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DEVELOPMENT OF BISPIDINE-DERIVED ARTIFICIAL RECEPTORS FOR ORGANIC MOLECULES

Master thesis in organic chemistry

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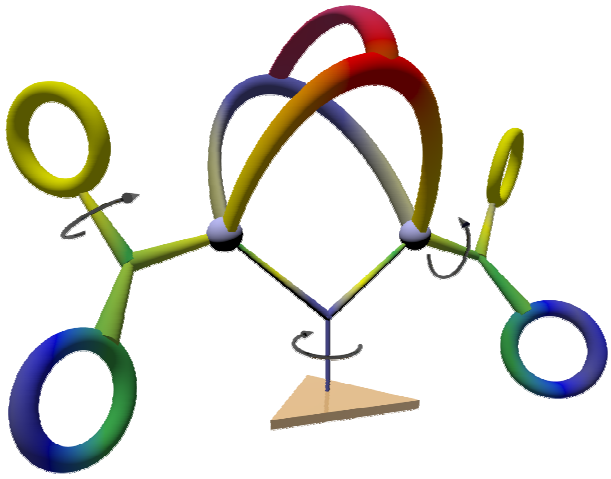

TARTU 2005

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LIST OF ABBREVIATIONS

Δ	–	Heating
AM1	–	Austin Model 1
Boc	–	*t*-Butyloxycarbonyl
Cbz	–	Benzyloxycarbonyl
DEPT	–	Distortionless Enhancement by Polarization Transfer
DMSO	–	Dimethyl sulphoxide
EXSY	–	Exchange Spectroscopy
gHMBC	–	Gradient enhanced Heteronuclear Multiple Bond Correlation
gHSQC	–	Gradient enhanced Heteronuclear Single Quantum Coherence
gNOESY	–	Gradient assisted Nuclear Overhauser Effect Spectroscopy
HETJSD	–	Selective Heteronuclear J-spectrum with DEPT Polarization Transfer for Sensitivity Enhancement
HSBC	–	Heteronuclear Single-Quantum Multiple-Bond Experiment
IR	–	Infrared
k_{obs}	–	Observed rate constant
MAS	–	Magic-Angle Spinning
MS	–	Mass Spectroscopy
NMR	–	Nuclear Magnetic Resonance
NOE	–	Nuclear Overhauser Effect
ORTEP	–	Oak Ridge Thermal Ellipsoid Plot
PM3	–	Parameterised Model 3
R_f	–	Retention Factor
r.t.	–	Room Temperature (*ca*. +20 °C)
TEA	–	Triethylamine
THF	–	Tetrahydrofurane
TLC	–	Thin Layer Chromatography
t_m	–	Melting Point
TOCSY	–	Total Correlation Spectroscopy
UV-VIS	–	Ultraviolet-visible

1. INTRODUCTION

We have been working on the development of host-guest systems for small organic molecules with the aim to bind these molecules to a host using a metal ion. Ultimately, we want to access structural information of the guest molecule, and to expand the variety of host and guest structures.

In the current investigation we describe the synthesis and characterisation of 3,7-diazabicyclo[3.3.1]nonane (bispidine) derivatives, which contain a rigid molecular scaffold. They provide an appropriate arrangement of two nitrogen atoms for chelating a Lewis acid centre that in turn mediates the binding of small guest molecules.

The structure and dynamic behaviour of the host-guest complex is then determined by NMR spectroscopy. Valuable information is also obtained from X-ray crystallography and pK_a measurements.

Appendixes included in this thesis

I. Gogoll, A., Toom, L., Grennberg, H. Ligand-Induced Formation of an Adamantanoid Hexanuclear (π-Allyl)Pd(II)-(μ_3-Hydroxo) Cluster Stacked as Hydrogen-bonded Double-Strands. *Angew. Chem., Int. Ed.*, **2005**, Accepted.

II. Gogoll, A., Toom, L., Grennberg, H. *N*,*N*'-Dibenzhydrylbispidine as a host candidate for (π-allyl)palladium complexes – synthesis, structure and behaviour as a sterically demanding base. *Experimental description*.

III. Toom, L., Kütt, A., Kaljurand, I., Leito I., Grennberg, H., Gogoll, A. Studies on substituted 3,7-diazabicyclo[3.3.1]nonanes. *Experimental description*.

2. LITERATURE SURVEY

2.1. "TOOLS" IN THE CONTEXT OF SUPRAMOLECULAR CHEMISTRY

Supramolecular chemistry is a very wide highly interdisciplinary field and may be shortly described as "chemistry beyond the molecule", bearing on the organised entities of higher complexity that result from the association of two or more chemical species held together by non-covalent intermolecular forces. Supramolecular assemblies involve spontaneous secondary interactions such as hydrogen bonding, dipole-dipole, charge transfer, van der Waals, and π–π stacking interactions. The partners of a supramolecular species have been named molecular receptor (or host) and substrate (or guest).[1,2]

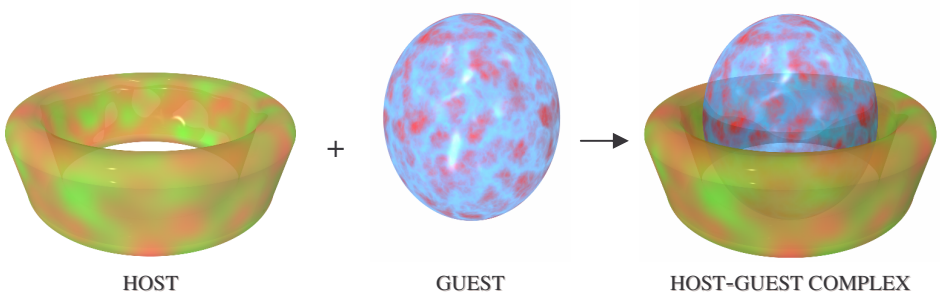


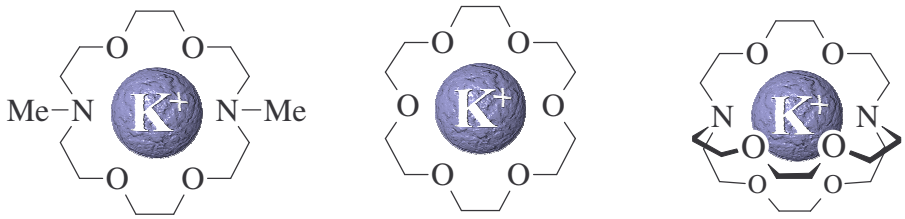
Figure 1. A schematic representation of a host-guest system

The scope of the binding species can reach from small molecules (*e.g.* primary amines) to very large and complicated macromolecules (*e.g.* enzymes). Binding of a substrate to its receptor involves a selective molecular recognition process, so both components should have proper complementary binding sites. Molecular interactions form the basis of the highly specific recognition, reaction, transport, and regulation processes that occur in biochemistry such as substrate binding to a receptor protein, enzymatic reactions, assembling of protein-protein complexes, immunological antigen-antibody association, intermolecular reading, translation and transcription of the genetic code, signal inductions by neurotransmitters, cellular recognition, etc. The molecular receptor may be considered as a tool that is used to perform certain operations with the substrate. Knowing how the two parts of the complex are structurally positioned can be very useful for understanding the binding process and for later design of improved binders.[1]

2.2. SYNTHETIC RECEPTORS

The area of host-guest chemistry is virtually unlimited – host molecules can be guests for other kinds of hosts, etc. Biological receptors are big, flexible and dynamic mole-

cules, adapting often a very different geometry when binding a substrate. Such dynamic behaviour is difficult to predict and control, making the study of the complexation processes difficult. The design of smaller and more easily investigable artificial binding systems is not limited to mimicking the nature's binders. There is a large number of synthetic substances that can be considered as a host in artificial host-guest systems, *e.g.* bidentate ligands (chapter 2.3), macrocyclic compounds (crowns, cryptands, cyclodextrins),[3,4] molecular tweezers (Figure 3).[5] For instance, macrocyclic ligands 18-crown-6 (**1** and **2**) and cryptand[2.2.2] (**3**) have cavities, which can bind a K^+-cation (Figure 2) with different stability constants. In the case of the cryptate, there are more donor atoms and also the compensation by the entropy factor ΔS is much bigger, and the complex is more stable:[6,7]



	K^+·**1**	K^+·**2**	K^+·**3**
$\log K_{stab.}$	4.10	6.07	10.49

Figure 2. Crown ethers 1,10-$(MeN)_2$-18-crown-6 **(1)** and 18-crown-6 **(2),** and cryptand[2.2.2] **(3)** complexed with a K^+ ion, stability constants ($\log K_{stab.}$) in methanol at 298 K.[7]

Molecular tweezers can selectively bind electron deficient aromatic and aliphatic substrates as well as organic cations, whereas electron rich neutral and anionic substrates are not bound by them.[8]

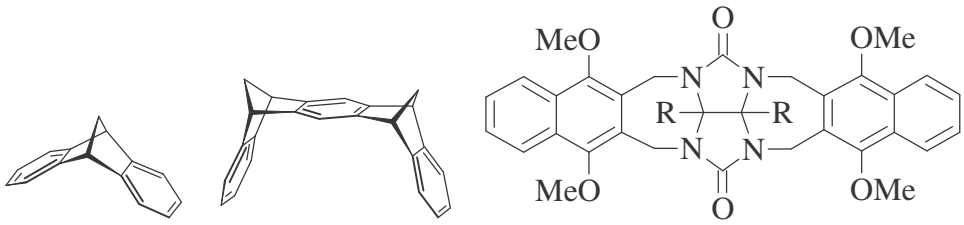


Figure 3. Molecular tweezers

The bidentate amines are the host ligands studied in this work.

2.3. BIDENTATE DINITROGEN "TOOLS" FOR TRANSITION METAL COMPLEXES

2.3.1. GENERAL BACKGROUND

Bonding occurs when a ligand donates electrons to a metal. When a metal ion donates electrons back to the ligand, this is called back-bonding. More effective back-bonding

takes place between electron-rich transition metals with low oxidation states and ligands having nonbonding orbitals (*e.g.* P that has empty *d*-orbitals). The combination of bonding and back-bonding creates a stronger bond between the ligand and the metal. Therefore ligands containing phosphorous (*e.g.* $Ph_2P(CH_2)_2PPh_2$, dppe, Figure 5) can form more stable complexes with transition metals with low oxidation states [*e.g.* Pd(0)].[9]

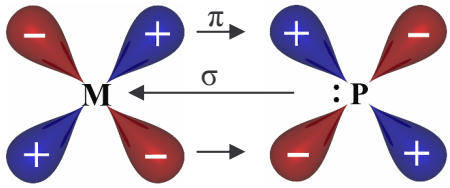
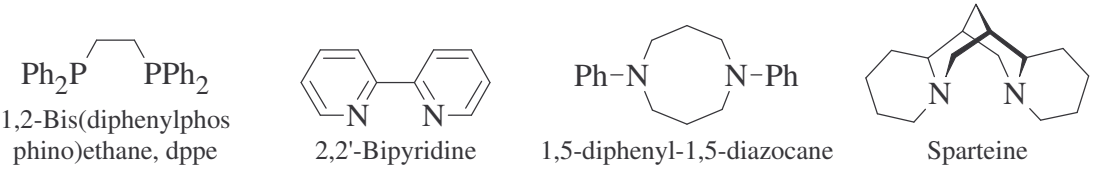


Figure 4. Back-bonding from a metal having electrons in its *d*-orbitals to phosphorus having empty *d*-orbitals

Ligands containing nitrogen as the donor atom have proved to be highly useful since such ligands are often effective in metal catalysis involving metals with higher oxidation states (*e.g.* Pd(II)), relatively stable (although they do not provide extra stabilisation by back-bonding), and easier to synthesise than the corresponding phosphorus ligands.[10]

A variety of ligands have been used, including diatomic ligands (CO, NO, CN^-), ligands containing linear or cyclic π-electron-systems (ethylene, butadiene, allyl, cyclopentadienyl, benzene), alkyl and acyl ligands, amines, phosphites and phosphanes. It has been known that the complexes resulting from coordination with chelating ligands (*e.g.* bidentate ligands that have two points of attachment to the metal ion centre and occupy two coordination sites) are much less flexible than complexes with the corresponding monodentate ligands. Flexibility is unfavourable when structural characterisation is the purpose of the complexation, as it can give rise to conformationally averaged parameters (*e.g.* nuclear Overhauser effects and vicinal coupling constants).



1,2-Bis(diphenylphosphino)ethane, dppe — 2,2'-Bipyridine — 1,5-diphenyl-1,5-diazocane — Sparteine

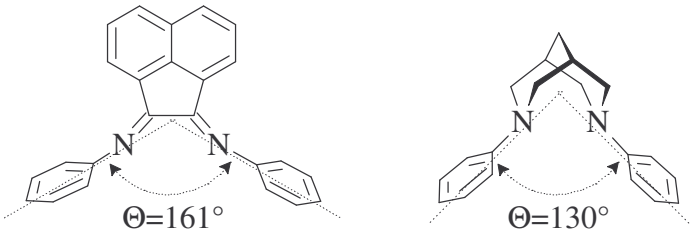
Figure 5. Examples of bidentate ligands

Important factors for bidentate host ligands are the flexibility of the structure, the size of the binding site and the interactions with the neighbouring substituents. The connecting

bridge between the binding sites plays a dominant role in the performance of the complexation. For instance, in the case of 2,2'-bipyridine versus 1,10-phenanthrolines, the possible free rotation about the C–C single bond for 2,2'-bipyridine is completely prohibited for 1,10-phenanthrolines (Figure 6).

Figure 6. 2,2'-Bipyridine and 1,10-phenanthroline ligands

Steric requirements for the guest ligand are at least as important as electronic effects and in terms of the stability of complexes can even be dominant. Steric repulsion between the complexed host and guest ligands diminishes strength of interaction, as two molecules cannot occupy the same space. An effective measure of the steric demands of a ligand is the ligand's cone angle θ, which indicates the approximate amount of space that the ligand occupies around the metal (Figure 7).



Bis(phenylimino)acenaphthene **4**

N,*N*'-Diphenylbispidine **5**

Figure 7. Cone angles θ between the phenyl rings calculated by using the semi-empirical method PM3 in Spartan 4.1.1.[11]

For **4**, the angle between the phenyl rings is too large, *i.e.* they are pushed too far from the binding centre to give rise to desirable steric interactions and other effects.

In 1990 Pregosin and co-workers came up with the reporter ligand concept in order to elucidate structural features of (π-allyl)palladium complexes. Reporter ligands possessed individual protons (or CH_3 groups) able to "see" across the metal (via NOEs, Figure 8) to the π-allyl moiety. They were using bidentate dinitrogen ligands of bipyridine and phenathroline type.[12]

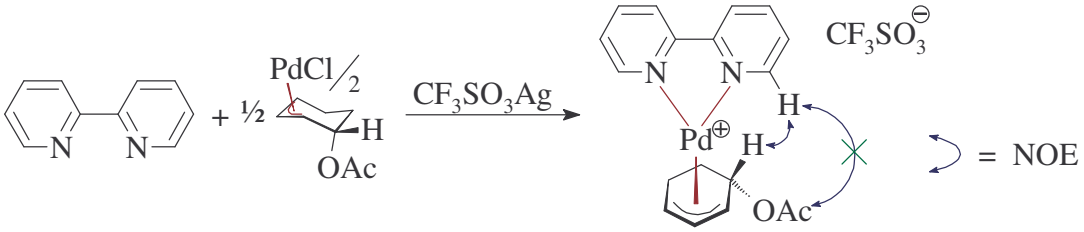


Figure 8. (4-Acetoxy-1,3-η^3-cyclohexenyl)palladium-2,2'-bipyridine complex

2.3.2. PREVIOUS WORK WITH SUBSTITUTED BISPIDINONE AND BISPIDINE TOOLS

Sometimes it is just enough to have small structural elements (*e.g.* individual H atoms or CH_3 groups) of that ligand to point towards the guest ligand, but for a better reporter ligand, larger steric interactions are required. Having phenyl groups as a source for these strong steric interactions, can give us more functional reporter ligands, which may also be used as chemical shift reagents for simplifying NMR spectra in case of overlapping signals. When an aromatic system is placed in an external magnetic field, B_0, there will be an induced magnetic field generated by the π-electron circulation called ring current. The effect on the NMR chemical shifts of the atoms positioned close to the aromatic system depends on the angle and distance (Figure 9).

