)). This is also proved by the fact that the constant of substrate's Ic interaction with 4-N,N-dimethylaminopyridine proceeds in accordance with the previously obtained Hammett equation ( $\sigma_{4-NO_2}^- = 1.0$ ) for a series of imidoyl chlorides I ( $R^1 = 3-CF_3, 3-NO_2, 3-NO_2-5-COOCH_3, 3,5-(NO_2)_2$ ).

#### About Selectivity of Molecular and Ion Forms of Imidoyl Chlorides in Reactions with Amines

Selectivity of substrates differing in their nature concerning the structure of nucleophilic reagents belongs to the identification criteria of the  $S_N1$  and  $S_N2$  mechanisms<sup>14</sup>. This statement is based on the assumption that the  $S_N1$  processes are more sensitive to nucleophile basicity than those of  $S_N2$ .

Table 5 presents the  $\beta$ -Brønsted parameters for different routes of the reaction of N-substituted benzimidoyl chlorides aminolysis in protoinert solvents. Unfortunately, the kinetics of those reactions did not yield any data about the reactivity of free nitrile cations. The results given in Table 5 are connected with the processes of bimolecular substitution (route B in scheme (2)), as well as with the ion-pair route with electrophilic substitution (route A in

Table 5

$\beta$ -Brønsted Parameters for  $S_N2$  and  $S_N2(IP)$  Aminolysis of Imidoyl Chlorides in Aprotic Media

No	Reaction series	Medium	Reaction route in scheme (6)	$pK_a$ amine in water	$\beta$
1		Aceto-nitrile	$S_N2$	0.76	0.80
2		"-	$S_N2(IP)$	0.76	0.47
3	"-	"-	$H_2O \cdot S_N2(IP)$	1.0	0
4		"-	$S_N2(IP)$	0.76	0.42
5		"-	$S_N2$	3.1	0.50 <sup>8</sup>
6		"-	$H_2O \cdot S_N2(IP)$	3.1	0.06 <sup>8</sup>
7		"-	$S_N2$	1.5	1.5 <sup>12</sup>
8		"-	$S_N2(IP)$	1.5	0.8 <sup>12</sup>
9	"-	Dioxane	$S_N2(IP)$	1.5	0.8 <sup>12</sup>
10		Benzene	$S_N2$	2.8	0.48 <sup>3</sup>
11		"-	$S_N2(IP)$	2.8	0.22 <sup>3</sup>
12		"-	$S_N2(IP)$	2.8	0.028 <sup>3</sup>

scheme (6),  $H_2O \cdot S_N2(IP)$  - mechanism) and without it (route B in scheme (6),  $S_N2(IP)$  - mechanism).

Table 5 shows that in a series of structurally similar imidoyl and different amines (primary aromatic, secondary aliphatic, and tertiary pyridinic amines), the process of  $S_N2(IP)$  tends to be less selective, concerning the nucleophilic reagent than that of  $S_N2$ . Nevertheless, the absolute values of  $\beta$  cannot be a strict criterion of any mechanism at all. Really, even the  $\beta$  values for one and the same route remarkably depend on the amine (Nos 1,10) and substrate (Nos 1, 5) nature, while at the same time the variation of medium properties does not affect them (Nos 8,9).

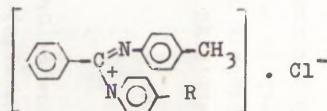
The ion-pair route of the reaction, with the electrophilic contribution of water (route A in scheme (6)) is less sensitive to the amine basicity than to that of the route, where such contribution occurs (cf. Nos. 2,3,6). This is in keeping with the above assumption that in the acetonitrile medium containing small amount of water, the solvent-divided ion pair Vc acts as a basic reaction form in scheme (8), while in the experiments with TEAC addition it is the contact ion pair IIIa. One should bear in mind that the tetraethyl-ammonium chloride additions ensuring that the reaction will proceed by route B ( $> 0.1 \text{ mol} \cdot \text{l}^{-1}$ ) exceed the water content in the solvent used ( $\approx 4.5 \cdot 10^{-2} \text{ mol} \cdot \text{l}^{-1}$ ). Evidently, these are the effects of specific solvation that mainly influence different forms of nitrile-cationic ion pairs (contact ion pair, sterically separated ion pair, solvent-separated ion pairs) as well as their reactivities in comparison with polar medium effects.



### Experimental

Methods of acetonitrile and tetraethyl-ammonium chloride purification have been described in<sup>9,10</sup>, 4-N-Morpholinopyridine and 4-N-piperidinopyridine were obtained by means of methods<sup>15</sup> and purified by repeated sublimation in vacuum. Imidoylpyridine salts were obtained as in<sup>4,5,7</sup>. The characteristics of the compounds that were synthesized

Table 6

Characteristics of Synthesized Imidoylpyridine Salts



R	Melting point, °C	$\lambda_{\text{max}}$ , nm ( $\epsilon$ , CH <sub>3</sub> CN)	% Found				Formula	% Calculated			
			C	H	Cl	N		C	H	Cl	N
N(CH <sub>3</sub> ) <sub>2</sub>	192-196	313.7 (23160)	71.64	6.35	10.22	12.00	C <sub>21</sub> H <sub>22</sub> ClN <sub>3</sub>	71.67	6.31	10.10	11.90
	204-208	293.8 (30410)	70.01	6.09	9.11	10.50	C <sub>24</sub> H <sub>26</sub> ClN <sub>3</sub>	70.12	6.15	9.06	10.67
	198-203	317.3 (28750)	73.37	6.54	9.01	10.61	C <sub>23</sub> H <sub>24</sub> ClN <sub>3</sub> O	73.54	6.70	9.04	10.72

for the first time are given in Table 6.

UV-spectra were recorded on a "Specord M40". The process was monitored spectrophotometrically and conductometrically according to the accumulation of imidoylpyridine salts in solution. The methods of kinetic measurements have been described in detail in papers<sup>4,9</sup>. When determining the constant values, the errors did not exceed 2%.

#### References

1. L.P. Drizhd and V.A. Savyolova, In: "Structure of Organic Compounds and Reaction Mechanisms" (in Russian), Kiev, Naukova dumka, 1986, p.3.
2. R. Ta-Shma and Z. Rappoport, J. Am. Chem. Soc., No 26, 8460 (1976).
3. R. Ta-Shma and Z. Rappoport, J. Am. Chem. Soc., No 6, 1845 (1977).
4. L.M. Litvinenko, L.P. Drizhd, E.N. Kryuchkova, and V.A. Savyolova, Ukr. khim. zh., 51, No 9, 965 (1985).
5. L.M. Litvinenko, L.P. Drizhd, E.N. Kryuchkova, and V.A. Savyolova, Ukr. khim. zh., 51, No 10, 1057 (1985).
6. A.F. Hegarty, Acc. Chem. Res., No 13, 448 (1980).
7. L.P. Drizhd, E.N. Kryuchkova, L.M. Litvinenko, V.A. Savyolova, and K.Yu. Chotij, Ukr. khim. zh., 50, No 12, 1194 (1984).
8. E.N. Kryuchkova, Abstract of Cand. of Sci. (Chemistry) thesis, (in Russian), Donetsk, 1986, 16 pp.
9. L.M. Litvinenko, L.P. Drizhd, A.P. Prudchenko, and V.A. Savyolova, Ukr. khim. zh., 51, No 5, 517 (1985).
10. L.P. Drizhd, E.N. Kryuchkova, V.A. Savyolova, and A.G. Gershikov, Ukr. khim. zh., 54, No 4, 350 (1988).
11. R. Hooke and T.A. Jeeves, J. Assoc. Comput. Math., No 8, 212 (1961).
12. L.M. Litvinenko, V.A. Mikhailov, L.P. Drizhd, V.A. Savyolova, and E.N. Kryuchkova, ZhOrKh, 20, No 6, 1253 (1984).

13. T.L. Pervishko, E.A. Ponomareva, and G.F. Dvorko, *Organic Reactivity*, 24, 199 (1987).
14. R.A. Sneen and J.W. Larsen, *J. Am. Chem. Soc.*, 91, 6031 (1969).
15. D. Jerchell and L. Jakob, *Chem. Ber.*, 91, 1266 (1958).

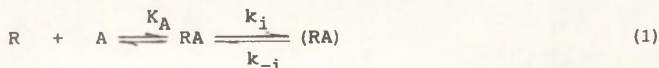
INFLUENCE OF NON-RADIOACTIVE LIGANDS ON KINETICS OF  
N-METHYL-<sup>3</sup>H]SCOPOLAMINE BINDING TO MUSCARINIC RECEPTOR

M.Eller, J.Järvi, and P.Palumaa  
Tartu State University, Tartu

Received January 19, 1989

This is a study of competition kinetics of a radioactive antagonist N-methyl-<sup>3</sup>H]scopolamine and non-radioactive antagonists N-methylquinuclidinyl benzilate and benzoylcholine for the binding site of muscarinic receptor from rat brain. The non-radioactive antagonists reveal different binding mechanisms. The benzilic ester forms a slowly dissociating complex while the benzoic ester dissociates fastly from its complex with the receptor. Thus, the kinetic approach makes it possible to differentiate between muscarinic antagonist subclasses.

Kinetic studies of the interaction of potent muscarinic antagonists quinuclidinyl benzilate (QNB), N-methylpiperidinyl benzilate (NMPB) and N-methylscopolamine (NMS) with the receptor have revealed the complex mechanism of this process<sup>1,2,3</sup>. In all those cases at least a two-step reaction scheme should be applied at low or moderate ligand concentrations.



The evidence for this reaction scheme has been obtained from the kinetic data for the binding of radioactive antagonists with membrane-bound and solubilized muscarinic receptor from

different tissues<sup>4,5</sup>. According to this reaction scheme the plots of the observed first-order rate constants against antagonist concentration reveal hyperbolic shape and allow the calculation of the equilibrium dissociation constant  $K_A$  and the rate constant  $k_i$  for the isomerization process of the receptor-ligand complex RA into (RA)<sup>1</sup>:

$$k_{\text{obs}} = \frac{k_i [A]}{K_A + [A]} + k_{-i} \quad (2)$$

The hyperbolic shape of the  $k_{\text{obs}}$  versus [A] plots points to the fact that only the complex (RA) can be determined by the routinely used assay procedure, i.e. by the classical filtration method applied for the separation of the receptor-bound radioligand from the excess of the free ligand. That means that the first complex RA dissociates fast enough to escape determination by the filtration assay. On the other hand, however, in the case of the antagonists studied, the complex (RA) dissociates slowly and the appropriate rate constant  $k_{-i}$  in Eqn (2) is negligibly small<sup>2,3,4</sup>.

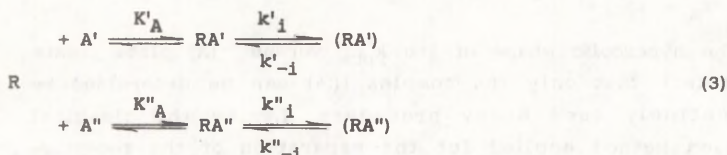
In the present report we extend the kinetic approach and analyze the simultaneous interaction of radioactive and non-radioactive ligands with the receptor. This makes it possible to obtain the binding data for also non-radioactive compounds, and thus considerably increase the number of muscarinic ligands for which the receptor-ligand interaction can be characterized by means of kinetic parameters. In the present investigation two typical muscarinic antagonists, N-methylquinuclidinyl benzilate (Me-QNB) and benzoylcholine (BzCh), were used as non-radioactive ligands. N-methyl-[<sup>3</sup>H]scopolamine ( [<sup>3</sup>H]NMS ) was used as the radioactive reporter ligand. Its relatively low affinity for muscarinic receptor makes this compound convenient for kinetic analysis under experimental conditions  $[R] < K_A$  and  $[A] < K_A$ .

#### THEORETICAL

A non-radioactive ligand may interact with the muscarinic receptor in two ways. Firstly, it can form an (RA)-type slowly dissociating complex according to the two-step reaction scheme (1). Secondly, this ligand may dissociate fast

from its complex with the receptor in comparison with the association rate of the radioactive reporter ligand, and thus affect the binding of the latter as a reversible inhibitor.

In the first case the radioactive reporter ligand A' and the non-radioactive ligand A'' compete for the same receptor site according to the following reaction scheme:



This system can be easily analyzed if we assume the excess of the concentrations of both the ligands A' and A'' to be over the receptor concentration and the fast equilibrium between the free receptor R and the complexes RA' and RA''. Under those conditions the dependences of the concentrations of both complexes (RA') and (RA'') upon time can be presented by the sum of two exponents, as shown by Varfolomeev and Zaitsev<sup>6</sup>:

$$C(RA') = C_{11}\exp(\beta_1 t) + C_{12}\exp(\beta_2 t) + C_{10} \quad (4)$$

$$C(RA'') = C_{21}\exp(\beta_1 t) + C_{22}\exp(\beta_2 t) + C_{20} \quad (5)$$

$$\text{where } \beta_1 = \frac{-d + \sqrt{d^2 - 4f}}{2} \quad (6)$$

$$\beta_2 = \frac{-d - \sqrt{d^2 - 4f}}{2} \quad \text{and} \quad (7)$$

$$d = \frac{k'_1[A']}{K'_A + [A']} + \frac{k''_1[A'']}{K''_A + [A'']} + k'_{-1} + k''_{-1} \quad (8)$$

$$f = \frac{k'_1[A']}{K'_A + [A']} k''_{-1} + \frac{k''_1[A'']}{K''_A + [A'']} k'_{-1} + k'_{-1}k''_{-1} \quad (9)$$

If the values of  $k'_{-1}$  and  $k''_{-1}$  are small compared to the observed on-rate constants, the following meaning for the roots  $\beta_1$  and  $\beta_2$  can be obtained:

$$\beta_1 = - \frac{k'_{-1} + k''_{-1}}{2} \quad \text{and} \quad (10)$$

$$\beta_2 = - (k'_{\text{obs}} + k''_{\text{obs}} - \beta_1), \quad \text{where} \quad (11)$$