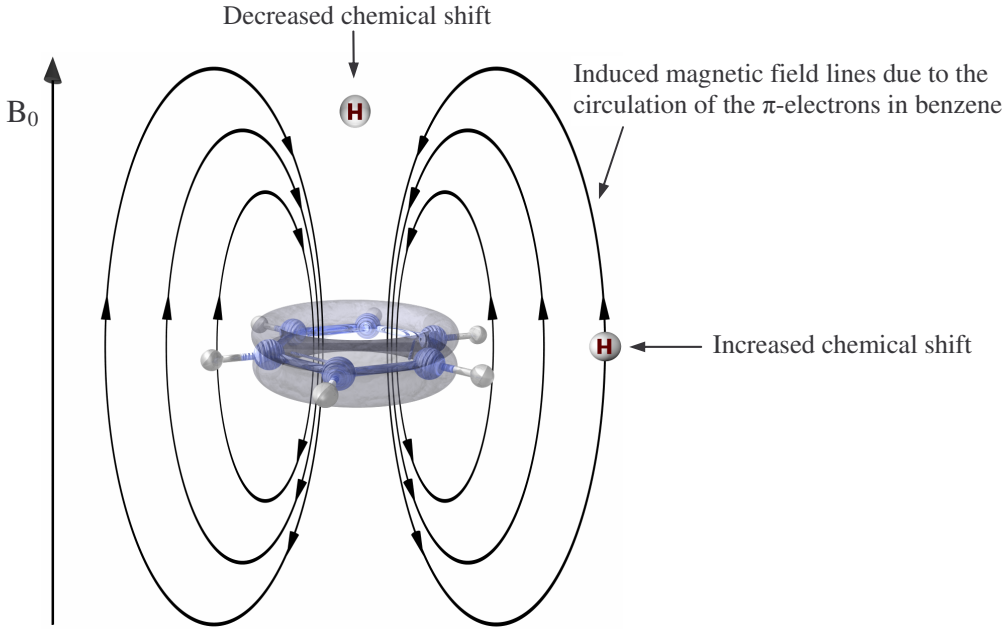


Figure 9. Anisotropic shielding effect of an aromatic ring. B_0 = External magnetic field[13]

The initially used reporter ligand, 2,2'-bipyridine is a flat structure and does not have a great influence on the guest ligand (Figure 10). Weak steric interligand interactions give small number of NOEs, therefore bipyridines are not good enough to be versatile reporter ligands.[12,14]

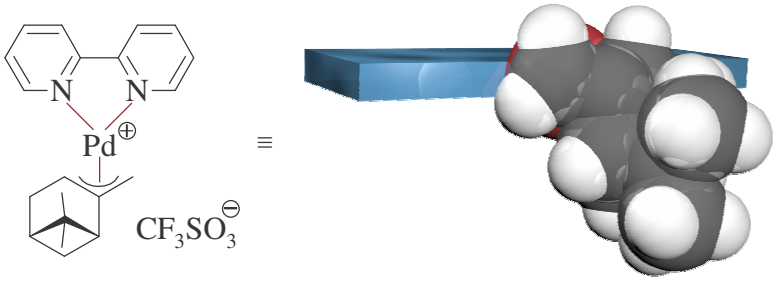


Figure 10. *β*-Pinene allyl palladium(II) complex with 2,2'-bipyridine

Bipyridine ligands with larger substituents forced the Pd atom out from the bidentate coordination plane, and again, the effect on the guest was not sufficient.[15] Therefore a different kind of bidentate ligands were introduced: bispidines and bispidinones.[16]

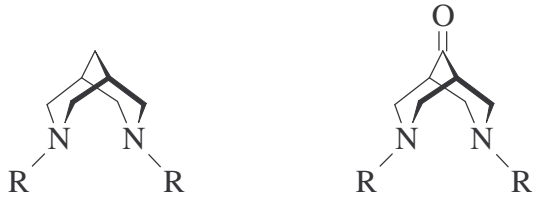
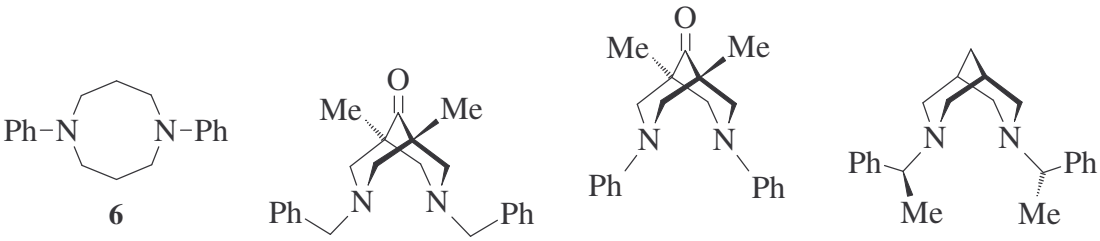


Figure 11. The 3,7-diazabicyclo[3.3.1]nonane is the skeleton of bispidines and bispidinones

Structures having a bispidine skeleton are interesting in several aspects. The cavity between the nitrogen atoms has a limited size and is shielded from sides (Figure 13), and the two sp^3 hybridised nitrogen atoms are well positioned in the bicyclic structure for chelation to a Lewis acid centre (*e.g.* a metal ion). A metal ion coordination gives a well-defined complex structure, resembling the rigid adamantane (tricyclo[3.3.1.$1^{3,7}$]decane) molecule. During the process of improving reporter ligands, some bidentate cyclic diamines were prepared and studied by A. Axén et al:[16]



6
Anisotropy and steric effects; flexibile

7
No effects

8
Anisotropy and steric effects

9
Steric effects, chiral

Figure 12. Structures for reporter ligands and their interaction effecs with a (π-allyl)palladium ligand[16]

All these derivatives were *N*,*N*'-disubstituted dinitrogen ligands, where the nitrogen atoms were intended to coordinate to the metal, while the aromatic substituents were ex-

pected to give the desired close steric interactions and to induce chemical shift changes due to anisotropic effects. All these ligands formed stable complexes with (π-allyl)-palladium. For example, a *β*-pinene allyl palladium(II) complex was formed with 3,7-diphenyl-1,5-dimethylbispidinone (**8**), and large NMR chemical shift effects were obtained for the protons closest to the aromatic rings.[16]

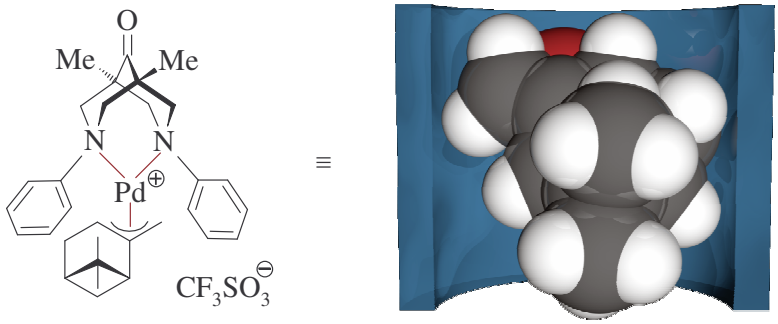


Figure 13. *β*-Pinene allyl palladium(II) complex with a bispidine derivative **8**

N,*N*'-diphenyldiazacyclooctane (**6**) showed more dynamic processes at all accessible temperatures than the other ligands. It had higher conformational flexibility of the carbon chain backbone, since it has missing the bridge present in bispidinones. Otherwise, phenyl substituents had stronger steric interactions with the π-allyl part than benzylic substituents. It was showed with (π-allyl)palladium complexes, where a bispidine ligand with strong steric effects was used, that it was possible to lock the guest ligand of interest in one single conformer. The bispidine ligand hindered the rotation around C–C single bonds and thereby locked the substrate into one conformer (Figure 14).[17]

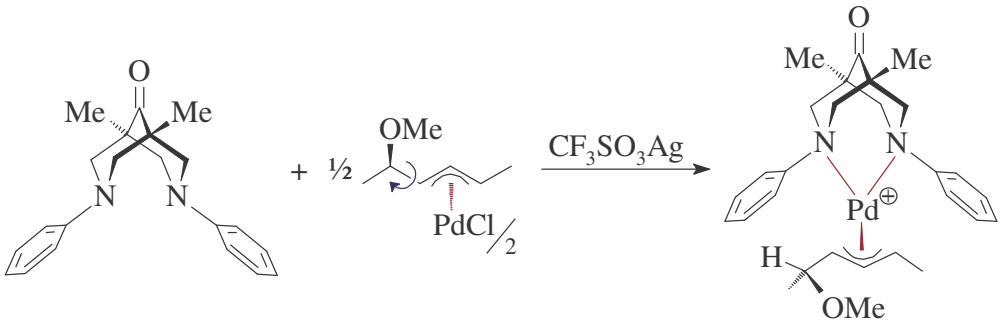


Figure 14. A (π-allyl)palladium complex with hindered rotation about a C–C bond

The concept of reporter ligands has also been used with a chiral host ligand, which gives the possibility of forming diastereomeric complexes or complexes only with certain enantiomers (Figure 15). Interligand NOEs allowed the absolute stereochemistry of the (π-allyl)palladium complex to be quickly and unambiguously determined.[18]

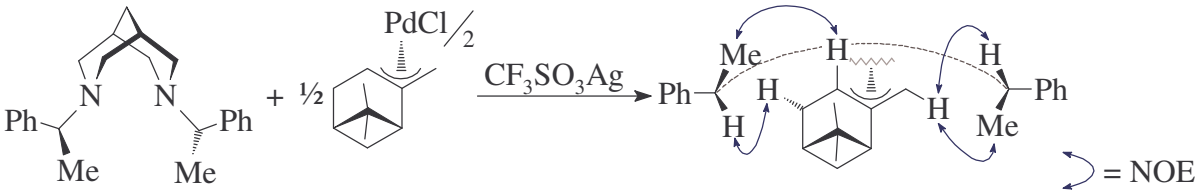


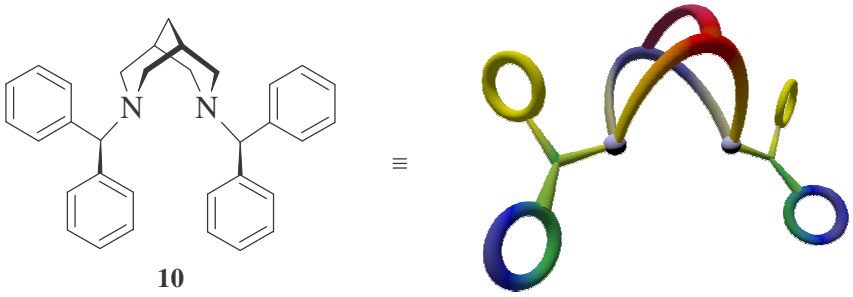
Figure 15. A complex between *β*-pinene allyl palladium(II) and *S*,*S*-3,7-diphenethylbispidine **9**

Bispidinone derivatives were found to have different complex formation abilities compared to bispidines. Also, relatively poor stability of some palladium complexes with bispidinones was observed. This effect was attributed to through-σ bond interactions (in principle an inductive effect) from the carbonyl group at C-9 position to the nitrogen atoms.[19,20]

Bispidine is a quite limited host ligand due to the sp^3 hybridised nitrogen atoms, because they do not possess sufficient π-accepting capability to be able to stabilise complexes. So far Pd(II) has been mainly used as the mediating metal ion and π-allylic compounds have been studied as the suitable guest ligands with the help of bispidine-type hosts. We are not so interested in using a large variety of metals in these complexes, but different metal ions can help to bind different kind of guest molecules more stably to the host molecule. For example, a small number of platinum[19] and nickel[21] η^2-alkene and η^2-alkyne complexes have been prepared and studied in more detail.

2.4. AIMS AND OUTLINE OF THIS THESIS

The previously reported *N*,*N*'-diphenylbispidinone derivatives were found to have the strongest steric interactions with the (π-allyl)palladium ligands compared to the *N*,*N*'-dibenzyl- and *N*,*N*'-diphenethylbispidine derivatives. The reason for this difference was that the phenyl group was the largest substituent and was rotated away from the guest. The first goal of the present project was to synthesise and study a bispidine derivative having large benzhydryl substituents (Figure 16).



10

Figure 16. *N*,*N*'-Dibenzhydrylbispidine (**10**)

It was expected to provide a larger extended cavity compared to the *N*,*N*'-diphenyl analogue, but still with strong steric interactions, because at least one of the phenyl rings had to stay close to the guest ligand and to the metal coordination plane. The benzylic CH proton would serve as usable sensor for the guest, with a ^{1}H NMR chemical shift at the region (4-6 ppm), where not so many other signals would be. The ligand would also have a high degree of symmetry to produce a reasonably simple ^{1}H NMR spectra – a necessary requirement to be useful as a reporter ligand.

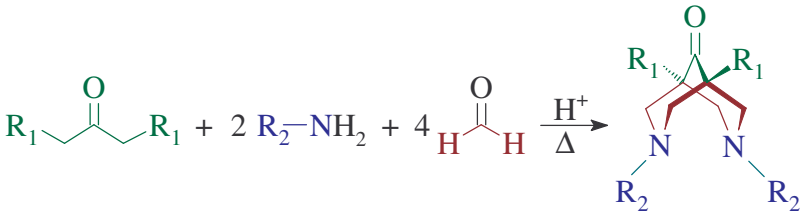
The synthesis and characterisation of a (π-allyl)palladium complex is described.

3. SYNTHESIS OF SUBSTITUTED BISPIDINES AND BISPIDINONES

This topic is about the synthesis of well-known class of compounds, but the available methods to synthesise these need still improvements.

3.1. SYNTHESIS OF BISPIDINONES (LITERATURE REVIEW)

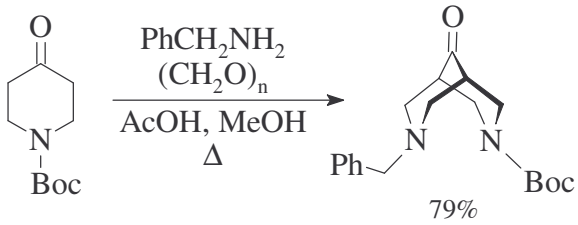
There are numerous methods which have been reported for the synthesis of the 3,7-diazabicyclo[3.3.1]nonane system. The most commonly used route to prepare bispidinone derivatives is via a double Mannich reaction (Scheme 1):



Scheme 1. Synthesis of substituted bispidinones by Mannich reaction

A ketone having acidic α-hydrogens, primary amine and an aldehyde are reacted in acidic conditions. The reaction goes better with ketones having more acidic α-hydrogens. The used aldehyde is usually formaldehyde (paraformaldehyde serves as a convenient source of formaldehyde), but there are examples of other aldehydes.

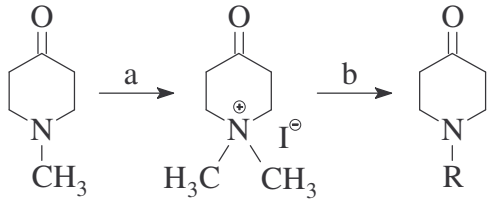
Asymmetric bispidinones can be easily synthesised also by the Mannich reaction, but starting from a *N*-substituted 4-piperidinone:



Scheme 2. Synthesis of asymmetric bispidinones by the Mannich reaction starting from a piperidinone[22]

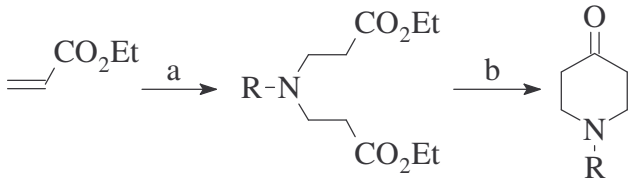
The piperidinone route is also superior if the acyclic ketone is not reactive enough. For example, the synthesis of various *N*,*N*'-dialkylbispidinones was reported in 1968 by Douglass and Ratliff[23] who utilised a double-Mannich condensation of *N*-methylpiperidin-4-one with methylamine and formaldehyde to give *N*,*N*'-dimethylbispidinone.

N-substituted piperidin-4-ones can be synthesied easyly from *N*-methyl-4-piperidinone methiodide:[24]



Scheme 3. a) MeI, Et_2O, Δ, 91%; b) R-NH_2, K_2CO_3, EtOH/H_2O (1:1), Δ

or alternatively, by using the Michael addition of ethyl acrylate on an amine in the presence of acid, cyclisation by the Dieckmann condensation using a base, followed by acidic hydrolysis and decarboxylation of the condensation product.[25]

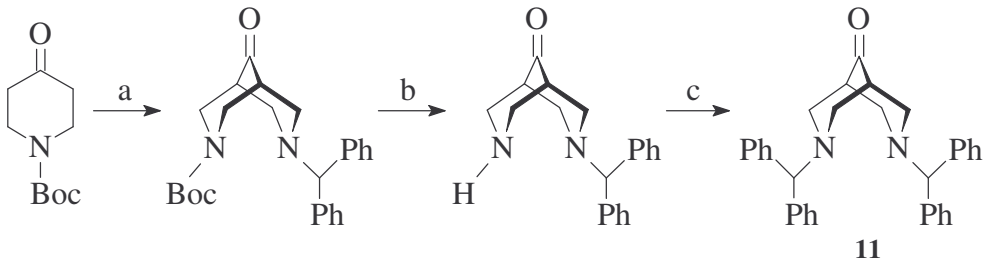


Scheme 4. a) R-NH_2, AcOH, Δ; b) NaOEt, $PhCH_3$, Δ; 6M HCl, Δ

The advantages of the Mannich method are: a) the yields vary from very good in many cases to low (from over 90% down to less than 10%) and it is easy to scale up; b) the length of the straightforward reaction sequence is very short, if the substrates are available; c) there are good possibilities to vary the substituents at all positions of the bispidinone skeleton just by using different substrates. The disadvantages: a) gives always a carbonyl group at the position nine; b) syntheses of smaller bispidinone derivatives (*e.g*. *N*,*N*'-dimethylbispidinone) has very low yields (even less than 10%); c) instability of the product sometimes or difficulties on purification due to possible formation of many by-products; d) very acid- and temperature labile substrates can not be used.

3.2. SYNTHESIS OF NEW BISPIDINONES

In the present work, a novel bispidinone derivative **11** was synthesised. This case a longer reaction sequence than generally necessary for the synthesis of symmetric bispidinone derivatives, was developed. The reason for this was purely pragmatic – the corresponding benzhydrylpiperidinone was not available and the synthesis of a very similar bispidinone derivative, starting from Boc-piperidinone, was already[22] well established:



Scheme 5. a) Ph_2CHNH_2, $(CH_2O)_n$, AcOH, MeOH, Δ, 62%; b) $ZnBr_2$, CH_2Cl_2, 84%; c) Ph_2CHBr, KOH, K_2CO_3, Bu_4NBr, CH_2Cl_2/H_2O, 97%.

The formation of the by-products in the first step was greatly reduced when a modification in the procedure was made. Namely, a suspension of paraformaldehyde was added to the reaction mixture not in the contrary order as reported. This kept the concentration of the formaldehyde low and prevented over-alkylation of the already formed product in the reaction mixture. The same modification of the procedure was used for the synthesis of other bispidinones as well.