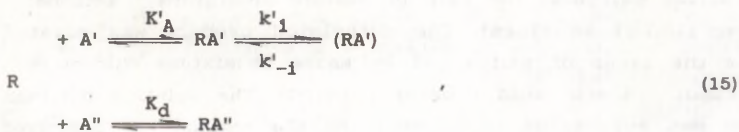
$$k'_{\text{obs}} = \frac{k'_1[A']}{K'_A + [A']} \quad \text{and} \quad (12)$$

$$k''_{\text{obs}} = \frac{k''_1[A'']}{K''_A + [A'']} \quad (13)$$

If the concentration of the radioactive ligand A' is constant throughout the series of kinetic runs at different concentrations of the non-radioactive ligand, equation (11) can be simplified as the value of  $k'_{\text{obs}}$  remains constant. Thus the data can be fitted to the simple hyperbolic function to calculate the kinetic parameters for the non-radioactive ligand interaction with the receptor binding site:

$$\beta_2 = - \left( \frac{k''_1[A'']}{K''_A + [A'']} + \text{const.} \right) \quad (14)$$

In the second case the binding of the non-radioactive ligand A'' to the receptor can be formally treated as a single-step equilibrium process characterized by the apparent dissociation constant  $K_d$ :



$$\text{where } K_d = \frac{[R][A'']}{[RA'']}$$

Under the first-order-conditions where  $[R]_0 \ll [A']_0$  and  $[R]_0 \ll [A'']_0$ , the rate equation for the formation of the complex (RA') can be obtained analogously to the reaction scheme (1) as described by Cornish-Bowden<sup>7</sup>. The overall kinetic curve can be described by a single exponent, allowing the calculation of the observed rate constant:

$$k_{\text{obs}} = \frac{k'_1[A']}{(1 + [A'']/K_d) K'_A + [A']} + k'_{-1} \quad (16)$$

It can be seen that at a constant concentration of the radioactive reporter ligand A' under conditions  $[A'] \ll K'_A$ , the dependence of the observed rate constants upon the concentration of the non-radioactive ligand A'' allows estimation of the apparent dissociation constant  $K_d$  by means of linear transformation of Eqn (16):

$$\frac{1}{k_{\text{obs}}} = \frac{K'_A}{k'_1[A']} + \frac{K'_A[A'']}{k'_1[A']K_d} \quad (17)$$

#### EXPERIMENTAL

L-[<sup>3</sup>H]Quinuclidinyl benzilate (39 Ci/mmole) and N-methyl-[<sup>3</sup>H]scopolamine (72 Ci/mmole) were obtained from "Amersham". Benzoylcholine iodide was obtained from "Chemapol", Czechoslovakia. Unlabelled L,D-quinuclidinyl benzilate and N-methylquinuclidinyl benzilate were generously donated by Prof. N.N.Godovikov, Institute of Heteroorganic Compounds, Moscow.

L-[<sup>3</sup>H]quinuclidinyl benzilate was methylated with methyl iodide in dry acetone<sup>8</sup>. The product was purified by TLC on silica gel, with the help of mixture chloroform : methanol : water (10:7:1) as eluent. The methylated product was eluted from the layer of silica gel by means of mixture chloroform : methanol : acetic acid : water (10:6:1:2). The solution obtained thus was evaporated to dryness and the residue was dissolved in a mixture of ethanol and water (1:1).

The membranes from rat cerebral cortex were prepared as described elsewhere<sup>9</sup>. The membrane-bound radioligand was determined by the filtration method by means of Whatman GF/B filters.

All experiments were carried out in 0.05 M K-phosphate buffer, pH 7.40, at 25°C. The incubation was started by mixing the ligands into a membrane suspension. The excess of the ligands over the receptor concentration was used to obtain the pseudo-first-order conditions. In making kinetic measurements, aliquots were taken from the incubation mixture after certain

time intervals and assayed for membrane-bound radioactivity. The kinetic curves of the binding of the radioligand alone and in the presence of BzCh were analyzed by means of the following equation:

$$B_t = B_{ns} + B_{sp}[1 - \exp(-k_{obs}t)] \quad , \quad (18)$$

where  $B_t$  - concentration of the membrane-bound radioligand at time  $t$ ,  $B_{ns}$  - concentration of the nonspecifically bound radioligand,  $B_{sp}$  - maximal concentration of the specifically bound radioligand.

The data for radioligand binding in the presence of Me-QNB were fitted to the following equation:

$$B_t = B_{ns} + B_{sp1}[1 - \exp(-k_1t)] + B_{sp2}[1 - \exp(-k_2t)] \quad . \quad (19)$$

In the case of displacement experiments the membrane suspension was incubated in the presence of various concentrations of non-radioactive antagonists for 3 h before [ $^3$ H]NMS was added. The whole reaction mixture was additionally incubated for 4 h. The displacement curves were obtained at 0.5 nM [ $^3$ H]NMS concentration and were analyzed according to the following equation:

$$[RA''] = \frac{[R]_0 [A'']}{IC_{50} + [A'']} \quad , \quad (20)$$

where  $IC_{50} = K''_d (1 + [A']/K'_d)$

The experimental data were processed on a PC/XT computer by using the nonlinear regression program from "Statgraphics" package.

## RESULTS

### Equilibrium Binding Data

Both non-radioactive antagonists, Me-QNB and BzCh, displaced [ $^3$ H]NMS from its complex with muscarinic receptor (Fig.1). These data can be statistically satisfactorily described by a simple binding isotherm characterized by the Hill coefficient  $n=0.93$  and  $n=1.02$  for Me-QNB and BzCh

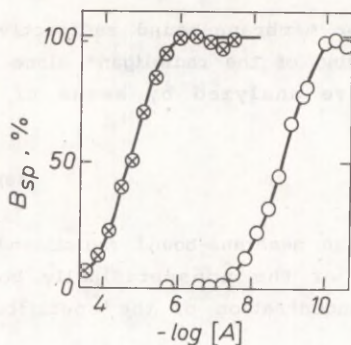


Fig 1. Competition for binding to muscarinic receptor from rat cerebral cortex between N-methyl- $^3\text{H}$ scopolamine (0.5 nM) and N-methylquinuclidinyl benzilate - ○ or benzoylcholine - ⊗ . 0.05 M K-phosphate buffer with pH 7.4, 25°C.

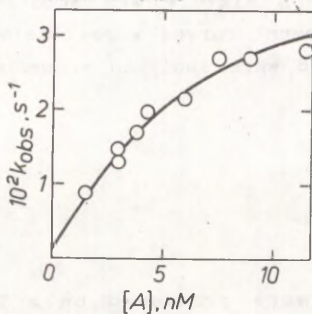


Fig 2. The dependence of  $k_{\text{obs}}$  on N-methyl- $^3\text{H}$ quinuclidinyl benzilate concentration. 0.05 M K-phosphate buffer with pH 7.4, 25°C.

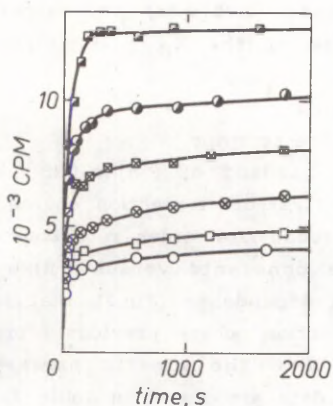


Fig 3. Time course of N-methyl- $^{3}\text{H}$ scopolamine (2 nM) binding to muscarinic receptor from rat cerebral cortex in the presence of N-methylquinuclidinyl benzilate at concentrations

0 nM -  $\blacksquare$  ,  
 1.45 nM -  $\bullet$  ,  
 2.9 nM -  $\boxtimes$  ,  
 5.8 nM -  $\otimes$  ,  
 8.7 nM -  $\square$  ,  
 11.6 nM -  $\circ$  .  
 0.05 M K-phosphate buffer with pH 7.4, 25°C.

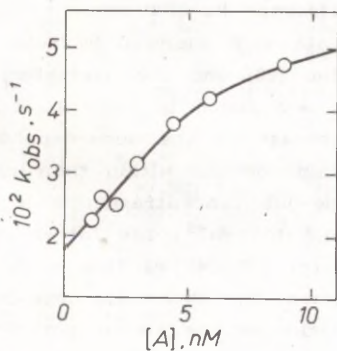


Fig 4. The dependence of  $k_{\text{obs}}$  on N-methylquinuclidinyl benzilate concentration. 0.05 M K-phosphate buffer at pH 7.4, 25°C.

respectively. The apparent dissociation constants for these ligands were  $(0.125 \pm 0.035)$  nM and  $(3.76 \pm 0.54)$   $\mu$ M, calculated from the  $IC_{50}$  values by means of the  $K_d = (82 \pm 8)$  pM for  $[^3H]NMS^3$ .

#### Kinetics of $[^3H]Me-QNB$ Binding with the receptor

The kinetic curves for binding of  $[^3H]Me-QNB$  with muscarinic receptor follow the first-order-reaction course and allow the calculation of the pseudo-first-order rate constants  $k_{obs}$ . The plot of these rate constants versus  $[^3H]Me-QNB$  concentration yields hyperbolic dependence (Fig.2), that is in agreement with the two-step reaction scheme previously proved for  $[^3H]QNB$ ,  $[^3H]NMPB$  and  $[^3H]NMS$ . The kinetic parameters  $K_A$  and  $k_1$  calculated from these data are listed in Table 2. The  $k_{-1}$  value  $(2.0 \pm 0.3) 10^{-3} s^{-1}$  for the dissociation of the receptor-ligand complex was measured elsewhere<sup>10</sup>.

#### Kinetics of $[^3H]NMS$ Binding with the Receptor in the Presence of Me-QNB

The kinetic curves of  $[^3H]NMS$  binding with muscarinic receptor in the presence of different Me-QNB concentrations are presented in Fig.3. These data were analyzed by means of the two-exponential rate equation (19) and the parameters  $k_1$  and  $k_2$  as well as  $B_{sp1}$  and  $B_{sp2}$  are listed in Table 1. It can be seen that the  $k_1$ -values increase in the dose-dependent manner, while the  $k_2$ -values remain constant within their error limits. The plot of  $k_1$  versus Me-QNB concentration is hyperbolic with an intercept at  $k = 1.8 10^{-2} s^{-1}$ . The latter value corresponds to the  $k_{obs}$  value for  $[^3H]NMS$  binding with the receptor at its 2 nM concentration. The hyperbolic dependence shown in Fig.4 allows the calculation of the kinetic parameters  $K_A$  and  $k_1$  for Me-QNB according to Eqn(14). The appropriate values are listed in Table 2.

The mean value for  $k_2 = (1.45 \pm 0.38) 10^{-3} s^{-1}$  enables to calculate the rate constant  $k_{-1} = (1.14 \pm 0.32) 10^{-3} s^{-1}$  for dissociation of the complex of MeQNB with receptor by means of Eqn (10). The sums of the  $B_{sp1}$  and  $B_{sp2}$  values listed in Table 1 characterize the equilibrium state of the system containing receptor and two ligands. This equilibrium state is

Table 1.

Kinetic analysis of binding of N-methyl-[<sup>3</sup>H]scopolamine to muscarinic receptor in the presence of N-methylquinuclidinyl benzilate at 25°C in 0.05 M K-phosphate buffer with pH 7.4.

[Me-QNB](nM)	B <sub>sp1</sub> (pM)	10 <sup>2</sup> k <sub>1</sub> (s <sup>-1</sup> )	B <sub>sp2</sub> (pM)	10 <sup>3</sup> k <sub>2</sub> (s <sup>-1</sup> )
1.09	128±6	2.25±0.53	24±5	1.42±0.94
1.45	114±6	2.62±0.15	26±5	0.98±0.42
2.18	92±9	2.43±0.30	29±7	1.86±0.89
2.9	80±5	3.18±0.14	23±4	1.12±0.35
4.35	52±3	3.80±0.24	26±3	1.56±0.30
5.8	46±7	4.40±0.72	28±3	1.58±0.22
8.7	36±4	4.78±0.68	23±5	1.03±0.36

Table 2.

Kinetic parameters for interaction of N-methylquinuclidinyl benzilate with muscarinic receptor at 25°C in 0.05 M K-phosphate buffer with pH 7.4.

Ligand	K <sub>A</sub> (nM)	10 <sup>2</sup> k <sub>i</sub> (s <sup>-1</sup> )
[ <sup>3</sup> H]Me-QNB	5.03±2.36	4.44±0.32
Me-QNB	6.89±2.35	5.57±1.07

Table 3

Kinetic analysis of binding of N-methyl-[<sup>3</sup>H]scopolamine to muscarinic receptor in the presence of benzoylcholine at 25°C in 0.05 M K-phosphate buffer with pH 7.4.

[BzCh](μM)	B <sub>sp</sub> (pM)	10 <sup>2</sup> k <sub>obs</sub> (s <sup>-1</sup> )
0.12	60±6	1.34±0.11
0.23	54±5	1.26±0.09
0.47	61±6	1.45±0.11
0.94	56±6	0.98±0.09
1.88	55±4	0.84±0.05
3.75	55±4	0.65±0.03

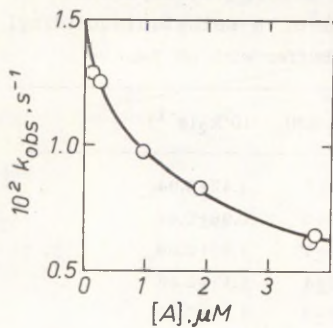


Fig 5. The dependence of  $k_{\text{obs}}$  on benzoylcholine concentration. 0.05 M K-phosphate buffer with pH 7.4, 25°C.