There were unexpected difficulties in the second step with the *t*-butyloxycarbonyl protecting (Boc) group cleavage with the common CF_3COOH in CH_2Cl_2 method. The reaction resulted in decomposition even at short reaction time. However, the same deprotection method worked well for the analogous benzyl bispidinone derivative. Anhydrous $ZnBr_2$ in CH_2Cl_2 was a convenient reagent for removal of the Boc group from the secondary amine.[26]

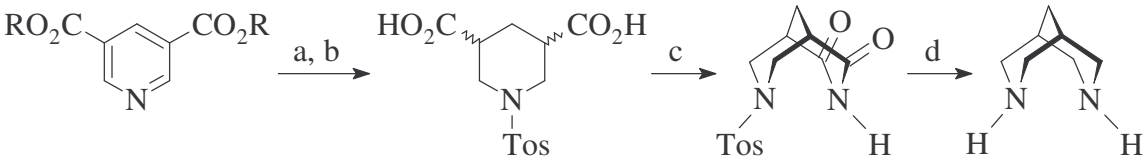
The phase-transfer catalytic *N*-alkylation with benzhydryl bromide in the last step worked very nicely, although long reaction time was used.

3.3. SYNTHESIS OF BISPIDINES (LITERATURE REVIEW)

As the bispidinone derivatives are known to have different or even unfavourable properties relative to the corresponding bispidines (see Chapter 2.3.2), we need to synthesise bispidines instead of bispidinones. However, the synthesis of bispidines is often more difficulty than the synthesis of bispidinones.

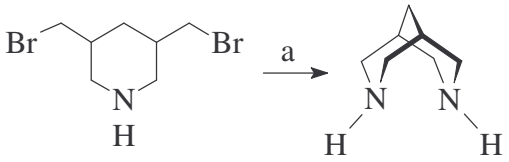
The main drawback of the Mannich reaction described above for the synthesis of compounds having the bispidine skeleton is that it gives a carbonyl group at position nine, which is relatively difficult to reduce afterwards. The existing methods for the synthesis of bispidine are often impractical, because many cumbersome steps are involved, long reaction times are required or low yields are obtained.

Since 1950s when several competing research groups developed several synthetic routes for bispidine using pyridine-3,5-dicarboxylic acid (dinicotinic acid) as common starting material, many *N*-alkyl derivatives of bispidine have been synthesised. Pyridine-3,5-dicarboxylic acid originally used is expensive and tedious to prepare. Synthesis of bispidine by Stetter *et al.*[27] involved imide formation and reduction:



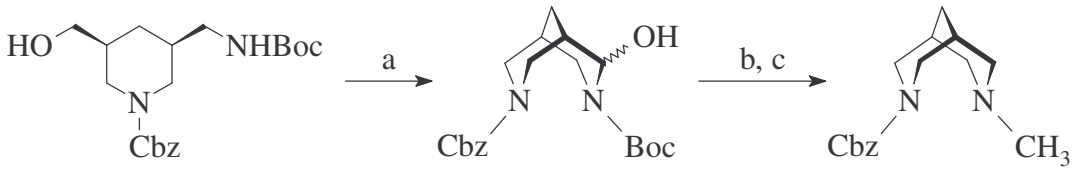
Scheme 6. a) Pt_2O, H_2, 77%; b) NaOH, TosCl; c) NH_3, Δ; d) $LiAlH_4$, THF; yield not given

Similar older methods for the synthesis of bispidines involved also a stepwise synthesis over a 3,5-substituted piperidines. Disadvantage of this approach is that the *cis*-positioning at the 3 and 5 positions are needed in order the final cyclisation to occur.



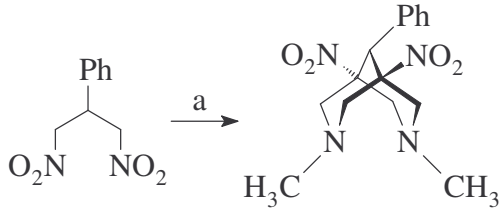
Scheme 7. a) NH_3, Δ; isolated as a salt, yield not given[28]

Otherwise, this method can be readily used for the synthesis of asymmetrically substituted bispidines:



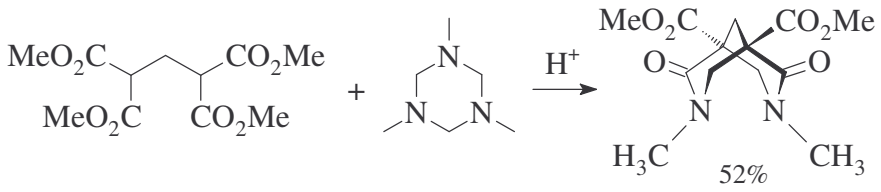
Scheme 8. a) $(COCl)_2$, DMSO, CH_2Cl_2, 90%; b) TFA, then aq. NaOH, 85%;
c) $NaBH_3CN$, $(CH_2O)_n$, THF, 71%[29]

A nice example of a Mannich reaction analogue, where a 1,3-dinitropropane derivative was used as a substrate was recently reported by Yunusov et al (Scheme 9). However, this method can be used for the synthesis of very specifically substituted bispidines.



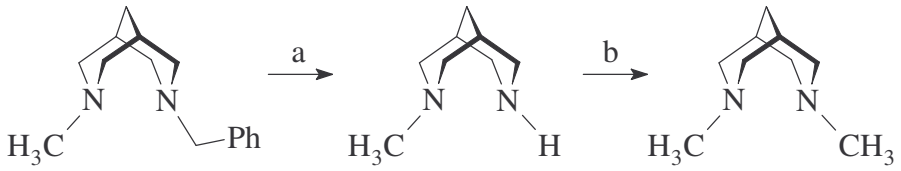
Scheme 9. a) 32% HCHO in H_2O, CH_3NH_2, $CHCl_3$-EtOH 5:1, r.t., 83%[30]

Another route for the preparation of the bispidine skeleton was proposed by C.J. Welch[31] (Scheme 10). The preparation of such dilactams seemed to be limited to *N*-methylamine as the amine, and the derivative obtained with the amine could not be reduced to the corresponding bispidine derivative.[19]



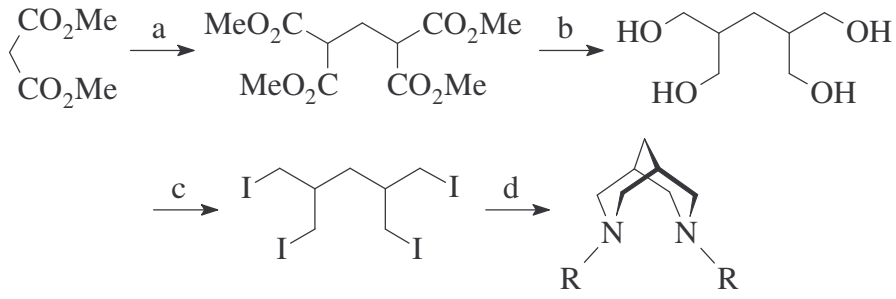
Scheme 10. Synthesis of 3,7-diazabicyclo[3.3.1]nonane-2,6-diones by C.J. Welch[31]

Sometimes it is easier to prepare bispidines by using a substituent replacement method. For example the preparation of *N*,*N*'-dimethylbispidine (which other synthetic methods have given very poor yields) by replacing the benzyl group:



Scheme 11. a) 10% Pd/C, CH_3COOH, H_2, 97%; b) CH_3Li, THF, -10 °C, CH_3I, 100%[32]

A more direct alternative synthesis of bispidines, but does not afford as many modifications as the Mannich reaction route, is the route starting from malonic ester:[33]

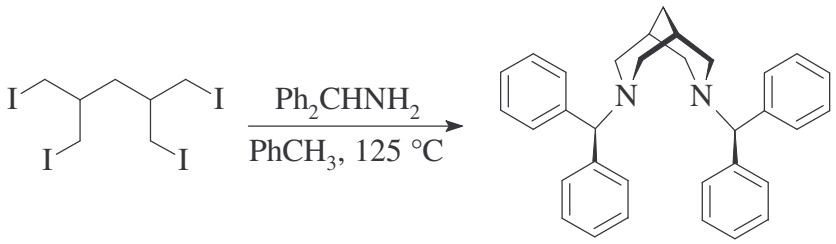


Scheme 12. a) $(CH_2O)_n$, Δ, 90%; b) $LiAlH_4$, THF, 90%; c) P_{red}, I_2, Δ, 75%; d) R-NH_2, toluene, Δ, <45%

3.4. SYNTHESIS OF NEW BISPIDINES

The last mentioned synthetic strategy (Scheme 12) is relatively inefficient in the last cyclisation step (yields less than 40%) and gives always substantial amounts of by-products. However, the reaction by-products had not been studied so far and no reasoning for the low yield had been given.

The bispidine derivative **10,** which was the main target of the first part of the project, was obtained by this condensation method between a halogeno-compound and a primary amine at high temperature:



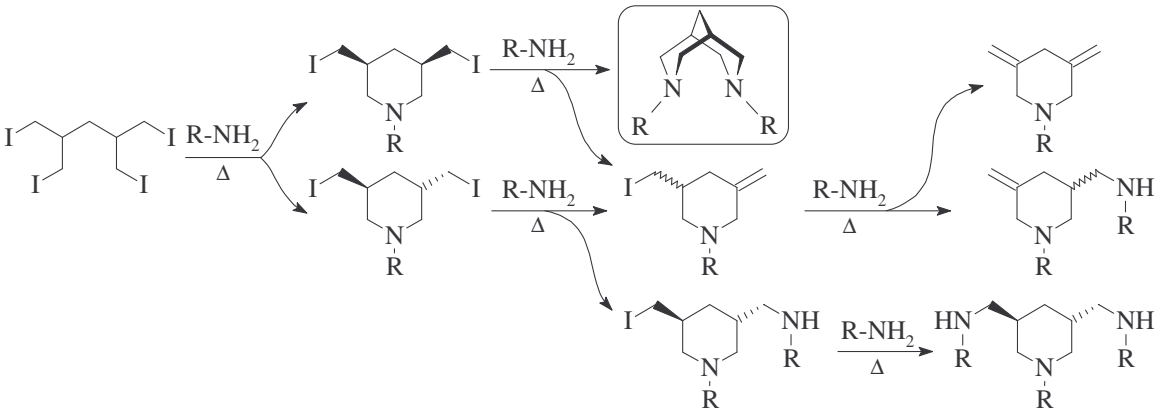
10

Scheme 13. Synthesis of *N*,*N*'-diphenylmethyl-3,7-diazabicyclo[3.3.1]nonane (**10**), 45% yield

Amine is required in large excess to bind the HI acid formed in the reaction, but can easily be recovered during the work-up. The reaction requires very long reaction times (more than 2-3 days), inert atmosphere and dry conditions. Initial experiments with conventional reflux method gave always a complicated product mixture because it was difficult to keep the system hermetically tight for that long time. Therefore, a sealed ampoule-method was developed, allowing the use of higher temperatures than the boiling point of the solvent, and completely isolated reaction mixture. The advantage of this modification was that the separation of the main product was very simple in some cases – the formed bispidine product had higher basicity than the primary amine and formed a crystalline ammonium salt that could be easily separated from the by-products in solution.

However, recent preliminary tests using controlled microwave heating in a closed reaction vessel at much higher temperatures (more than 180 °C) and polar aprotic solvent (acetonitrile) show that the condensation reaction is finished already after 1-2 hours.

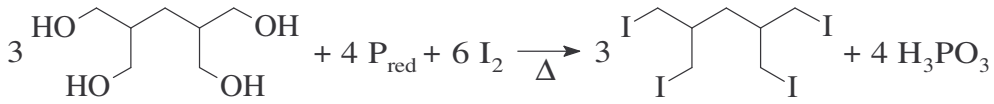
The substitution-elimination ratio depended strongly on the basicity of the amine and of the whole reaction medium. β-elimination is quite easy to occur, especially in strongly basic conditions and at higher temperatures. A phase-transfer catalytic conditions for *N*-alkylation was attempt to increase the speed of the condensation at lower temperatures, but more β-elimination took place. In less basic conditions (*e.g.* when aniline was used) *N*-alkylation dominates, and there are less unsaturated by-products. Based on the information above, the formation of the target product and by-products can be depicted in the following scheme:



Scheme 14. Formation of the desired product and by-products

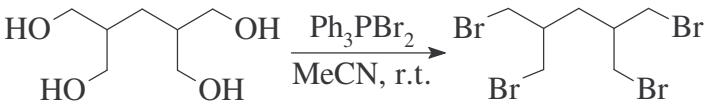
As the starting halogeno-compound has two pro-chiral centres, the first ring closure can result in *cis*- or *trans*-substituted piperidine derivatives, which react further. Assuming that there is no preference in the formation of the *cis*- or *trans*-compound, statistically 50% of the starting halogeno-compound cannot be transformed into the bispidine derivative.

The yields for the synthesis of the substrate for the cyclisation step was also greatly improved – yields up to 80% were obtained in the present work compared to the previously reported 38%.[18] It was just not necessary to take so huge excess of phosphorus and iodine as reported previously – stoichiometric amount was completely sufficient:



Scheme 15. Iodination of 2,4-bis(hydroxymethyl)pentane-1,5-diol, 80% yield

An extra idea was to replace the tetra-iodo compound with an equivalent substrate with a lower molecular weight. Previously reported bromination with conc. HBr acid in 64% yield.[34] Bromination by triphenylphosphine dibromide was used in this project:



Scheme 16. Bromination of 2,4-bis(hydroxymethyl)pentane-1,5-diol, yield 72%

However, much longer reaction time was needed for the condensation (Scheme 13) to be finished due to the poorer leaving group.

4. LIGAND CHARACTERISATION

The characterisation of the compounds can be performed with a wide variety of experimental methods. Some techniques, like NMR spectroscopy and X-ray crystallography, are especially valuable, because of the direct and straightforward information that these methods provide. While X-ray crystallography is limited only to the solid state, NMR spectroscopy can also yield data of the solution state structure and dynamic behaviour.

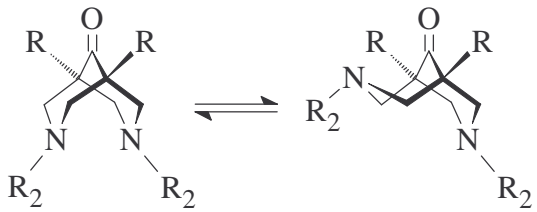
4.1. CONFORMATIONAL STUDY

The purpose of conformational analysis is to obtain a description of the three-dimensional structure of molecules. Such knowledge is later required in order to understand the interactions between molecules. The conformation of a molecule may be described at different levels of detail. In the simplest case, a single conformer, *i.e.* three-dimensional structure, may be sufficient to explain experimental data. The assumption of a single conformer may not result in a physically reasonable structure, if the molecule is flexible. In such cases, data may be better fitted by assuming an equilibrium between several conformers.[35]

4.1.1. METHOD

NMR spectroscopy is the main method to study the structure, conformational and dynamic behaviour of organic molecules in solution. Nowadays the one-dimensional ^{1}H and ^{13}C NMR spectra are recorded on a routinely basis at room temperature. The obtainable information from those spectra is rather limited: chemical shifts, coupling constants, and offer very little information about the three-dimensional structure of the molecules. However, chemical shifts are influenced by the electronic environments of the atoms, that in turn are very sensitive to conformational and chemical (*e.g.* complexations) changes. In addition, the chemical shifts are not yet very accurately predictable. The sizes of coupling constants are directly related to molecular conformation, depending on the number of bonds that separate the coupled nuclei, the configuration of the electrons and their spatial arrangement. The relationship is particularly distinct for vicinal ^{3}J couplings (both homo- and heteronuclear, $^{3}J_{HH}$, $^{3}J_{CH}$) and the dependence on the dihedral angle around the connecting bond is described by Karplus type equations.[36]

Bispidine derivatives are known to undergo conformational equilibria in solution which are mostly shifted to the side of the chair-chair conformer (Scheme 17) even with large substituents on nitrogen.[23,37]



Scheme 17. Chair-chair ↔ chair-boat isomerisation

Because of the slow time-scale of the NMR spectroscopy, the acquired information can be a population-weighed average of quickly interconverting structures. If this conformational change is slowed at lower temperature, additional signals or just some broadening of the signals can appear in the NMR spectra. Variable temperature experiments can give quantitative data (activation energy, rate constants) about the dynamic interconversions in the solution.

Even though NMR spectroscopy is a very powerful method, it is not always sufficient and some additional information from other experimental techniques is required. X-ray crystallography is one of these powerful tools for structure determination. However, the NMR study may reveal a presence of several isomers in solution, but X-ray structures do not necessarily correspond to the conformer (or isomer of the complex) favoured in solution, because during the process of crystallisation the conformation of the molecules is stabilised by intermolecular interactions in the crystal lattice. Solid-state structures can naturally give little information about the flexibility of molecules. The positions of hydrogen atoms can very rarely be determined with acceptable precision, resolution is just not good enough. If the accurate positions of hydrogen atoms are of interest, neutron diffraction may be used.

Theoretical calculations of the ligand geometries are not always required. Building of molecular models and comparison with the data from the NMR investigations might give a clear picture, what is happening in the solution. Even when NMR data themselves are not sufficient to determine conformational equilibria, useful interpretations can often be made if combined with molecular dynamics simulations, using experimental values as restraints or by comparison with values calculated from simulations.