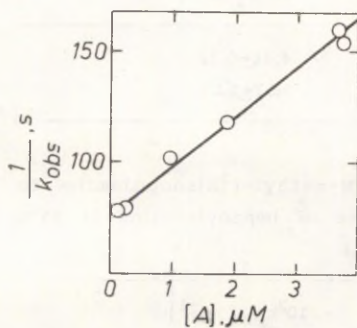


Fig 6. The dependence of  $1/k_{\text{obs}}$  on benzoylcholine concentration. 0.05 M K-phosphate buffer with pH 7.4, 25°C.

determined by the concentrations of the ligands and the dissociation constants  $K_d$  for them. Therefore the plot of  $(B_{sp1} + B_{sp2})$  versus Me-QNB concentration can be directly compared with the displacement curve obtained under the equilibrium conditions and shown in Fig.1. Taking into account the concentration of  $[^3H]NMS$  in the reaction medium and the  $K_d$ -value for this ligand, the overall dissociation constant  $K_d = (0.14 \pm 0.02) nM$  can be obtained for Me-QNB, that is in good agreement with the corresponding data presented above.

#### Kinetics of $[^3H]NMS$ Binding with the Receptor in the Presence of BzCh

The kinetic curves of  $[^3H]NMS$  binding with muscarinic receptor in the presence of different BzCh concentrations were analyzed by means of the two-exponential and single-exponential rate equations (19) and (18). It was found that the latter equation described well those kinetic curves and the calculated values for  $k_{obs}$  and  $B_{sp}$  are listed in Table 3. These data reveal that in the presence of the non-radioactive ligand the observed binding rate of the radioactive reporter ligand decreases in the dose-dependent manner. This dependence is illustrated also in Fig 5. The effect can be analyzed in terms of reversible inhibition of  $[^3H]NMS$  binding at the receptor binding site. The plot of  $1/k_{obs}$  versus  $[BzCh]$  yields a linear relationship (Fig.6) according to Eqn (17), allowing to calculate the dissociation constant  $(3.55 \pm 0.16) \mu M$  for the complex of BzCh and muscarinic receptor. This value is in good agreement with the constant  $K_d$  obtained from the equilibrium displacement experiment, as described above.

#### DISCUSSION

Both of the non-radioactive ligands, studied in the present communication belong to the class of muscarinic antagonists, although their potency is quite different. The results obtained show that these compounds influence the kinetics of  $[^3H]NMS$  binding with the receptor in principally different ways.

In the presence of the benzilic ester, Me-QNB, the observed rate constants of the radioligand binding increase according to the situation described by the reaction scheme

(3). This means that the compound forms with the receptor a slowly dissociating complex of (RA) type. The kinetic parameters for this process, obtained from the experiments on the kinetic competition of non-radioactive and radioactive ligands, are listed in Table 2.

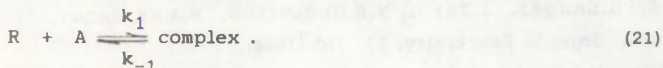
In the case of Me-QNB these results can be verified by comparison with the values of the constants  $K_A$  and  $k_i$  obtained from the kinetic analysis of the radioligand binding. The latter results are also listed in Table 2. As it can be seen, within the experiment error limits the appropriate values are in good agreement. On the other hand, it should be mentioned that the radioligand was synthesized from the L-derivative of QNB, while the non-radioactive compound was used as the racemic mixture. If the receptor retains stereoselectivity against the N-methylated derivative of QNB, a two-fold difference should be revealed in the  $K_A$  values because the concentration of the racemic mixture was used in the calculations. However, the data listed in Table 2 show that the effect of stereoselectivity may remain within the limits of experimental errors, although the  $K_A$  value for the pure L-isomer is somewhat smaller than this constant for the racemic mixture.

In the presence of benzoylcholine the observed rate constants for the binding of [ $^3\text{H}$ ]NMS with the receptor decrease, as predicted by the second kinetic model discussed above. That means that no slowly dissociating complexes form in the case of this antagonist and the overall process can be presented as a simple equilibrium. The latter conclusion is supported by the good agreement of the  $K_d$  values obtained for benzoylcholine from the kinetic study and the equilibrium displacement curve shown in Fig.1.

In summary, the present results show that by means of kinetic analysis the muscarinic antagonists can be divided into two classes. Ligands of the first type induce a conformational transformation of the binding site, yielding the slowly dissociating "isomerized" complex (RA). Antagonists of the second type dissociate fast from the receptor complex and behave like normal reversible ligands. The structural factors which govern these changes in the binding mechanism are not

clear yet, but the kinetic approach reliability of which was proved in this paper will offer a possibility for a more thorough analysis of this phenomenon.

It should be mentioned that an attempt has been made by Schreiber et al.<sup>11,12</sup> to compare the kinetic properties of muscarinic antagonists and agonists. In their study also the two-step reaction scheme (1) has been applied for potent muscarinic antagonists, NMPB and NMS, used as radioactive reporter ligands to measure the kinetics of the binding of non-radioactive ligands. But these authors assume that both the receptor-antagonist complexes RA and (RA) remain on the glass-fiber filter and can thus be detected simultaneously. According to that presumption two-exponential kinetic curves should be obtained for the binding reaction at low ligand concentrations where  $[A] < K_A$ . At high ligand concentrations, on the other hand, where  $[A] > K_A$ , the kinetic curves of ligand binding should be described by a single exponent and the  $k_{\text{Obs}}$  vs  $[A]$  plots should be linear, as the overall process (1) can be formally reduced to a single-step equilibrium:



According to this reaction scheme the observed first-order rate constants depend linearly upon the ligand concentration:

$$k_{\text{Obs}} = k_{-1} + k_1 [A] . \quad (22)$$

In fact, that is not characteristic of potent antagonists for which the hyperbolic  $k_{\text{Obs}}$  versus  $[A]$  plots have been found experimentally. Such hyperbolic dependences can be obtained if only the isomerized complex (RA) is detected on the glass-fiber filter, as emphasized in our previous papers<sup>1,2</sup>.

Owing to the inadequate presumptions made by Schreiber et al. for the radioactive reporter ligands used in kinetic runs, it is also hard to discuss the conclusions drawn in their paper about the muscarinic agonists.

#### Literature

1. J.Järv, B.Hedlund, T.Bartfai, *J. Biol. Chem.*, 254, 5595 (1979).
2. J.Järv, R.Sillard, T.Bartfai, *Proc. Acad. Sci. Estonian S.S.R. Chemistry.*, 36, 172 (1987).
3. M.Eller, J.Järv, *Neurochem. Int.*, in press (1989).
4. J.Järv, R.Sillard, in: *Synaptic Transmitters and Receptors* (S.Tucek,ed.), Prague, 1987.
5. A.Kõiv, A.Rinken, J.Järv, *Organic Reactivity*, 23, 403 (1986).
6. S.D.Varfolomeev, S.V.Zaitsev, *Kinetic Methods in Biochemical Studies*, Moscow University Press, Moscow, 1982.
7. A.Cornish-Bowden, *Principles of Enzyme Kinetics*, Butterworths, London, 1976.
8. E.C.Hulme, N.J.M.Birdsall, A.S.V.Burgen, P.Mehta, *Mol. Pharmacol.*, 14, 737 (1978).
9. Ü.Langel, A.Rinken, L.Tähepõld, J.Järv, *Neirokhiimiya*, 1, 343 (1982).
10. R.Sillard, Ü.Langel, J.Järv, N.N.Godovikov, N.A.Kardanov, S.A.Trifonova, *Organic Reactivity*, 23, 370 (1986).
11. G.Schreiber, Y.I.Henis, M.Sokolovsky, *J. Biol. Chem.*, 260, 8789 (1985).
12. G.Schreiber, Y.I.Henis, M.Sokolovsky, *J. Biol. Chem.*, 260, 8795 (1985).

AMINOACID ADDITION EFFECTS ON THE STRUCTURE OF TETRAALKYL-  
AMMONIUM HALIDE AQUEOUS SOLUTIONS

Helle Kuura and Mati Karelson

Laboratory of Chemical Kinetics and Catalysis, Tartu State  
University, Tartu, 202400, Estonian S.S.R., U.S.S.R.

Received June 15, 1988

The effect of the small additions of the glycine, beta-alanine and gamma-aminobutyric acid on the electrical conductivity of the aqueous solutions of various tetraalkylammonium salts (tetramethylammonium bromide, tetraethylammonium bromide and tetrabutylammonium bromide) is measured conductometrically. The results are interpreted according to the two-state structural theory of solutions. All the aminoacids investigated are characterized by the structure-forming ability in these solutions. The absolute value of this effect is substantially dependent on the structure of the tetraalkylammonium salt and its concentration in the solution.

In the previous communication /1/ the results of the differential-conductometric investigation of the aminoacid addition effect on the electrical conductivity of the potassium chloride aqueous solutions were presented. It was established that in the terms of the two-state theory this effect corresponds to the structure-formation in the solution for every aminoacid studied (glycine, beta-alanine and gamma-aminobutyric acid) and the restructurization volume  $V_s$  remains practically unchanged over a wide range of the KCl concentration

in solution. A linear relationship between the numerical values of the  $V_s$  and the intrinsic volumes of the aminoacids, estimated from their molecular refractions ( $\sum RD$ ), was obtained.

In the biological systems a large number of various organic ions and polyelectrolytes are present aside the simple inorganic electrolytes. The structure of the aqueous solutions of these substances may be rather different from that of the pure water due to the possible hydrophobic interactions between the alkyl side chains of organic ions and solvent molecules. Therefore it is essential to study the influence of the aminoacid additions on the structure of the aqueous solutions of model organic electrolytes, too. In this paper the results of the differential-conductometric investigation of the small aminoacid addition effects on the electrical conductivity of three organic electrolytes, tetramethylammonium bromide (TMABr), tetraethylammonium bromide (TEABr) and tetrabutylammonium bromide (TBABr) are presented. The three aminoacids studied previously /1/ were used (glycine, beta-alanine and gamma-aminobutyric acid).

#### Experimental.

The quantity

$$Y = \frac{1000k}{c} \left( \frac{1}{R_0 + \Delta R} - \frac{1}{R_x} \right) \quad (1)$$

is calculated in the differential conductometry from the experimentally measured data. In this formula  $k$  denotes the conductometric cell constant ( $\text{cm}^{-1}$ ),  $c$  is the concentration of the substance added to the solution ( $\text{mol/l}$ ), and  $R_0$  and  $R_x$  are the resistances of the solution before and after the addition ( $\text{ohm}$ ). The term  $\Delta R$  is taking into account the change in the resistance due to the dilution of the solution by addition.

The quantity  $Y$  is according to the simple two-state theory

of solutions /2/ related to the molar volume  $V_s$  where the structure of the solvent is changed by the given small addition:

$$Y = V_s \kappa \quad (2)$$

where  $\kappa$  denotes the specific conductivity of the initial electrolyte solution. The positive slopes  $V_s$  correspond to the structure-formation and negative slopes to the structure-breaking in solution. More specifically, in the first case the electrolyte ions are transferred into a non-conducting state in the volume  $V_s$  along the additional solute molecule. In the case of negative volumes  $V_s$  all ions in it are transferred into a conducting state. Naturally in both cases this volume corresponds to the statistically average effect and in reality the structure perturbation may occur at much larger distances from the solute, but with only partial transfer of ions from one to other state.

The differential-conductometric measurements were made by the experimental technique described elsewhere /3/. For the balancing instrument a universal procentmeter designed at the Tallinn Technical University was used /4/. All the experiments were proceeded at the temperature  $25\text{ C} + 0.1\text{ C}$  preserved during one complete measurement with the accuracy of  $0.001\text{ C}$ . The conductivity cell was isolated by the anidrone tubes to avoid the adsorption of the water from the atmosphere. The cell constant was  $19.40\text{ cm}^{-1}$ . A constant resistance  $R_p = 9907.0$  was used in parallel joint to the cell in the investigation of dilute solutions with low specific conductivities. The dilution term DR was calculated as given elsewhere /5/.

The preparations of glycine, beta-alanine and gamma-aminobutyric acid by "Reanal" (Hungary) were used.

The bidistilled deionized water was used for the preparation of aqueous solutions.

### The results and discussion.

The results of the conductivity measurements are given in Tables 1-3. The value of  $V_s$  calculated according to the Eq. (2) remains practically constant for every aminoacid studied in TMABr and TEABr solutions over the wide range of the electrolyte concentration. In order to find the statistically average value of the volume  $V_s$  and to eliminate possible systematic errors in the measurement of resistance, the treatment of the experimental data according to the linear relationship

$$Y = V_s \kappa + a_0 \quad (3)$$

was proceeded by the least-squares method. The validity of this linear relationship for aminoacids in TMABr and TEABr solutions is demonstrated in the Fig. 1. and 2., and the results of the statistical treatment are presented in Table 4.

A more complicated picture is observed for the aminoacid additions to the TBABr solutions. In the case of every aminoacid studied a significant increase of the  $V_s$  value in parallel with the increase of the electrolyte concentration in solution is inherent (cf. Table 3. and Fig. 3.). This phenomenon may be caused by the strong ion-like interaction between the tetrabutylammonium cations in more concentrated solutions, leading to the collective interionic effects which are reflected in higher values of the  $V_s$  for the additional solute. The physical nature of this effect is probably connected with the hydrophobic interaction between the long aliphatic side chains in large organic ions as discussed elsewhere /6-8/. The observed nonlinearity between the quantity  $Y$  and specific conductivity  $\kappa$  (cf. Fig. 3.) can be described formally by the addition of the quadratic term into Eq. (3):

$$Y = V_s \kappa + a_0 + a' \kappa^2 \quad (4)$$

This correction leads to a much better statistical description of the experimental data than Eq. (3) (cf. the respective values of the correlation coefficient and standard devia-

tion in Table 4.) and gives altogether the better estimates of the parameters  $V_s$ .