4.1.2. CONFORMATION OF THE NEUTRAL LIGAND

The compound 3,7-bis(1,1-diphenylmetyl)-3,7-diazabicyclo[3.3.1]nonane (**10**) has a reasonably simple ^{1}H NMR spectrum:

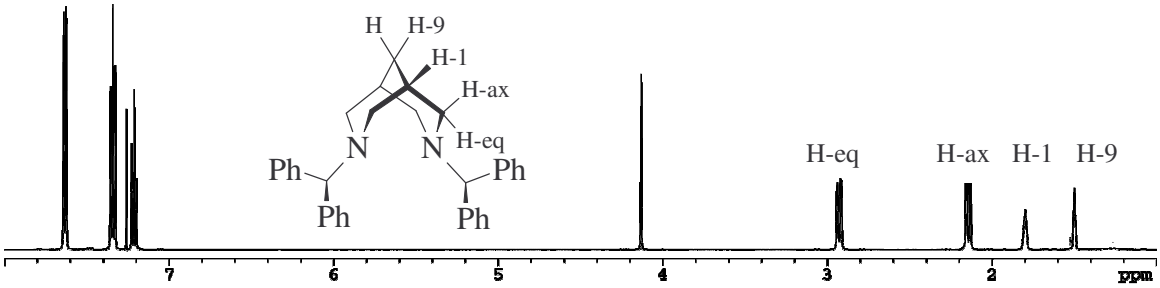
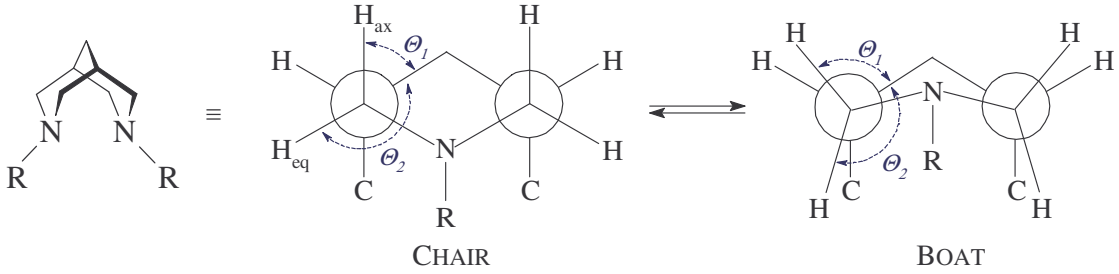


Figure 17. ^{1}H NMR spectrum of dibenzhydrylbispidine (**10**) in $CDCl_3$

Low temperature (-90 °C) experiments did not show any splitting or broadening of the signals, indicating that the possible conformational flips between twin-chair and chair-boat conformers do not take place. This is probably due to the very large substituents on the nitrogen atoms. In order to confirm the twin-chair conformation of the compound, the heteronuclear coupling constants should be determined between the bridge carbon and axial-equatorial protons at position 2. In the chair conformer, H_{ax} and H_{eq} would have different angles to the bridge carbon C-9 (Scheme 18).



Scheme 18. Chair and boat conformers

Karplus equation for the calculation of $^3J_{CH}$ coupling constants:[38]

$$^3J_{CH} = 4.50 - 0.87 \cdot \cos\Theta + 4.03 \cdot \cos 2\Theta$$

Table 1. Dihedral angles from molecular modelling* and calculated coupling constants for **10**

	Θ (H_{ax}–C-9)	**^{3}J(H_{ax}–C-9)**	**Θ (H_{eq}–C-9)**	**^{3}J(H_{eq}–C-9)**
Chair conformer	70.3°	1.1 Hz	173.4°	9.3 Hz
Boat conformer	138.0°	5.6 Hz	106.1°	1.3 Hz
X-ray structure	64.5°		178.3°	

* Conformations were optimised with PC Spartan Plus[39] using the semi-empirical AM1 method.

The determination of the vicinal coupling constants has so far been unsuccessful. Two-dimensional HSBC[40] and HETJSD[41] spectra were recorded, but the resolution was too low to extract accurate coupling constants.

The structure of the ligand was investigated by X-ray crystallography (see Appendix II). An ORTEP[42] presentation of the structure is shown in Figure 18. The geometry of the compound shows a C_2 symmetry (not C_2v symmetry as in solution due to some distortions caused by the substituents and neighbouring molecules in the crystal cell). The compound exists in a chair-chair conformation. The benzylic protons are oriented towards the exterior of the molecule.

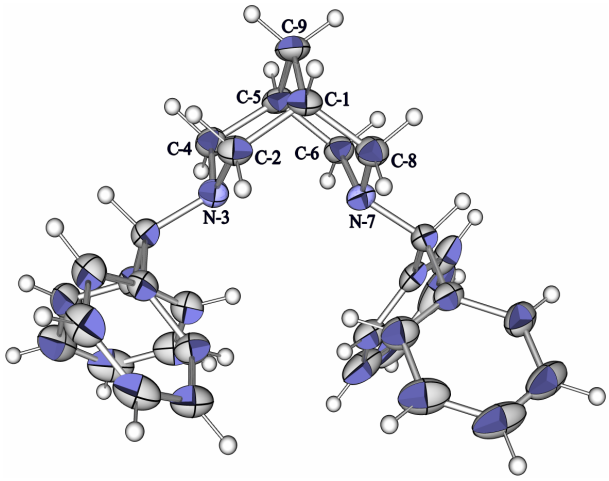


Figure 18. Molecular structure (ORTEP view) of the ligand **10**, thermal ellipsoids at the 50% probability level

4.1.3. CONFORMATION OF THE PROTONATED LIGAND

Bispidines are Brønsted bases that can bind protons and form ammonium salts. However, there is just a very limited number of examples in the literature, where double-protonated bispidine derivatives have been observed. One of the examples is a commercial antiarrhythmic agent Tedisamil dihydrochloride:[43,44]

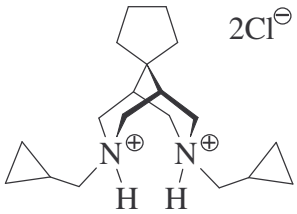
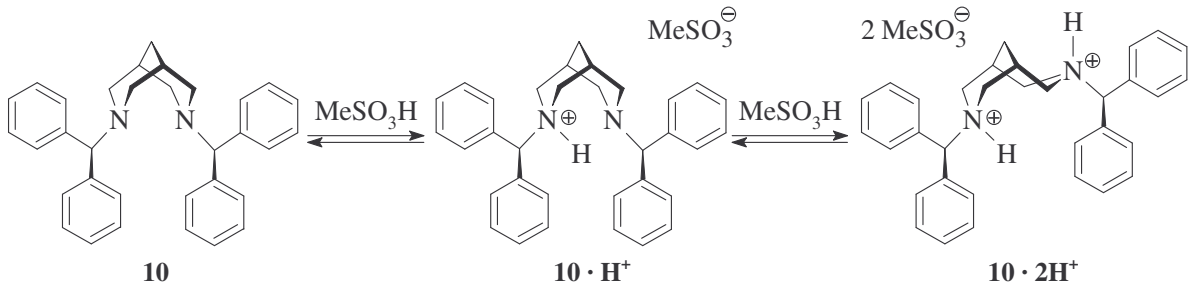


Figure 19. Tedisamil dihydrochloride

Protonation study can be used as a simple method to see how the host can behave as a base. In order to obtain information about the protonation behaviour of our bispidine

ligand, a quailtative NMR titration experiment was carried out. Small volumes of methanesulphonic acid solution were added to the solution of bispidine, and ^{1}H NMR spectra were recorded after each addition.



10 **10 · H^{+}** **10 · 2H^{+}**

Scheme 19. Titration of the bispidine **10** with methanesulphonic acid

The first protonation step was found to be as expected. A ^{1}H NMR spectrum indicated that the symmetry of the diamine ligand was preserved at room temperature for the first protonation step. The positive charge seems to be spread equally over the two N atoms, resulting in an adamantane-like structure, as proposed for monocationic 3,7-diazabicyclo[3.3.1]nonanes by Douglass and Ratliff (1968). However, the C_{2v} symmetry observed on the NMR timescale in solution could also be explained by rapid proton hopping between the two nitrogen atoms.[45]

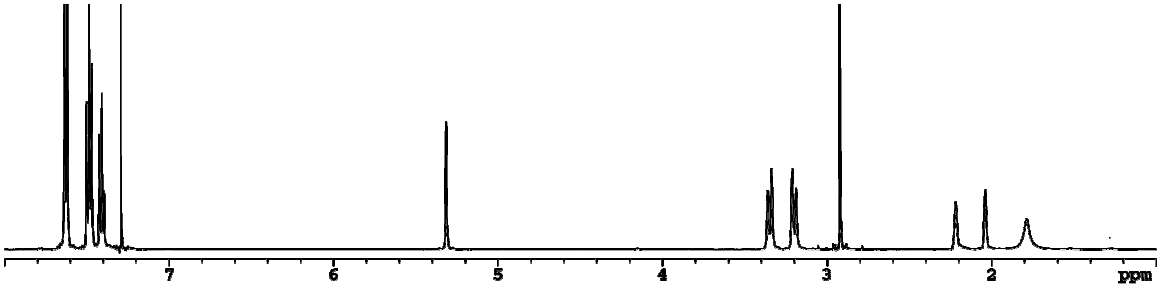


Figure 20. ^{1}H NMR spectrum for the mono-protonated species **10 · H^{+}** at r.t. in $CDCl_3$

Cooling of the solution did not show any splitting or broadening of the signals. The solid-state ^{13}C MAS-NMR would discriminate between the two sides of the molecule and give extra signals for the two piperidine rings.

The structure of the monoprotonated ligand was investigated by X-ray crystallography (see Appendix II). An ORTEP presentation of the structure is shown in Figure 21.

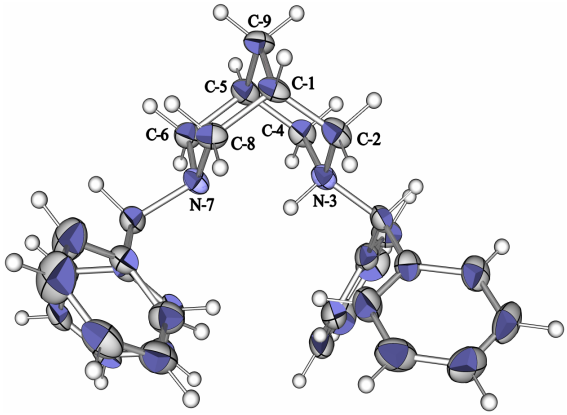
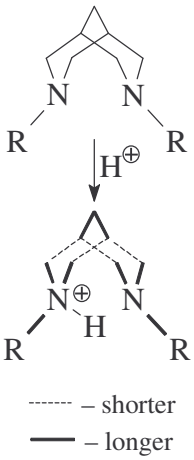


Figure 21. ORTEP view of the cation **10 · H$^+$**, with thermal ellipsoids drawn at the 50% probability level

Extra acquired electron-density on the N-H bond will decrease the electron density on the N-C bonds, and thus resulting in longer N-C bonds. The N-C bond lengths of the nitrogen atom (position 7), that is not connected to a proton, are also longer, but the differences are *ca*. two times smaller. This can be contributed to some hydrogen bonding: N-7···H–N-3.

Table 2. Comparison of the bond lengths between the free ligand (**10**) and the protonated ligand (**10 · H$^+$**)

Bonds	10	10 · H$^+$	Difference
C-1 – C-2	1.539 Å	1.522 Å	-0.017 Å (shorter)
C-2 – N-3	1.475 Å	1.514 Å	0.039 Å (longer)
N-3 – C-4	1.477 Å	1.524 Å	0.047 Å (longer)
C-4 – C-5	1.531 Å	1.519 Å	-0.012 Å (shorter)
C-5 – C-6	1.537 Å	1.531 Å	-0.006 Å (shorter)
C-6 – N-7	1.475 Å	1.490 Å	0.015 Å (longer)
N-7 – C-8	1.475 Å	1.500 Å	0.025 Å (longer)
C-8 – C-1	1.536 Å	1.527 Å	-0.009 Å (shorter)
C-1 – C-9	1.529 Å	1.535 Å	0.006 Å (longer)
C-5 – C-9	1.526 Å	1.528 Å	0.002 Å (longer)
N-3…N-7	2.854 Å	2.727 Å	-0.127 Å (shorter)
N-3 – C-Bnz	1.473 Å	1.523 Å	0.050 Å (longer)
N-7 – C-Bnz	1.470 Å	1.494 Å	0.024 Å (longer)



The monoprotonated bispidine is not symmetric in solid state. The largest effect of the protonation is for the C–N bond lengths. The fact that the N-3…N-7 distance is smaller for the protonated compound indicates also that there is hydrogen-bonding.

The N-3…N-7 distance for the Pd-complex is larger (Table 3) than for the protonated bispidine due to the larger size of the metal ion. Larger distance between the nitrogen atoms indicates flattening of the bicyclic system.

Table 3. Comparison of N-3…N-7 distances of some bispidine derivatives having a chair-chair conformation

Bispidine	Distance, Å
3,7-Diphenyl-3,7-diazabicyclo[3.3.1]nonane (**5**)	3.072[46]
Dibenzhydrylbispidine (**10**)	2.854
2,2-Dimethyl-5,7-diphenyl-1,3-diazaadamantane	2.436[47]
3,7-Dibenzhydryl-7-aza-3-azoniabicyclo[3.3.1]nonane trifluoromethylsulphonate (**10** · H^+)	2.727
3,7-Dimethyl-1,5-diphenyl-7-aza-3-azoniabicyclo[3.3.1]nonane-9-one hydrogen sulphate	2.670[48]
3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9,9-diol dihydrochloride	3.203[49]
Tedisamil dihydrochloride	3.15 [49]
[(1,5-Dimethyl-3,7-diphenylbispidinone)(π-allyl)Pd]CF_3SO_3	2.966[16]
(3,7-Dimethyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonane-9-one)$CuBr_2$	2.765[50]
(3,7-Dimethyl-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonane-9-one)$CuCl_2$	2.714[51]

Dihydrochlorides adopt highly flattened CC conformation for its bicyclic skeleton. This conformation is achieved by flattening the piperidine rings at their nitrogen ends and puckering at the corresponding carbon ends. The CC conformation of those is stabilised by a pair of hydrogen bonds formed by a chlorine ion with both of the piperidine nitrogen atoms.

The second step of the protonation took place only at the presence of excess of the acid. The ^{1}H NMR spectrum showed that the structure was clearly not symmetric any more.

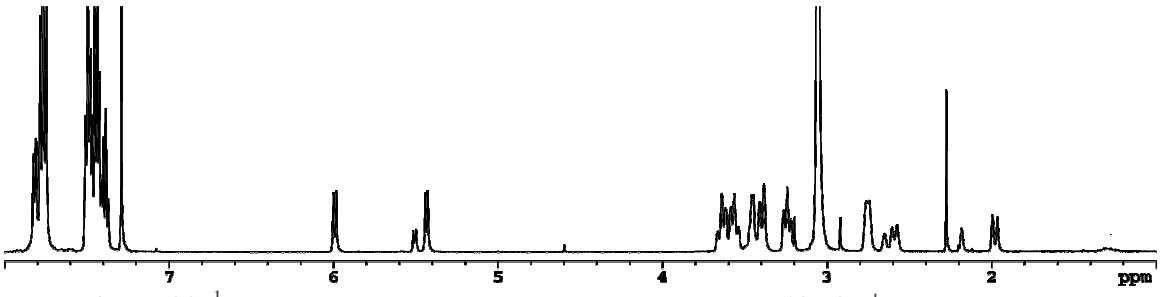


Figure 22. ^{1}H NMR spectrum for the di-protonated species **10** · $2H^+$ at r.t. in $CDCl_3$

All of the aliphatic signals were assigned and the chair-boat conformation was confirmed from NMR spectra for the diprotonated species:

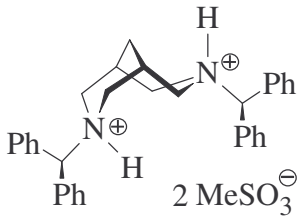


Figure 23. A structure based on the signal assignment from the NMR spectra

4.2. PROTONATION OF BISPIDINONES

Bispidinones behaved differently than bispidines at similar conditions. For example, the bispidinone **11** formed two monoprotonated species in the first protonation step. The ratio between these species was not equal, but depended on the concentration of the starting bispidinone. A more close study indicated that the second unknown substance was the corresponding 9,9-diol.

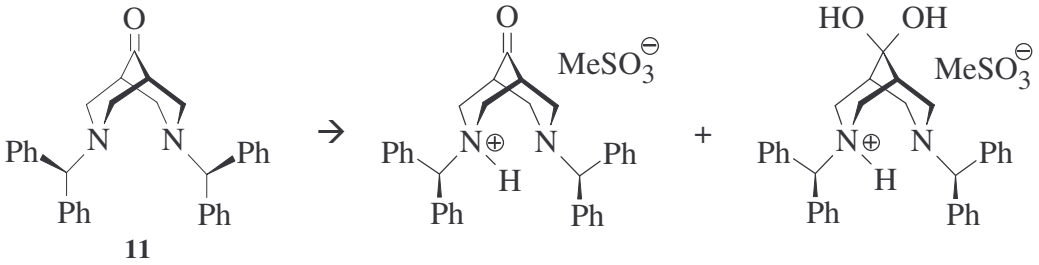


Figure 24. Protonation of a bispidinone with $MeSO_3H$ in $CDCl_3$ gave a mixture of two compounds

The formation of such diols may occur via a possible protonation of the carbonyl oxygen atom, followed by a nucleophilic addition of water molecule to the activated carbonyl carbon atom to produce the diols. Another conceivable mechanism could involve initial protonation for N-3, which in turn could increase the electronic deficit at the carbon of the C=O group (via an induction effect). After initial protonation of the oxygen atom of the C=O group, a fast nucleophilic addition of water to the cation could occur to generate the 9,9-diols.

Geminal diols of aldehydes and ketones have long been known, but the specific cases found from literature revealed that such hydrates have powerful electronegative groups (usually halogens) very close to the carbonyl function. Chloral, hexachloroacetone and hexafluoroacetone are classical examples. Hydrogen bonding is one theory to account for stabilisation of these hydrates. Intermolecular hydrogen bonding occurs between one oxygen atom of a diol group in one molecule with a hydrogen atom of a hydroxyl group of a diol group in a second molecule.[49]

This phenomenon can partly the reason why bispidinones are not as good host ligands as bispidines.