All aminoacids studied in this work are characterized by the positive values of the  $V_s$  in tetraalkylammonium bromide solutions, i.e. they are the structure-makers. The same result was previously obtained in the case of the KCl solutions /1/. However, the numerical value of the  $V_s$  for glycine and beta-alanine is now substantially dependent on the particular salt used as electrolyte in solution (cf. the Table 4.). A systematic increase in the value of  $V_s$  has been obtained going from the short-chain TMABr to long-chain TBABr (cf. Fig. 4). The values of  $V_s$  in the TMABr solutions are also significantly higher than in the KCl solutions ( $V_s(\text{glycine})=89.3$  and  $V_s(\text{betaalanine})=147.1$ , respectively). Therefore the zwitterionic aminoacid additions have enhanced structure-making volumes in the aqueous solutions of electrolytes with large organic cations probably due to some cooperative interaction between the charged aminoacid residues and these ions. It has to be mentioned that this effect was not observed for many electro-neutral organic solutes in various electrolyte aqueous solutions where they are characterized by a constant value of  $V_s$  independently of the electrolyte nature in solution /2/.

A substantial difference has been observed in this respect in the behaviour of the gamma-aminobutyric acid. Namely, it has a practically constant value of  $V_s$  in the solution of every tetraalkylammonium halide (cf. Fig. 4.). This difference in comparison with smaller aminoacids may be caused by the specific conformation of the gamma-aminobutyric acid in solution (e.g. cyclic structure, where the hydrogen bonding between the carboxylate and ammonium groups leads to much less zwitterionic charge distribution in this molecule). The corresponding theoretical quantum-chemical investigation of the aminoacid conformations in polar solvents is in progress by us and the results and discussion will be published elsewhere.

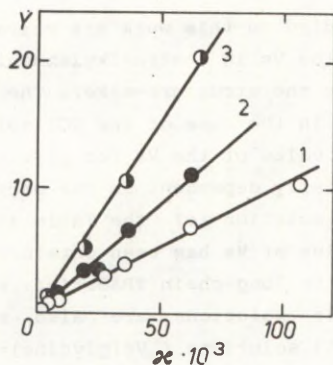


Fig. 1. The Relationship Between the Differential Conductivity of Various Aminoacids Y and the Equivalent Conductivity of the Aqueous Solutions of TMABr,  $\kappa$  at 25°C. (1 - Glycine; 2 - beta-Alanine; 3 - gamma-Aminobutyric Acid).

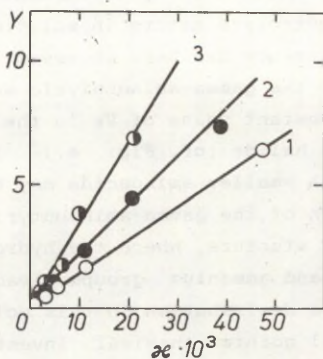


Fig. 2. The Relationship Between the Differential Conductivity of Various Aminoacids Y and the Equivalent Conductivity of the Aqueous Solutions of TEABr,  $\kappa$  at 25°C. (1 - Glycine; 2 - beta-Alanine; 3 - gamma-Aminobutyric Acid).

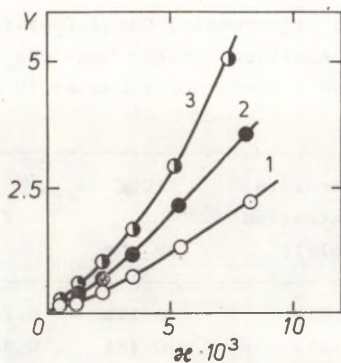


Fig. 3. The Relationship Between the Differential Conductivity of Various Aminoacids Y and the Equivalent Conductivity of the Aqueous Solutions of TBABr,  $\alpha$  at 25°C. (1 - Glycine; 2 - beta-Alanine; 3 - gamma-Aminobutyric Acid).

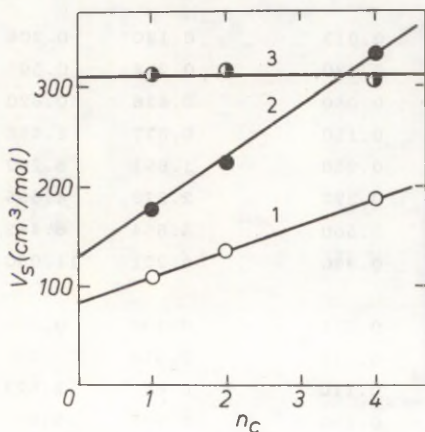


Fig. 4. The Relationship Between the Volume of Structure-Making,  $V_s$  of Various Aminoacids and the Number of Carbon Atoms in a Single Alkyl Chain of the Respective Tetraalkylammonium Bromide in Solution. (1 - Glycine; 2 - beta-Alanine; 3 - gamma-Aminobutyric Acid).

Table 1.

The Results of the Differential-Conductometric Measurements of the Aminoacid Addition Effect on the Electrical Conductivity of the TMABr Aqueous Solutions at 25 C.

No	Aminoacid	Electrolyte concentration (mol/l)	100% 1 cm ohm	Y	Vs
1.	Glycine	0.014	0.129	0.255	198
		0.051	0.434	0.810	187
		0.110	0.877	1.061	121
		0.250	1.832	2.274	124
		0.400	2.773	2.905	105
		0.540	3.559	3.911	109
		1.000	6.257	6.958	111
2.	beta-Alanine	0.013	0.120	0.206	172
		0.030	0.264	0.505	191
		0.050	0.426	0.820	193
		0.110	0.877	1.688	193
		0.260	1.891	3.262	172
		0.370	2.578	4.585	178
		0.550	3.664	6.442	176
0.996	6.201	11.050	177		
3.	gamma-Amino-butyrac acid	0.011	0.102	0.301	296
		0.048	0.410	1.251	306
		0.110	0.877	2.523	288
		0.250	1.825	5.056	277
		0.530	3.542	10.601	300
		1.050	6.550	20.404	311

Table 2.

The Results of the Differential-Conductometric Measurements of the Aminoacid Addition Effect on the Electrical Conductivity of the TEABr Aqueous Solutions at 25° C.

No	Aminoacid	Electrolyte concentration (mol/l)	100%		Vs
			1 cm ohm	Y	
1.	Glycine	0.012	0.091	0.119	131
		0.013	0.095	0.137	144
		0.032	0.221	0.290	136
		0.052	0.338	0.483	143
		0.100	0.590	0.845	143
		0.230	1.161	1.629	141
		0.650	2.722	3.640	134
2.	beta-Alanine	0.011	0.084	0.195	232
		0.020	0.145	0.340	234
		0.048	0.316	0.667	211
		0.080	0.489	1.088	223
		0.200	1.036	2.377	229
		0.460	2.025	4.446	220
		0.950	3.881	7.030	181
3.	gamma-Amino- butyric acid	0.010	0.077	0.265	345
		0.022	0.158	0.550	348
		0.042	0.281	0.952	339
		0.115	0.662	1.701	256
		0.190	0.997	3.458	347
		0.500	2.171	6.819	320

Table 3.