4.3. BASICITY OF BISPIDINES AND BISPIDINONES

Possible screening methods for this are pK_a measurements of the conjugate acid form of the host systems in order to predict the abilities to bind Lewis acids, and ^{15}N NMR chemical shifts (Chapter 4.4) to estimate the possibilities to donate electrons by looking at the electron density around the nucleus. For instance, the relationships between ^{15}N NMR chemical shifts and the pK_a values of 2,4-dinitroanilinium salts were found to be linear, indicating that these properties are influenced by same factors.[52] The binding abilities of the host ligands can be directly related to their pK_a values. This gives information about their σ-donating properties of the nitrogen atom. Bidentate nitrogen ligands with higher base strengths will presumably also form more stable transition metal complexes. As solvation effects may mask true electronic contributions, meaningful comparisons are seldom possible. Some of the compounds may be sparingly soluble in the used solvent, so the determination and evaluation of the pK_a values through array of nitrogen compounds may not be so easy.[10]

4.3.1. METHOD

Normally, acid-base ionisation constant (pK_a value) determination is based on a stepwise monitoring of a change of some property (*e.g.* chemical shift, amount of the added titrant) against the p*H* of the solution. At the halfway point in the titration, the p*H* equals the pK_a. However, it is advantageous to eliminate any p*H* measurements, which often are the limiting factor in pK_a studies.

In the present work, an UV-VIS spectrophotometric titration technique for measurements of relative acidities (ΔpK_a) in acetonitrile was used. A solution containing two bases, the base under investigation and a reference base, for which the pK_a value of the conjugate acid was known, was titrated with a solution of methanesulphonic acid in acetonitrile. A UV-VIS spectrum was recorded after each addition of the titrant. From the spectra, the relative basicity of the two bases could be calculated. This UV-VIS spectrophotometric method employed has advantages over others methods (potentiometry, ^{13}C NMR spectroscopy, *etc.*): in certain cases sufficiently low concentrations of solutes may be used to minimise possible association processes; the requirement for purity of samples is quite low (the only demand is that the impurities must not behave as bases). The method can be used even if the studied compound does not have absorption in the UV-VIS spectral region.

Solvents such as DMSO and MeCN have sufficiently high dielectric constants (46.6 and 36.0, respectively) that ion-pairs are usually completely dissociated into free ions. The used solvent, acetonitrile has some advantages over other aprotic solvents as a medium for acid-base studies. It is a very weakly basic dipolar aprotic solvent, has very low ability to solvate anions, and is more suitable for studies of strong acids than DMSO.[53,54]

4.3.2. RESULTS

The pK_a values were determined* for the conjugate acid forms of several 3,7-diazabicyclo[3.3.1]nonanes (*see* Table 4, below) and are summarised in Table 5**.**

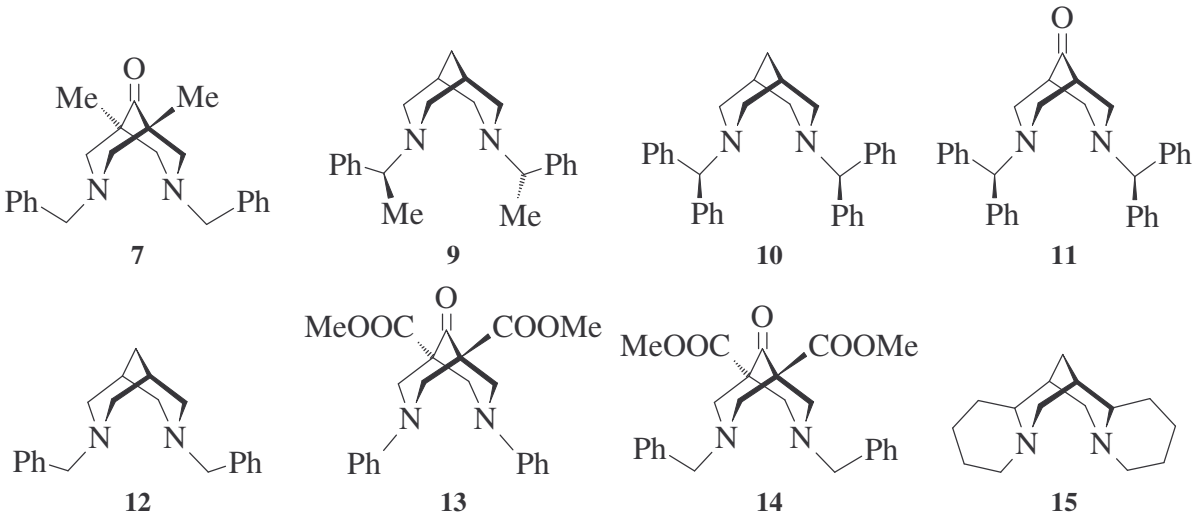


Table 4. Various 3,7-diazabicyclo[3.3.1]nonanes, for which pK_a values of the conjugate acids were determined

The pK_a values for solutions of the conjugate acid forms of compounds **7, 13** and **14** in dimethyl sulphoxide had been determined potentiometrically previously in our research group.[16] These three compounds were involved in the present study for comparison. To investigate how the substitution at the benzylic position influences the basicity, compounds **9**, **10**, **11**, and **12** were included. Compounds **10** and **11** might indicate the effect of the carbonyl group**.** The commercially available compound **15** [(–)-sparteine] was expected to have stronger basicity than the other bispidines, because there is no electron withdrawing substituent on the nitrogen atoms.

---

* The investigations were done by A. Kütt, I. Kaljurand and Prof. I. Leito at University of Tartu, Estonia.

Table 5. pK_a^{MeCN} values (for the conjugate acid forms) of various 3,7-diazabicyclo[3.3.1]nonanes

Compound	pK_a^{MeCN}	Reported pK_a*
7	17.48	7.7 in DMSO[16]
9	21.33	–
10	17.81	–
11	13.47	–
12	21.27	–
13	8.11	4.4 in DMSO[16]
14	13.79	5.3 in DMSO[16]
15	21.67	17.50 in MeCN[55]

* measured potentiometrically, probably not so dry conditions.

pK_a^{MeCN} values follow the same trend as pK_a^{DMSO}, but the values are up to 10 pK_a units differrent.

As can be seen from the table, the substituents have a huge effect on the pK_a values. If we compare the value for **12** (pK_a=21.27) to **7** (pK_a=17.48), then we can see a change by *ca*. four orders of magnitude. Such an effect has been attributed to interactions between the nitrogen lone pairs and the π-orbitals of the carbonyl group through σ bonds.[20] Compound **14** (pK_a=13.79) has more carbonyl groups than **7** and this lowers the basicity of the ligand additional 4 orders of magnitude in a similar way. Compounds **9**, **12** and **15** have the pK_a values more or less similar to each other. For compound **10** the low pK_a is probably due to the phenyl groups that decrease the electron density on nitrogen, and decrease the basicity of the amine (*e.g.* the order of basicity decreases linearly[56] in MeCN from methyl amine>benzylamine>benzhydrylamine>tritylamine, see Table 6).

Table 6. pK_a^{MeCN} values of conjugate acid forms for series of primary amines[56] and bispidines

Amine	pK_a^{MeCN}
CH_3NH_2	18.37
$PhCH_2NH_2$	16.76
Ph_2CHNH_2	14.91
Ph_3CNH_2	13.40

Bispidine	pK_a^{MeCN}
Dimethylbispidine	22.74[57]
Dibenzylbispidine (**12**)	21.27
Dibenzhydrylbispidine (**10**)	17.81

The correlation between the pK_a^{MeCN} values of bispidines is not as linear as for primary amines (Figure 25). The reason for this might be steric effects in the bicyclic system. The higher basicity of the bispidine derivatives, as compared to the corresponding primary amines, is most likely due to the chelating effect.

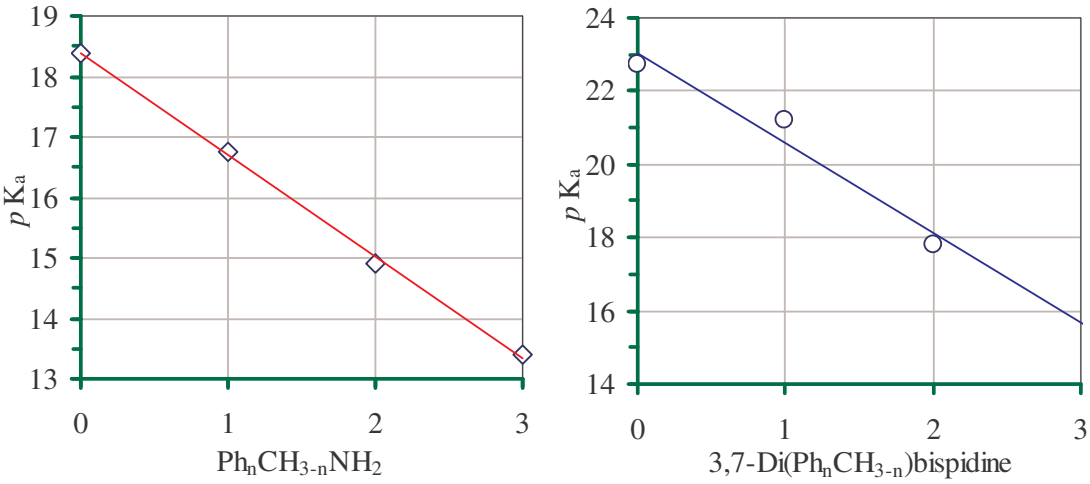


Figure 25. Correlation between the pK_a^{MeCN} values and the number of phenyl groups

The basicity of aliphatic amines is determined by inductive effects of the groups bound to nitrogen. Steric effects are generally less important; in cases of heavy crowding however, significant base-weakening steric effects have been observed.[56]

4.4. ^{15}N NMR SPECTROSCOPY

Nitrogen-15 NMR chemical shifts provide valuable information about the shielding of the nitrogen atoms and allow greatly discriminate structural features, as the ^{15}N shift scale extends over a range of >800 ppm. Lower chemical shift indicates higher electron density around the nucleus. Higher electron density for the nitrogen atom in turn indicates the possibilities for being a stronger electron donor.[58]

4.4.1. METHOD

The only practically usable nitrogen isotope for NMR investigation is the isotope ^{15}N, which has a spin quantum number I=½. However, this isotope is suffering from low sensitivity (relative sensitivity $1.04 \cdot 10^{-3}$ compared to ^{1}H) due to its low gyromagnetic ration (γ) and its relatively low natural abundance (0.37%). Inverse-detected NMR methods are mainly used to acquire long-range ^{1}H-^{15}N heteronuclear shift correlation data. The ^{15}N NMR chemical shifts in our investigation were obtained by ^{1}H-^{15}N gHMBC method at natural abundance.

4.4.2. RESULTS

The results from the ^{15}N chemical shift measurement are combined in Table 7. The following conclusions can be drawn from the results:

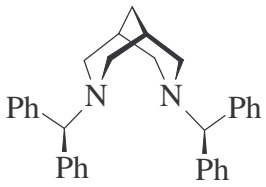
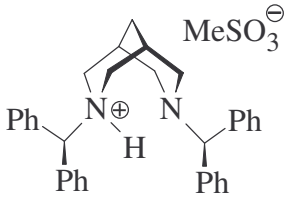
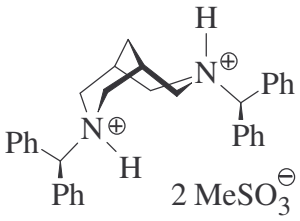
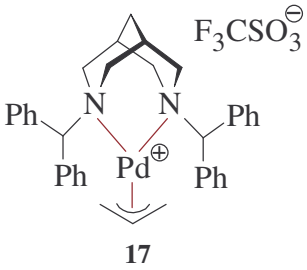
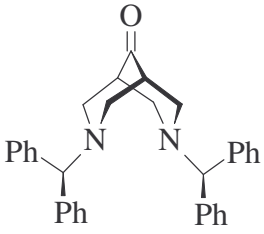
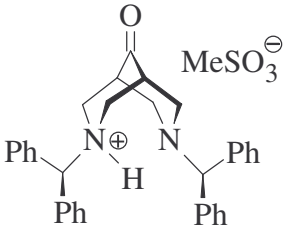
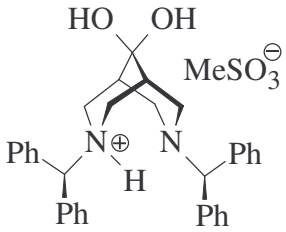
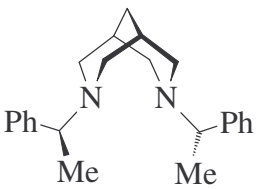
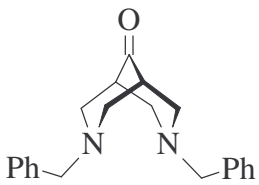
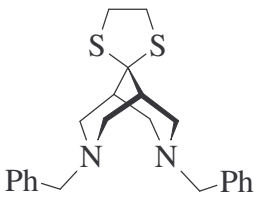
a) protonation increases the chemical shifts, because the shielding of the ^{15}N nucleus becomes smaller as some of the electron density of the nitrogen atoms will be transferred to the hydrogen atom;

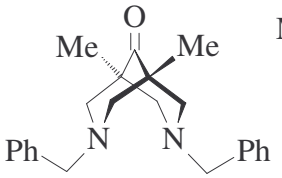
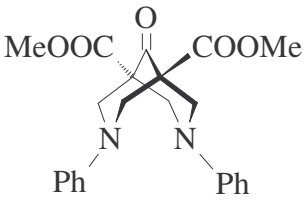
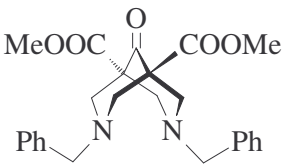
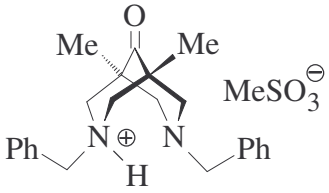
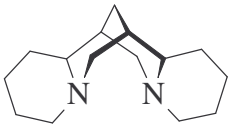
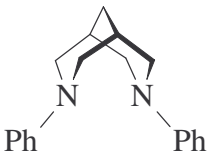
b) substitution of the nitrogen atoms with groups having stronger electron withdrawing potential elevates the chemical shift [*e.g.* dibenzylbispidine **12** (-335.6 ppm) → dibenzhydrylbispidine **10** (-326.4 ppm) → diphenylbispidine **5** (-315.4 ppm)]; it may partly be also due to some flattening of the bicyclic structure in case of sterically more demanding substituents (the distance between the free electron pairs on the two nitrogen atoms gets slightly larger);

c) presence of the carbonyl group at position nine lowers the chemical shift [*e.g.* dibenzylbispidinone **16** (-336.7 ppm) → dibenzylbispidine **12** (-335.6 ppm); dibenzhydrylbispidinone **11** (-329.6 ppm) → dibenzhydrylbispidine **10** (-326.4 ppm)];

d) complexation with the (π-allyl)palladium ligand lowers the chemical shift.

Table 7. ^{15}N chemical shifts of various bispidine derivatives (in $CDCl_3$) referenced to CH_3NO_2

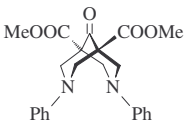
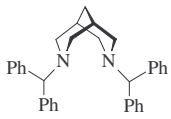
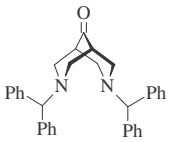
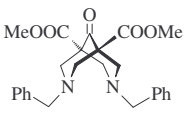
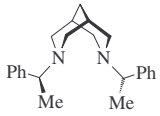
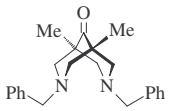
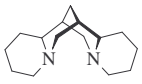
 **10** -326.4 ppm	 **10 · H$^+$** -314.2 ppm	 **10 · 2H$^+$** -322.4, -325.3 ppm	 **17** -340.9 ppm (in acetone at -70 °C)
 **11** -329.6 ppm	 **11 · H$^+$** -316.5 ppm	 -314.9 ppm	
 **9** -328.2 ppm	 **12** -335.6 ppm	 **18** -336.7 ppm	 **19** -339.8 ppm

			
7	**13**	**14**	**20**
-333.3 ppm	-322.0 ppm	-336.2 ppm	-322.8 ppm
			
15	**5**		
-325.2, -326.3 ppm	-315.4 ppm		

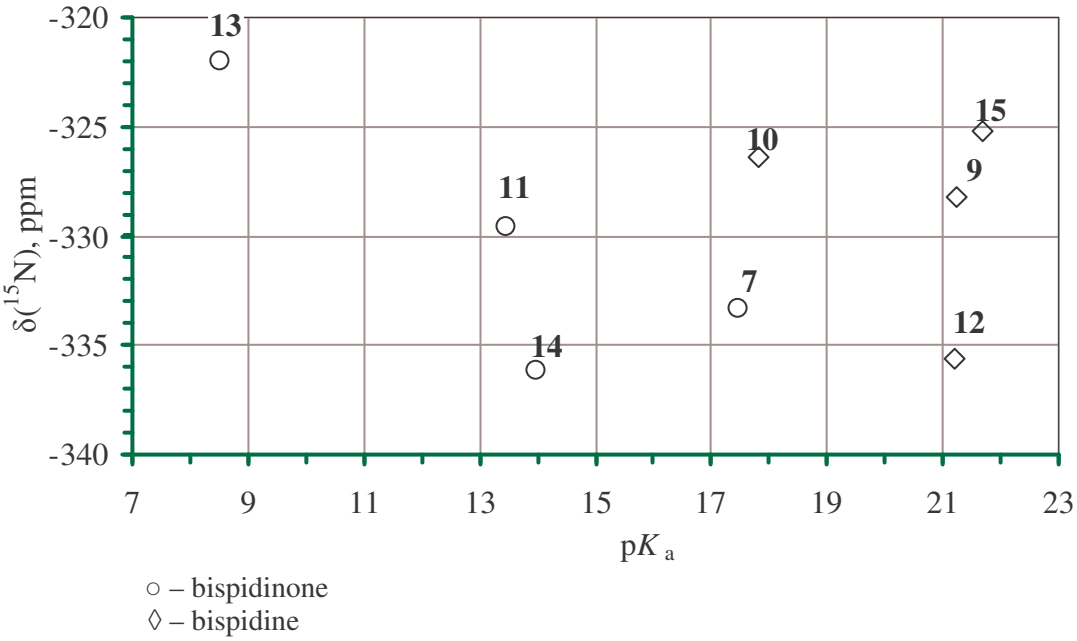
4.5. CONCLUSIONS

The acidity of a compound in a given medium is influenced by both electronic effects of the substituents and the solvent effects of the medium, but the chemical shift is much less dependent on the solvent and steric effects. Obviously, the pK_a values of the conjugate acids in aprotic solvent (acetonitrile in our case) is a better screening test than the ^{15}N NMR chemical shifts for estimating the complex formation abilities of the bispidine derivatives.

Table 8. Summary of pK_a^{MeCN} values and ^{15}N chemical shifts of some non-protonated bispidines (in $CDCl_3$)

Compound	pK_a^{MeCN}	δ(^{15}N), ppm	Compound	pK_a^{MeCN}	δ(^{15}N), ppm
 **13**	8.11	-322.0	 **10**	17.81	-326.4
 **11**	13.47	-329.6	 **12**	21.27	-335.6
 **14**	13.79	-336.2	 **9**	21.33	-328.2
 **7**	17.48	-333.3	 **15**	21.67	-325.2

A linear relationship between the pK_a^{MeCN} values and the ^{15}N chemical shifts can not be drawn due to too large differences between the compounds, and due to the small number of examples for each type of bispidine derivatives.



○ – bispidinone
◊ – bispidine

5. INTERACTION OF A BISPIDINE LIGAND WITH A (π-ALLYL)PALLADIUM COMPLEX

From the large variety of available guest ligands, (π-allyl)palladium ligands are almost the only suitable guests for binding with the bidentate bispidine type host ligands. The advantages of these ligands are that they are readily available as chloro dimers, form reasonably stable complexes with bidentate amines and can have a vide range of substituents.

5.1. (π-ALLYL)PALLADIUM UNITS: STRUCTURE AND DYNAMIC PROPERTIES

(π-Allyl)palladium compounds can be synthesised by: a) the reaction of palladium salts with substituted propenes; b) the reaction of palladium salts with dienes; c) reactions of palladium salts or labile palladium(II) precursors with substituted cyclopropanes and cyclopropenes; d) treating palladium salts with allyl halides, allyl alcohols and related substrates under certain conditions; e) alkyne dimerisation. The readily available (π-allyl)palladium chloro dimers may be separated into monomers in the presence of chelating ligands (*e.g.* bidentate dinitrogen ligands, Figure 26).[59]

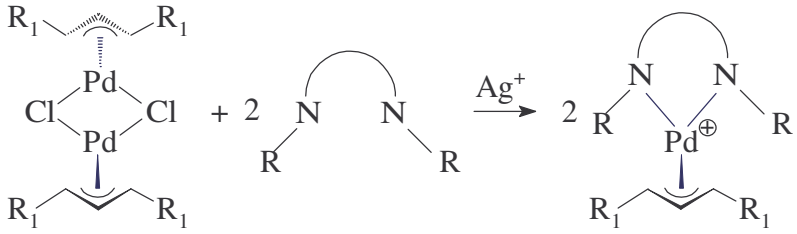


Figure 26. Separation of the chloro dimers into monomers with the aid of Ag^+ ions and subsequent formation a (π-allyl)palladium ammine complex

Allyl ligands are ligands that can bind in both a monohapto (η^1) and trihapto (η^3) form (Figure 27). Hapticity (η^x) is a term used to describe the bonding mode of a ligand to a metal centre. The η^3-form, in general, is more stable than the η^1-form because of the delocalised π-electron system of the allylic group and some back-bonding from the transition metal to the ligand.

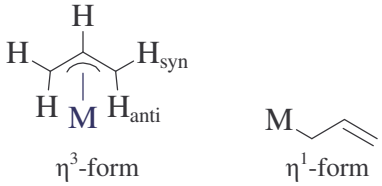


Figure 27. Allyl ligands

(π-Allyl)palladium complexes are subject to different forms of dynamic processes which have to be taken into consideration when analysing their solution structure or trying to control the stereochemical outcome of reactions where they are involved. The most important processes are *syn-anti* isomerisation and apparent π-allyl rotation.

The *syn-anti* isomerisation takes most likely place by change in hapticity, from an η^3-allyl into η^1-complex, which allows free rotation around the formed C–C single bond, followed by re-formation of an η^3-allyl complex (Figure 28). The activation energy $\Delta G^{\ddagger}$ is relatively high (> 80 kJ/mol), and a ^{1}H NMR spectrum shows separate signals for the isomers at room temperature.

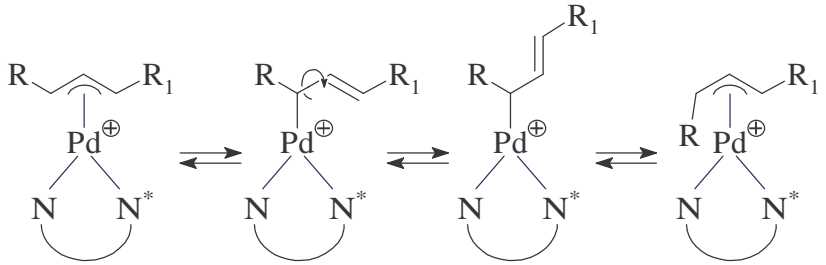


Figure 28. The *syn-anti* isomerisation

Apparent π-allyl rotation has been shown to occur via cleavage of a palladium-nitrogen bond, which means that the intermediate involves a monodentate nitrogen ligand and a tri-coordinated palladium metal centre. The activation energy $\Delta G^{\ddagger}$ is not so high (40-65 kJ/mol), and a ^{1}H NMR spectrum shows usually coalesced signals at room temperature.[60]

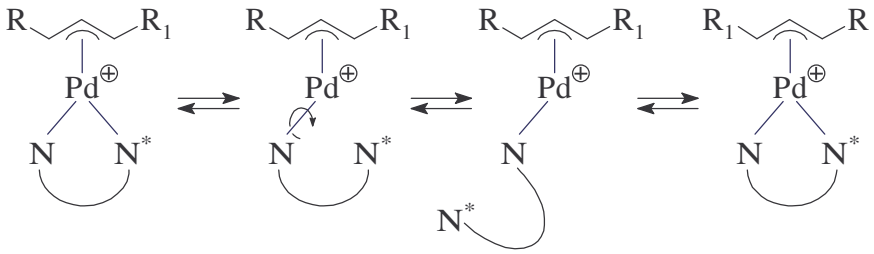


Figure 29. Mechanism of apparent π-allyl rotation in (π-allyl)palladium complexes with bidentate nitrogen ligands

5.2. COMPLEXES

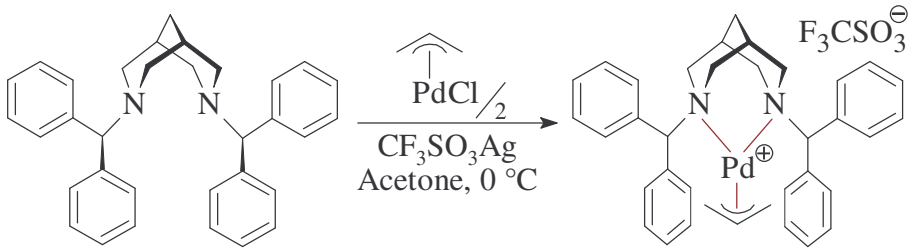
(π-Allyl)palladium complexes are intermediates in a number of palladium-catalysed reactions and it is important to know the structure of these complexes. Most important information of the solution-phase conformation can be obtained from the observation of the inter-ligand NOEs. Also, the chemical shifts may be very informative due to the

anisotropy effects. Solid phase crystal data is obtainable from X-ray crystallography studies. The degree of conformational freedom of the ligands is reduced somewhat during complex formation, resulting in higher order of the system. The host and the guest compounds of the system are both forced into a smaller number of possible conformations, making the structural characterisation simpler. Stronger bonds between the host and guest ligands reduce the abilities of the complexes to isomerise.

(1,3-η^3-Propenyl)palladium ligand is the simplest possible model for the π-allyl type guest molecules.

5.2.1. METHOD

The Pd(II) complex was prepared by treating the chloro-bridged π-allyl complex with two equivalents of $AgCF_3SO_3$ to remove Cl^-, followed by addition of two equivalents of the bispidine ligand **10**.



10 **17**

Scheme 20. Synthesis of the (π-allyl)palladium complex [(**10**)(π-allyl)Pd]CF_3SO_3

Characterisation of the complex was done by NMR spectroscopy.

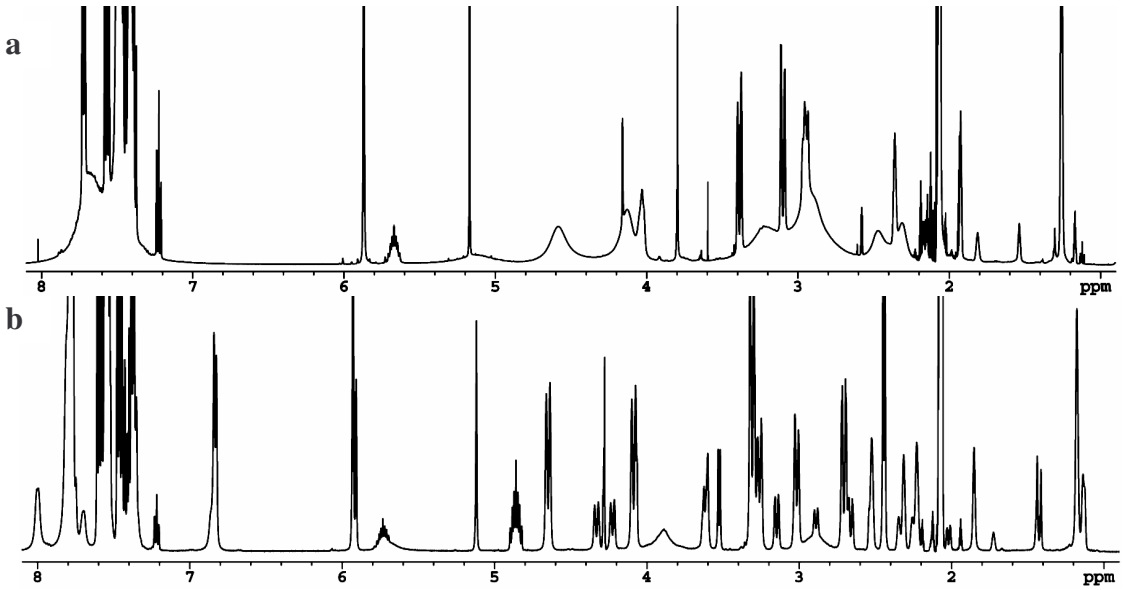


Figure 30. Variable temperature ^{1}H NMR (500 MHz) spectra for [(**10**)(π-allyl)Pd]CF_3SO_3 in $CDCl_3$. a) Temp.=+25 °C, b) temp.=–70 °C.

The were two isomers of the complex present in the solution, the ratio of these isomers changed from 2.8:1 at -70 °C to 2.5:1 at -35 °C. Signals for the protonated bispidine, and smaller signals for the unreacted bispidine and (π-allyl)palladium chloride dimer were also present. These compounds did not show dynamic processes, and were almost unchanged at all used temperatures.

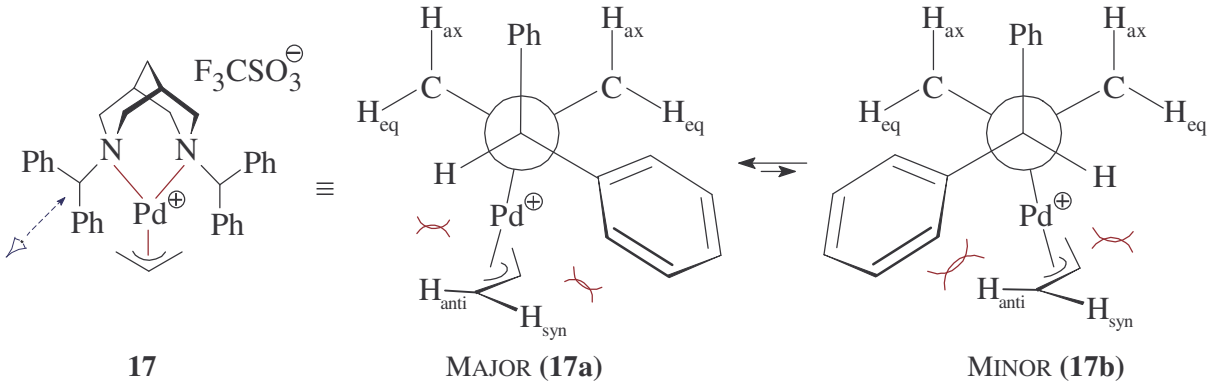
Negative Δδ values indicate that protons are located above the face of the phenyl rings and due to ring current effects, the protons are strongly shielded. The protons that are close to the plane of the phenyl ring are deshielded and appear at higher chemical shift (Δδ is positive).

Table 9. ^{1}H NMR chemical shifts of π-allyl ligand protons in acetone-d_6

	δ (syn), ppm		δ (anti), ppm		δ (meso), ppm	
$(\pi\text{-allyl-PdCl})_2$	4.02		3.04		5.59	
π-allyl in the major isomer **17a**	2.40	Δδ= -1.62	3.27	Δδ= 0.23	4.87	Δδ= -0.72
π-allyl in the minor isomer **17b**	3.50	Δδ= -0.52	1.38	Δδ= -1.66	5.70	Δδ= 0.11

For the minor isomer, the Δδ for the allyl anti protons is large, showing that the anti protons are spatially close to the top of phenyl rings. Similar Δδ for the major isomer is observed for the syn protons, indicating corresponding positions with respect to the phenyl group.

The phenyl group pointing towards the base of the complex is enforcing a certain N-$CHPh_2$ conformation by avoiding steric contact with the π-allyl ligand. In the major isomer, there are less steric interactions. Schematic presentation of the two isomers, based on the above description, is shown in Figure 31.



17 MAJOR **(17a)** MINOR **(17b)**

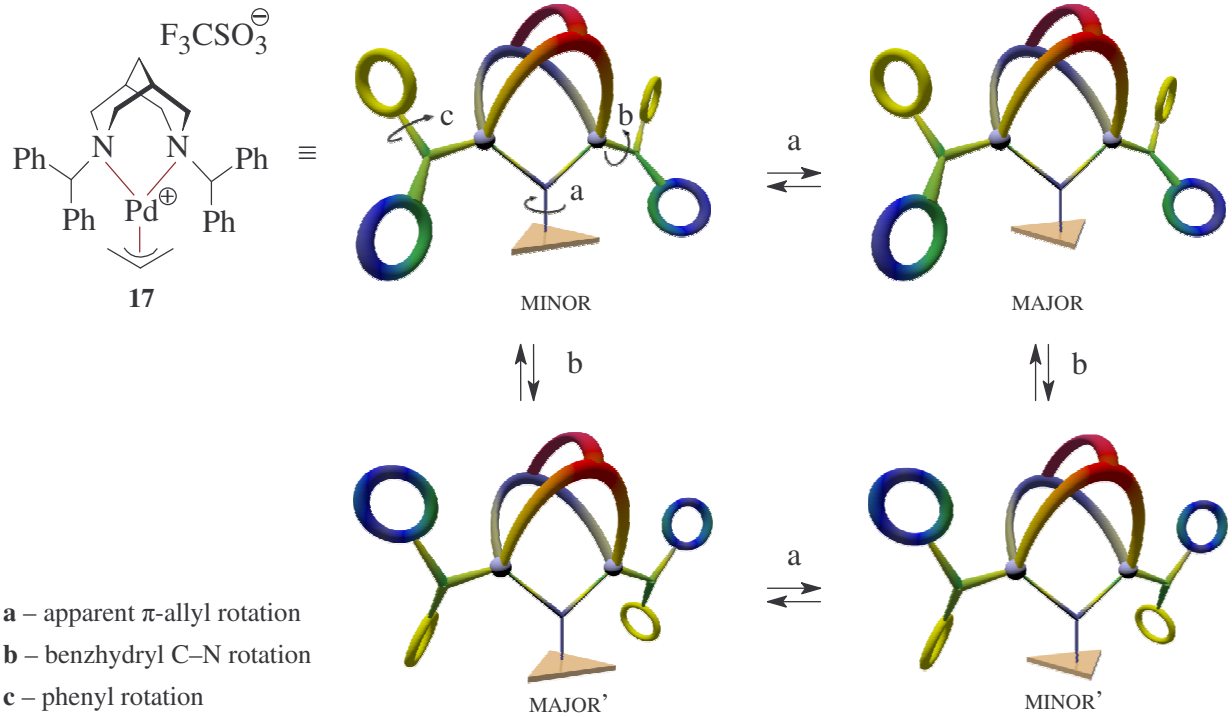
Figure 31. Orientation of the allyl group and transformation of the major isomer to the minor isomer

5.2.2. RESULTS: DYNAMICS

As the NMR spectra of this type of complexes usually are characterised by dynamic phenomena, we needed to investigate these in more detail (Scheme 21).

The two-dimensional EXSY[61] spectrum at -30 °C shows large exchange cross-peaks between the two different species and small exchange cross-peaks between the two sides of each of the isomers. The two forms are different, and will have different energies and populations. A third dynamic process, which can be observed, is restricted phenyl rotation. At very low temperatures (less than -70 °C), where the other dynamic processes have been frozen out, only this can be seen. Overlapping signals in the aromatic region prevented a quantitative evaluation of this process.