The Results of the Differential-Conductometric Measurements of the Aminoacid Addition Effect on the Electrical Conductivity of the TBABr Aqueous Solutions at 25°C.

No	Aminoacid	Electrolyte concentration (mol/l)	100% 1 cm ohm	Y	Vs
1.	Glycine	0.008	0.048	0.072	149
		0.022	0.114	0.176	154
		0.052	0.222	0.428	193
		0.100	0.348	0.749	215
		0.220	0.541	1.363	251
		0.530	0.813	2.288	281
		1.050	1.581	2.089	132
2.	beta-Alanine	0.011	0.063	0.135	213
		0.026	0.130	0.353	270
		0.053	0.225	0.685	304
		0.100	0.348	1.221	351
		0.210	0.529	2.147	406
		0.520	0.805	3.572	443
		1.100	1.703	3.409	201
3.	gamma-Amino-butyrlic acid	0.010	0.058	0.199	342
		0.026	0.130	0.528	405
		0.053	0.225	0.998	443
		0.100	0.348	1.679	483
		0.200	0.516	2.922	566
		0.440	0.740	5.040	681
		1.040	1.565	5.386	345

Table 4.

The Results of the Statistical Estimation of Structure-Formation Volume,  $V_s$  by the Least-Squares Treatment of the Experimental Data.

No Aminoacid	Salt Eq.No.	ao	$V_s$	$a'$	1 r	2 s	3 so
1. Glycine	TMABr (3)	17.5	106.9	-	0.9981	15.7	0.028
		9.0	3.0				
	TEABr (3)	2.2	133.8	-	0.9997	3.5	0.011
		1.7	1.5				
	4 TBABr (3)	-17.2	292.7	-	0.9956	8.9	0.047
		6.0	13.8				
(4)	-4.1	188.7	121	0.9998	2.4	0.013	
	2.4	14.7	17				
2. beta-Ala- nine	TMABr (3)	2.8	176.8	-	0.9998	7.6	0.008
		3.8	1.4				
	4 TEABr (3)	1.4	220.5	-	0.9997	4.8	0.013
		2.8	2.9				
	4 TBABr (3)	-28.7	468.3	-	0.9971	11.0	0.037
		7.7	17.7				
(4)	-10.8	334.8	154	0.9997	4.3	0.015	
	4.8	28.8	32				
3. gamma-Ami- nobutyric acid	TMABr (3)	-22.2	311.6	-	0.9994	29.2	0.017
		16.7	5.3				

1	2	3	4	5	6	7	8	9	10
		TEABr	(3)	0.7	315.3	-	0.9959	25.2	0.045
				14.7	14.4				
			4						
		TBABr	(3)	-47.0	703.3	-	0.9901	28.6	0.070
				20.4	50.0				
			(4)	3.1	303.2	504	0.9999	2.8	0.007
				3.2	20.3	25			

1

The correlation coefficient.

2

The standard deviation.

3

The normalized standard deviation (so =  $s / \sigma$ , where  $\sigma$  is the dispersion of the experimental data.

4

The point of highest concentration is eliminated.

#### References.

1. H. Kuura and M.M. Karelson, This journal, 24, 332 (1987).
2. M.M. Karelson, This journal, 14, 74 (1977).
3. U.L. Haldna and V.A. Palm, Dokl. AN USSR, 135, 667 (1960).
4. M. Min, personal communication.
5. H. Kuura and M.M. Karelson, This journal, 20, 397 (1983).
6. D.G. Oakenfull and D.E. Fenwick, Aust. J. Chem., 26, 2649 (1973).
7. W.J.M. Heuvelsland, C. DeVisser and G. Somsen, J. Phys. Chem., 82, 29 (1978).
8. M.M. Karelson, This journal, 21, 160 (1984).

## C O N T E N T S

U.H. M ö l d e r, I.A. K o p p e l, R.J. P i k v e r, and J.J. T a p f e r, Photoelectron Spectra of Molecules. 10. Amides. . . . .	255
I.A. K o p p e l, J.B. K o p p e l, A.O. K ö r g e s a a r, and V.O. P i h l, Acidity of Some Substituted Bicyclo [2.2.2] Octane-1-, Bicyclo [2.2.2] oct-2-ene-1-, and Cubane-1- Carboxylic Acids in DMSO. . . . .	272
A.F. P o p o v, A.E. S h u m e i k o, A.A. A f o n k i n, and Zh.P. P i s k u n o v a, Kinetics of Hexachlorocyclophosphazotriene Phenolysis Under Conditions of Interphase Transfer. . . . .	302
A.E. P o p o v, A.E. S h u m e i k o, A.A. A f o n k i n, and Zh.P. P i s k u n o v a, Mechanism of Interphase-Catalyzed Phenolysis of Hexachlorocyclophosphazotriene . . . . .	313
J.K. K i h o and A.N. J a l a s, Retrieval System of "Cis-TARTU" Data Bank . . . . .	322
V.A. S u b b o t i n, V.N. B a b u s h k i n, A.V. I v a n o v, and S.S. G i t i s, Substituent Effect on Chemical Shifts of Aromatic Protons in Sulfur-Containing Diphenyl Systems. . . . .	330
L.P. D r i z h d, E.N. K r y u c h k o v a, L.I. B o n d a r e n k o, and V.A. S a v y o l o v a, Reactions of Imido Acid Derivatives with Nucleophilic Reagents . Activation Parameters of $S_N1$ and $S_N2$ Processes with N-Substituted Benzimidoyl Chlorides . . . . .	337
L.P. D r i z h d, N.A. T a r a n, V.A. S a v y o l o v a, and A.G. G e r s h i k o v, Reactions of Imido Acid Derivatives with Nucleophilic Reagents. Selec -	

- tivity of Molecular and Ionic Forms of Imidoyl Chlorides in Reactions with Amides in Acetonitrile 351  
 M. E l l e r, J. J ä r v, and P. P a l u m a, Influence of Non-Radioactive Ligands on Kinetics of N-Methyl- $^{3}\text{H}$  Scopolamine Binding to Muscarinic Receptor 372  
 H. K u u r a and M. K a r e l s o n, Aminoacid Addition Effects on the Structure of Tetraalkylammonium Halide Aqueous Solutions 387

РЕАКЦИОННАЯ СПОСОБНОСТЬ ОРГАНИЧЕСКИХ СОЕДИНЕНИЙ.  
 Том. XXV. Вып. 3(91)-4(92). Сентябрь-декабрь 1988.  
 На английском языке.  
 Тартуский государственный университет.  
 ЭССР, 202400, г.Тарту, ул.Вликооли, 18.  
 Vastutav toimetaja V. Palm.  
 Paljundamisele antud 12.04.1989.  
 Formaats 60x84/16.  
 Kirjutuspaber.  
 Masinakiri. Rotaprint.  
 Tingtrükipoognaid 8,60.  
 Arvestuspooignaid 8,29. Trükipoognaid 9,25.  
 Trükiarv 350.  
 Tell. nr. 318.  
 Hind rubl. 1.70.  
 TRÜ trükikoda. ENSV 202400 Tartu, Tiigi t. 78.