There can be two dynamic processes for the unequal-population exchange process of the major complex to the minor complex: a) apparent π-allyl rotation and b) benzhydryl rotation about the C–N bond (Scheme 21). It is not possible to differentiate the NMR parameters for these two processes. If the two processes take place sequentially, then there is mutual exchange between the two faces of the same complex and the NMR parameters before and after the exchange are identical. A distinction of the processes can not be made, due to the symmetry of the π-allyl ligand.



a – apparent π-allyl rotation
b – benzhydryl C–N rotation
c – phenyl rotation

Scheme 21. Dynamic behaviour of the (π-allyl)palladium complex **17**

Rate constants (*k*) for the rotation of the allyl and benzhydryl groups were obtained via line-shape analysis from ^{1}H NMR spectra recorded at 4 different temperatures in the temperature range 203-298 K. Line-shape calculations were performed with the gNMR program[62] by fitting of the exchange rate and several resonance frequencies (*e.g.* CH-2 of the allyl group, or bispidine skeleton equatorial-CH) of the exchanging species. This calculated spectrum can then be compared to the real spectrum, and adjustments made to the parameters to improve the fit. It was assumed that the observed dynamic processes have zero speed at -70 °C. The errors were estimated also from the lineshape-fitting.

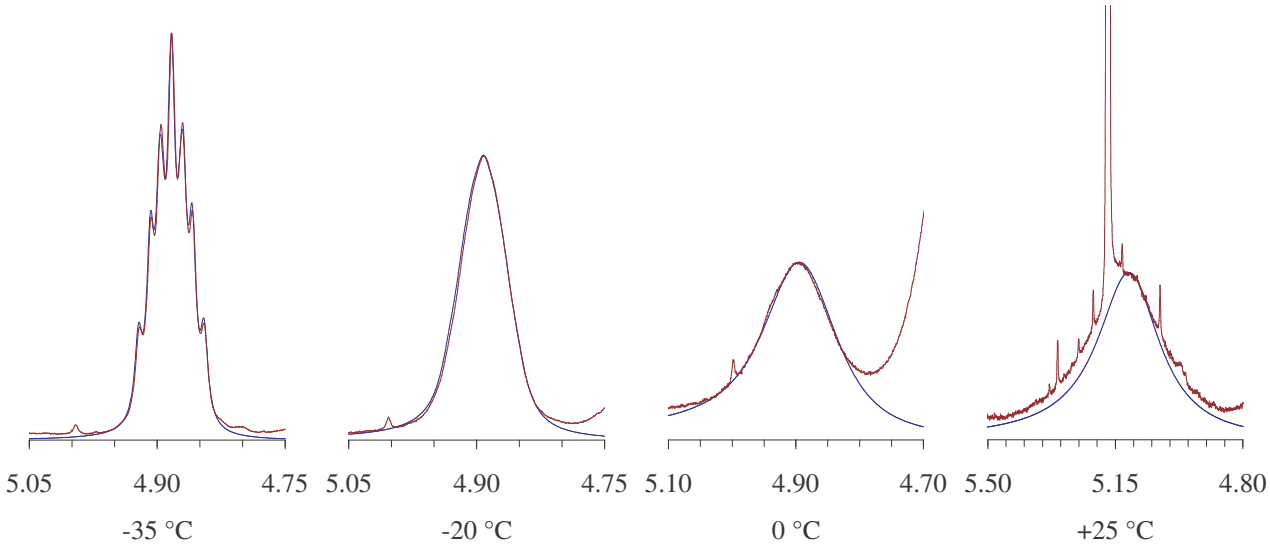


Figure 32. Allylic H-2 ^{1}H NMR signal region of **17** at 4.9 ppm at different temperatures (— simulated spectrum, — measured spectrum)

Rotation of the bispidine bicycle: $k_{obs1} = A \cdot k_a + B \cdot k_b$

Mutual rotation of the bispidine bicycle: $k_{obs2} = C \cdot (k_a + k_b)$

Appearent π-allyl rotation: $k_{obs3} = k_{obs1} + k_{obs2}$

* A, B, C are constants. C is a small number,

k_a – rate of π-allyl rotation; k_b – rate of benzhydryl C–N bond rotation

Table 10. Dynamic NMR data for the π-allyl and benzhydryl rotations of **17**

T, K	**k_{obs1}, s^{-1}**	**k_{obs2}, s^{-1}**	**k_{obs3}, s^{-1}**
203	0	0	0
238	32 ± 3	3 ± 1	36 ± 1
253	110 ± 20	27 ± 10	125 ± 5
273	600 ± 100	135 ± 40	600 ± 30
298	2500 ± 400	160 ± 60	2600 ± 400

The activation parameters ($\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) were determined from an Eyring plot (Figure 34) of ln(k/T) versus 1/T.[63] The slope gives the enthalpy of activation, and the intercept gives the entropy.

$$\ln\left(\frac{k_{obs}}{T}\right) = -\frac{\Delta H^{\ddagger}}{R \cdot T} + \frac{\Delta S^{\ddagger}}{R} + \ln\left(\frac{k_B}{h}\right)$$

Figure 33. The Eyring equation

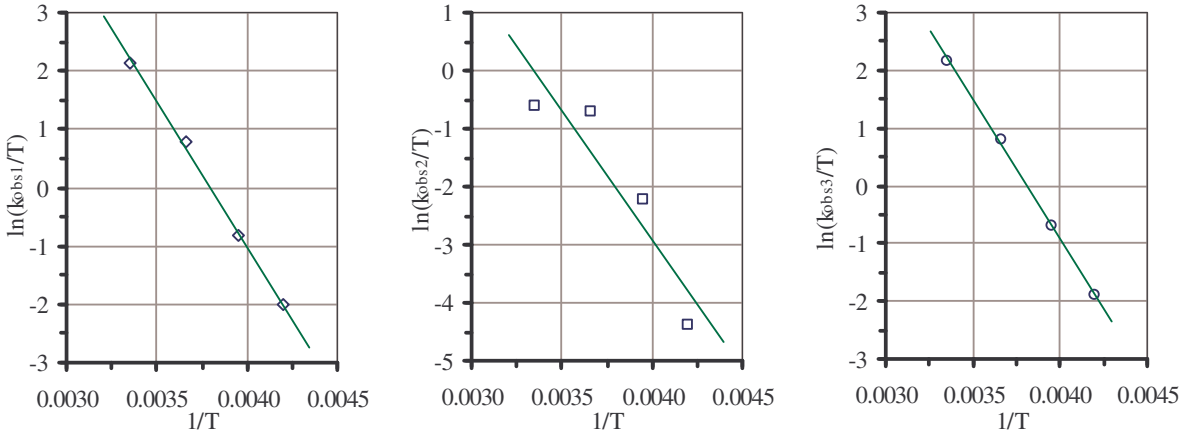


Figure 34. Eyring plots for the observed dynamic processes of **17**

Table 11. The activation parameters

	$\Delta H^{\ddagger}$, kJ·mol^{-1}	$\Delta S^{\ddagger}$, J·K^{-1}·mol^{-1}	$\Delta G^{\ddagger}_{-20\,°C}$, kJ·mol^{-1}
k_{obs1}	41.3 ± 0.6	–41.0 ± 3.6	51.6 ± 0.3
k_{obs2}	37.0 ± 0.3	–73.9 ± 4.5	55.7 ± 0.9
k_{obs3}	40.2 ± 1.3	–44.5 ± 5.5	51.4 ± 0.1

Large negative value for the entropy factor $\Delta S^{\ddagger}$ is consistent with associative processes and bond making steps, also expected for highly ordered transition states. However, getting reliable values of $\Delta S^{\ddagger}$ requires recording the NMR over a large range of temperatures because the error associated with the Eyring plot is large. At higher temperature, the error gets larger because the line-shape analysis is affected by broad overlapping signals.

The current investigation is quite in line with the previous data (Table 12), although the current results are not for any single process. Ligands with higher pK_a of the conjugated acid have higher activation energies for the apparent π-allyl rotation due to the stronger nitrogen-palladium bond.

Table 12. Previously reported $\Delta G^{\ddagger}$ values for the apparent π-allyl rotation at coalescence temperature[16] and the pK_a^{MeCN} values of the bispidinones

Complex	pK_a^{MeCN}	$\Delta G^{\ddagger}$, kJ·mol^{-1}
[(**13**)(π-allyl)Pd]CF_3SO_3	8.11	40
[(**14**)(π-allyl)Pd]CF_3SO_3	13.79	52.7
[(**7**)(π-allyl)Pd]CF_3SO_3	17.48	57.5

As the investigation with the smallest possible (π-allyl)palladium ligand indicated, the steric interactions were very tight, therefore the complex was quite labile. Attempts to use larger (π-allyl)palladium ligands (*e.g.* bis[(1,3-η^3-butenyl)palladium chloride]) in identical manner did not result in formation of bispidine complexes. *N*,*N*´-Dibenzhydrylbispidinone **11** gave only traces of possible complexes, which were not analysed further.

5.2.3. Adamantanoid Hexanuclear (π-Allyl)Pd(II)-(μ_3-Hydroxo) Cluster

It was very important to obtain accurate X-ray crystallographic structural information for at least one of the (π-allyl)palladium complexes detected in the solution by NMR spectroscopy. During the crystallisation: after one day small white needle-like crystals appeared, and after 2-3 days small cubic yellow crystals formed (Appendix I and II). X-ray crystallography showed that they did not contain bispidine but a cluster that had a distorted adamantanoid geometry:

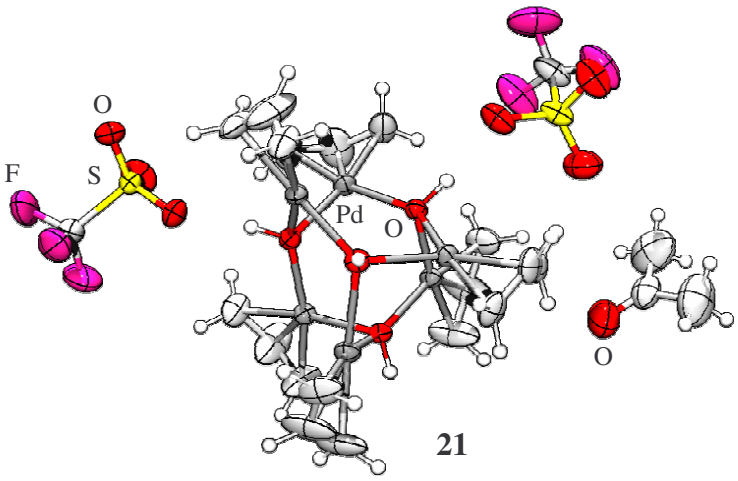


Figure 35. Treating bis[(1,3-η^3-propenyl)palladium chloride] with a bulky, basic dinitrogen ligand in the presence of traces of water results in the formation of an unusual, adamantanoid (η^3-propenyl-Pd)$_6$(μ_3-OH)$_4$ cluster **21**. Thermal ellipsoids at the 50% probability level.

The yield of the cluster **21** was estimated to be around 5%. Those yellow crystals decomposed within a week, forming Pd-black precipitate.

Hydroxo complexes of transition metals usually form by ligand exchange with water.[64] We propose that this is the case also in formation of the cluster. The sequence of steps leading to **21** is coupled to the dynamic process of apparent π-allyl rotation observed in (π-allyl)Pd complexes with chelating dinitrogen ligands.[60] The initial steps leads to the formation of complex **17**, in which steric strain between the organic ligands is released by dissociation of one of the chelating nitrogen atoms. The resulting coordinatively unsaturated complex is then stabilised by hydroxyl ions, generated by deprotonation of water by the strongly basic ligand **10**.[65] In conclusion, ligand **10**, although itself not part of the cluster **21**, appears to be responsible for the formation of this new type of palladium complex.

6. SUMMARY AND OUTLOOK

In the present study, a range of bispidines and bispidinones were synthesised and studied by the means of NMR methods and pK_a values of their conjugate acid forms in acetonitrile were measured. The (1,3-η^3-propenyl)palladium complex with *N*,*N*'-dibenzhydrylbispidine was prepared and studied in solution. All the aliphatic signals in the ^{1}H and ^{13}C NMR spectra were identified and also dynamic parameters were calculated. Interligand NOEs allowed the determination of the three-dimensional structures of the two (π-allyl)palladium complex isomers. The bispidine host ligand gave the expected anisotropy effects, but the steric interactions were too tight to form suitable crystals for the X-ray crystallographic study. Instead, due to the presence of traces of water, we isolated an unusual, adamantanoid (η^3-propenyl-Pd)$_6$(μ_3-OH)$_4$ cluster. It was also found that larger (π-allyl)palladium ligands did not form complexes with this bulky bispidine ligand at all.

A more distant goal is to extend the scope of host molecules. The bispidine-type molecules afford making complexes with a limited group of guests, (π-allyl)palladium complexes, and also the cavity in the bispidines is oriented unfavourably for complexation of longer guests. Therefore, we need a new kind of molecular tool that has a differently oriented cavity (Figure 36):

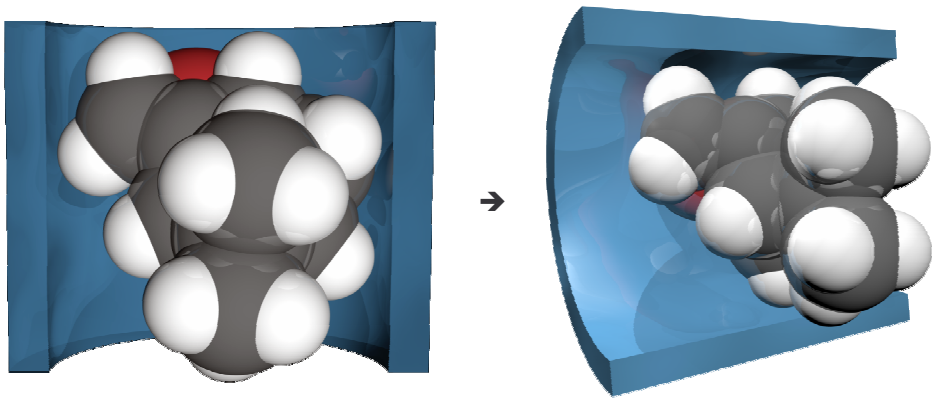


Figure 36. A schematic figure showing different orientation of the cavity with respect to the coordination plane

7. KOKKUVÕTE

Käesoleva magistritöö „Bispidiinil põhinevad kunstlikud retseptorid orgaaniliste molekulide struktuuri uurimiseks" eesmärgiks oli laiendada bispidiinil põhinevate kunstlike retseptorite valikut, mida annaks kasutada nendega komplekseeruvate molekulide struktuuri uurimiseks. Sünteesiti rida bispidiini ja bispidinooni derivaate, uuriti nende TMR spektreid ja määrati aluselisusi atsetonitriili keskkonnas. Ühe peaeesmärgina sünteesiti *N*,*N*´-dibenshüdrüülbispidiini kompleksühend (1,3-η^3-propenüül)pallaadiumligandiga. Määrati kindlaks kõik alifaatsetele vesinikele ja süsinikele vastavad ^{1}H ja ^{13}C TMR-i signaalid ning arvutati dünaamilised parameetrid. Ligandidevahelised NOE-d võimaldasid määrata selle kompleksühendi isomeeride 3-mõõtmelised struktuurid. Antud bispidiini derivaat omas ligandina oodatud anisotroopseid efekte, kuid röntgenstruktuuranalüüsiks sobivaid kristalle saada ei õnnestunud. Hoopiski, tänu lahuses olevale niiskusele tekkisid ebatavalise adamantaanilaadse (η^3-propenüül-Pd)$_6$(μ_3-OH)$_4$ klasteri kristallid. Samuti leiti, et suuremad (π-allüül)palladium ligandid ei moodusta samades tingimustes *N*,*N*´-dibenshüdrüülbispidiiniga kompleksühendeid, millest järeldus, et antud bispidiini derivaadil on kunstliku retseptorina vaid väga kitsas rakendus.

8. ACKNOWLEDGMENTS

Hereby, I would like to express my sincere gratitude to all the persons who have helped during my studies in Estonia and in Sweden.

I want to thank Assoc. Prof. Adolf Gogoll for accepting me as a research student in his group and for guidance during these years. It is seldom that one encounters a person with so much idealism, strictness, enthusiasm and dedication as he has.

I would like to thank Assoc. Prof. Uno Mäeorg – really the best supervisor I have ever had – for keeping good contacts with me during the last years, for his invaluable suggestions concerning synthetic challenges and also for administrative assistance.

Many thanks to Prof. Helena Grennberg for occasional suggestions, critical comments and proof-reading of the present thesis.

Most of the investigation was carried out at Uppsala University. However, Prof. Ivo Leito kindly offered help for measuring a series of pK_a values by his research group. I am sure I would have struggled for months trying to measure some (and very likely not so reliable) basicity values on my own. It has been a pleasure being in a collaboration with you!

I am also very much obliged to my first supervisor in Sweden, Ph.D. Karl-Johan Winberg, for help and for being a good friend.

I would like to thank past and present members of the GG-group and of the whole department for being around and for lively discussions concerning also other things than chemistry.

Special thanks to the administrative and technical personnel of the department for making things work.

I am very grateful to my old friends outside the department for not forgetting me, and new friends for trying to find out what kind of person I actually am.

Last but not least, I would like to thank my family for their support and encouragement.

9. REFERENCES

[1] Lehn, J.-M. Supramolecular Chemistry – Scope And Perspectives. Molecules – Supermolecules – Molecular Devices. *Nobel lecture*, December 8, **1987**.

[2] König, B. Supramolecular Chemistry – where we are and where we go! *European Chemistry Chronicle*, **1999**, *3*, 17-20.

[3] Goswami, S., Hamilton, A.D., Engen, D.V. Nucleotide base recognition: a macrocyclic receptor for adenine employing hydrogen bonding and aromatic stacking interactions. *J. Am. Chem. Soc.*, **1989**, *111*, 3425-3426.

[4] Lüning, U. Concave reagents. *J. Mater. Chem.*, **1997**, *7*, 175-182.

[5] Zimmerman, S.C., Zeng, Z., Wu W., Reichert, D.E. Synthesis and structure of molecular tweezers containing active site functionality. *J. Am. Chem. Soc.*, **1991**, *113*, 183-196.

[6] Lehn, J.M., Sauvage, J.P. [2]-Cryptates: stability and selectivity of alkali and alkaline-earth macrobicyclic complexes. *J. Am. Chem. Soc.*, **1975**, *97*, 6700-6707.

[7] Solov'ev, V.P., Strakhova, N.N., Kazachenko, V.P., Solotnov, A.F., Baulin, V.E., Raevsky, O.A., Rüdiger, V., Eblinger, F., Schneider, H.-J. Steric and Stereoelectronic Effects in Aza Crown Ether Complexes. *Eur. J. Org. Chem.*, **1998**, 1379-1389.

[8] Klärner, F.G., Panitzky, J., Preda, D., Scott, L.T. Modeling of supramolecular properties of molecular tweezers, clips, and bowls. *J. Mol. Model.*, **2000**, *6*, 318-327.

[9] Shriver, D.F., Atkins, P.W., Langford, C.H. *Inorganic Chemistry*, Oxford University Press, 2nd Ed., **1995**.

[10] Togni, A., Venanzi, L.M. Nitrogen donors in organometallic chemistry and homogeneous catalysis. *Angew. Chem. Int. Ed.*, **1994**, *33*, 497-526.

[11] Johansson, C. Molecular tools for structure determination by NMR spectroscopy. *Licentiate thesis*, **2001**.

[12] Albinati, A., Ammann, C., Pregosin, P.S., Ruegger, H. Two-dimensional ^{1}H NOESY of Pd(II) π-allyl complexes. The concept of reporter ligands and the molecular structure of [cyclic][Pd(η^3-$CH_2CCHCH_2CH_2CH_2$)(biquinoline)]CF_3SO_3. *Organometallics*, **1990**, *9*, 1826-1833.

[13] Johnson, C.E.J., Bovey, F.A. Calculation of nuclear magnetic resonance spectra of aromatic hydrocarbons. *J. Chem. Phys.*, **1958**, *29*, 1012–1014

[14] Gogoll, A., Gomes, J., Bergkvist, M., Grennberg, H. Configuration assignment of acyclic (π-allyl)palladium complexes: analytical application of chelating nitrogen ligands. *Organometallics*, **1995**, *14*, 1354-1364.

[15] Deeming, A.J., Rothwell, I.P., Backer-Dirks, J.D.J., Hursthouse, M.B. Pyramidal nitrogen atoms in a diquinolyl chelate ring: X-ray crystal structure of allyl (8,8'-dimethyl-2,2'-diquinolyl)-palladium(II) perchlorate dichloromethane solvate. *J. Chem. Soc., Chem. Commun.*, **1979**, 670-672.

[16] Axén, A., Grennberg, H., Gogoll, A. (π-Allyl)palladium Complexes with *N*,*N*'-diphenylbispidinone derivatives as a new type of chelating nitrogen ligand: complexation studies,

spectroscopic properties, and an X-ray structure of (3,7-diphenyl-1,5-dimethylbispidinone)[(1,3-η^3-propenyl)palladium] Trifluoromethanesulfonate. *Organometallics*, **1997**, *16*, 1167–1178.

[17] Gogoll, A., Grennberg, H., Axén, A. Conformational restriction of acyclic π-allyl ligands in (3,7-diphenyl-1,5-dimethylbispidinone)(η^3-alkenyl)palladium complexes. *Organometallics*, **1998**, *17*, 5248-5253.

[18] Johansson, C., Axén, A., Grennberg, H., Gogoll, A. Determination of absolute configuration of (π-allyl)palladium complexes by NMR spectroscopy and stereoselective complexation. *Chem. Eur. J.*, **2001**, *7*, 396–403.

[19] Axén, A. Bispidine derivatives as molecular tools for studies of (π-allyl)palladium complexes. Ph.D. Thesis, Uppsala University, **1998**.

[20] Sasaki, T., Eguchi, S., Kiriyama, T., Sakito, Y. Studies on heterocage compounds. IV. Through-σ-bond interaction of β-amino ketone moiety in 1,3-diazaadamantan-6-one and 3,6-diazahomoadamantan-9-one systems. Structure and reactivity. *J. Org. Chem.*, **1973**, *38*, 1648-1652.

[21] Haack, K.-J., Goddart, R., Pörscke, K-R. Applying the macrocyclic effect to smaller ring structures. *N*,*N*'-dimethyl-3,7-diazabicyclo[3.3.1]nonane nickel(0) complexes. *J. Am. Chem. Soc.*, **1997**, *119*, 7992-7999.

[22] a) Huttenloch, O., Laxman, E., Waldmann, H. Solid-phase development of chiral phosporamidite ligands for enantioselective conjugate addition reactions. *Chem. Eur. J.*, **2002**, *8*, 4767-4780. b) Huttenloch, O., Laxman, E., Waldmann, H. Combinatorial development of chiral phosphoramidite-ligands for enantioselective conjugate addition reactions. *Chem. Commun.*, **2002**, 673-675.

[23] Douglass, J.E., Ratliff, T.B. The Synthesis of Some 3,7-Dialkyl-3,7-diazabicyclo[3.3.1]nonanes and a Study of Their Conformations. *J. Org. Chem.,* **1968**, *33*, 355-359.

[24] Kuehne, M.E., Muth, R.S. Total syntheses of *yohimbe* alkaloids, with stereoselection for the normal, allo, and 3-epiallo series, based on annelations of 4-methoxy- l,2-dihydropyridones. *J. Org. Chem.*, **1991**, *56*, 2701-2712.

[25] Miyahara, Y., Goto., K., Inazu, T. Convenient synthesis of 3,7-diazabicyclo[3.3.1]nonane (bispidine). *Synthesis*, **2001**, *3*, 364-366.

[26] Nigam, S.C., Mann, A., Taddei, M., Wermuth, C.-G. Selective removal of the *tert*-butoxycarbonyl group from secondary amines. $ZnBr_2$ as the deprotecting reagent. *Synth. Commun.*, **1989**, *19*, 3139-3142.

[27] Stetter, H., Henning, H. Über Verbindungen mit Bispidin-Struktur, VI. Mitteil.: Synthese des 1,3-Diaza-adamantans. *Chem. Ber.*, **1955**, *88*, 789-795.

[28] Galinovsky, F., Langer, H. Synthesis of 1,3-diazaadamantane and of bispidine. *Monatsh. Chem.*, **1955**, *86*, 449-453.

[29] Danieli, B., Lesma, G., Passarella, D., Silvani A., Viviani, N. An efficient chemoenzymatic access to chiral 3,7-diazabicyclo[3.3.1}nonane derivatives. *Tetrahedron*, **1999**, *55*, 11871-11878.

[30] Yarkmukhamedov, N.N., Baibulatova, N.Z., Dokichev, V.A., Tomilov, Y.V., Yunusov, M.S. A new method for the synthesis of 3,7-diazabicyclo[3.3.1]nonanes. *Russian Chem. Bull., Int. Ed.*, **2001**, *50*, 753-754.

[31] Welch, C.J. An experiment to demonstrate magnetic nonequivalence in proton NMR. *J. Chem. Ed.*, **1997**, *75*, 247-248.

[32] Smissman, E.E., Ruenitz, P.C. Analogues of sparteine II. Synthesis of *N*-monoalkylbispidines and *N*,*N*'-dialkylbispidines. *J. Org. Chem.*, **1976**, *41*, 1593-1597.

[33] Zefirov, N.S., Gogozina, S.V. Conformational study of heteroanalogues of bicyclo[3.3.1]nonane. *Tetrahedron*, **1974**, *30*, 2345-2352.

[34] Galík, V., Landa, S. Über Sticksoffhaltige Adamantanverbinungen II. Synthese von 1,3-Diazaadamantan. *Collect. Czech. Chem. Commun.*, **1973**, *38*, 1101-1103.

[35] Džakula, Z., Westler, W.M., Edison, A.S., Markley, J.L. The "CUPID" method for calculating the continuous probability distribution of rotamers from NMR data. *J. Am. Chem. Soc.*, **1992**, *114*, 6195-6199.

[36] Karplus, M. Vicinal proton coupling in nuclear magnetic resonance. *J. Am. Chem. Soc.*, **1963**, *85*, 2870-2871.

[37] McCabe, P.H., Milne, N.J., Sim, G.A. Conformational control in the 3,7-diazabicyclo[3.3.1]nonane system. *J. Chem Soc., Chem. Commun.*, **1985**, 625-627.

[38] Gogoll, A., Grennberg, H., Axén, A. Chemical shift assignment of geminal protons in 3,7-diazabicyclo[3.3.1]nonanes: an unexpected deviation from the axial/equatorial chemical shift order. *Magn. Reson. Chem.*, **1997**, *35*, 13-20.

[39] PC Spartan Plus, v. 2.0.0, Wavefunction, Inc, **2000**.

[40] Kövér, K.E., Prakash, O., Hruby, V.J. Improved 2D inverse proton detected C,H-correlation NMR techniques for the total assignment of carbon resonances of a highly delta opioid receptor agonist peptide. *Magn. Reson. Chem.*, **1993**, *31*, 231-237.

[41] Uhrín, D., Liptaj, T., Hricovini, M., Capek, P. Determination of long-range proton carbon-13 coupling constants using modified 2D J-resolved experiments. *J. Magn. Reson.*, **1989**, *85*, 137-140.

[42] Farrugia, L. J. ORTEP-3 for Windows - a version of ORTEP-III with a graphical user interface. *J. Appl. Cryst.*, **1997**, *30*, 565.

[43] Garrison, G.L., Berlin, K.D., Scherlag, B.J., Lazzara, R., Patterson, E., Fazekas, T., Sangiah, S., Chen, C.L., Schubot, F. D., van der Helm, D. Novel 3,7-Diheterabicyclo-[3.3.1]nonanes that possess predominant class III antiarrhythmic activity in 1-4 day post infarction dog models: X-ray diffraction analysis of 3-[4-(1*H*-Imidazol-1-yl)benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane dihydroperchlorate. *J. Med. Chem*, **1996**, *39*, 2559-2570.

[44] Henck, J.O., Finner, E., Burger, A. Polymorphism of Tedisamil dihydrochloride. *J. Pharm. Sci.*, **2000**, *89*, 1151-1159.

[45] Katrusiak, A., Kałuski, Z., Skolik, J. Molecular and crystal structure of β-isosparteine monoperchlorate. *J. Crystallogr. Spectrosc. Res.*, **1988**, *18*, 353-364.

[46] Levina, O.I., Potekhin, K.A., Kurkutova, E.N., Struchkov, Y.T., Palyulin, V.A., Zefirov, N.S. Crystal and molecular structure of 3,7-diphenyl-3,7-diazabicyclo[3.3.1]nonane, $C_{19}H_{22}N_2$. *Dokl. Akad. Nauk SSSR*, **1984**, *277*, 367-370.

[47] Zefirov, N.S., Palyulin, V.A., Levina, O.I., Potekhin, K.A., Kurkutova, E.N., Struchkov, Y.T. Crystal and molecular structure of 2,2-dimethyl-5,7-diphenyl-1,3-diazaadamantane. *Vestn. Mosk. Univ., Ser. 2: Khim.*, **1987**, *28*, 276-279.

[48] Levina, O.I., Kurkutova, E.N., Potekhin, K.A., Struchkov, Y.T., Palyulin, V.A., Zefirov, N.S. 3,7-Dimethyl-1,5-diphenyl-3-aza-7-azoniabicyclo[3.3.1]nonan-9-one hydrogen sulfate hemihydrate, $[C_{21}H_{25}N_2O]^+ HSO_4^-·½H_2O$. *Cryst. Struct. Commun.*, **1982**, *11*, 1915-1919.

[49] Tyagi, S., Berlin, K.D., Hossain, M.B., Sinars, C., Van Der Helm, D., Sangiah, S. Novel 9,9-diol systems starting from a 3,7-diazabicyclo[3.3.1]nonan-9-one nucleus. Single crystal X-ray diffraction analysis of 3-(2-propyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane-9,9-diol hydrobromide, 3-(2-propyl)-7-[3,4-dimethoxybenzyl)-3,7-diazabicyclo[3.3.1]nonane-9,9-diol hydrobromide, and 3,7-diisopropyl-3,7-diazabicyclo[3.3.1]nonane-9,9-diol dihydrochloride. *Phosphorus, Sulfur and Silicon*, **1997**, *123*, 385-406.

[50] Vatsadze, S.Z., Zyk, N.V., Churakov, A.V., Kužmina, L.G. Structure of 3,7-diazabicyclo-[3.3.1]nonane complexes as the basis of creating new metallocyclic supramolecular ensembles. *Chem. Heterocyclic Comp.*, **2000**, *36*, 1103-1107.

[51] Levina, O.I., Potekhin, K.A., Kurkutova, E.N., Struchkov, Y.T., Zefirova, O.N., Palyulin, V.A., Zefirov, N.S. Crystal and molecular structure of 1:1 complex of 3,7-dimethyl-1,5-diphenyl-9-bispidone with copper(II) chloride. *Dokl. Akad. Nauk SSSR*, **1986**, *289*, 876-879.

[52] Gierczyk, B., Łeska, B., Nowak-Wydra, B., Schroeder, G., Wojciechowski, B., Bartl, F., Brzezinski, B. ^{15}N NMR and FTIR studies of 2,4-dinitroanilines and their salts. *J. Mol. Struct.*, **2000**, *524*, 217-225.

[53] Leito, I., Kaljurand, I., Koppel, I.A., Yagupolskii, L.M., Vlasov, V. Spectrophotometric acidity scale of strong neutral Brønsted acids in acetonitrile. *J. Org. Chem.*, **1998**, *63*, 7868-7874.

[54] Kaljurand, I., Rodima, T, Leito, I., Koppel, I.A., Schwesinger, R. Self-consistent spectrophotometric basicity scale in acetonitrile covering the range between pyridine and DBU. *J. Org. Chem.*, **2000**, *65*, 6202-6208.

[55] Boczoń, W., Jasiewicz, B. Synthesis and conformational analysis of disubstituted sparteine derivatives. *Collect. Czech. Chem. Commun.*, **2003**, *68*, 696-710.

[56] Dahn, H., Farine, J.-C., Nguyên, T.T. On the basicity of triarylmethylamines in solution. *Helv. Chm. Acta*, **1980**, *63*, 780-787.

[57] Kütt, A., Kaljurand, I., Miyahara, Y., Leito, I. Unpublished results, **2004**.

[58] Marek, R., Lyčka, A. ^{15}N NMR spectroscopy in structural analysis. *Current Organic Chemistry*, **2002**, *6*, 35-66.

[59] Davies, J.A. Palladium-carbon π-bonded complexes. *Comprehensive Organometallic Chemistr II*, Eds. Abel, E.W., Stone, F.G., Wilkinson, G. *Vol. 9*, Pergamon Press, **1995**.

[60] Gogoll, A., Örnebro, J., Grennberg, H., Bäckvall, J.-E. Mechanism of apparent π-allyl rotation in (π-allyl)palladium complexes with bidentate nitrogen ligands. *J. Am. Chem. Soc.,* **1994**, *116*, 3631-3632.

[61] Perrin, C.L., Dwyer, T.J. Application of two-dimensional NMR to kinetics of chemical exchange. *Chem. Rev.*, **1990**, *90*, 935-967.

[62] gNMR version 4.1.0. IvorySoft/Cherwell Scientific Publishing: Oxford, **1999**.

[63] Eyring, H. The activated complex in chemical reactions. *J. Chem. Phys.*, **1935**, *3*, 107-115.

[64] Appleton, T.G, Bailey, J.A., Bedgood, D.R., Hall, J.R. Amino acid complexes of palladium(II). 1. NMR study of the reactions of the diaqua(ethylenediamine)palladium(II) cation with ammonia, betaine, and the amino acids $^{+}NH_3(CH_2)_nCO_2^{-}$ (n=1-3). *Inorg. Chem.* **1994**, *33*, 217.

[65] The pK_a of (**2**·H)$^{+}$ in acetonitrile is 17.81: Toom, L., Kütt, A., Kaljurand, I., Leito, I., Grennberg, H., Gogoll, A. *In preparation*.

I

Angew. Chem., Int. Ed., **2005**, Accepted

LIGAND-INDUCED FORMATION OF AN ADAMANTANOID HEXANUCLEAR (π-ALLYL)Pd(II)-(μ_3-HYDROXO) CLUSTER STACKED AS HYDROGEN-BONDED DOUBLE-STRANDS

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Hydroxo complexes of transition metals are of interest to *e.g.* materials science as precursors for intricate metal oxides,[1] and as intermediates in metal-mediated or catalyzed processes. Hydroxopalladium intermediates have been postulated in some palladium-catalyzed reactions,[2] and they may explain the unexpected stability of some palladium catalysts in the presence of water.[3] In most of its hydroxo complexes, palladium is coordinated to further heteroatom ligands containing P and/or N atoms. Notable exceptions are (μ_2-hydroxo)bis(η^2,η^2-cyclooctadiene)dimethyl-di-palladium(II)hexafluoro antimonate[4a] and bis(tetrabutylammonium)bis[(μ_2-hydroxo)bis(pentafluorophenyl)palladium],[4b] which contain palladium coordinated to η^2-alkene or σ-C ligands, respectively. Isolated hydroxopalladium complexes usually display polynuclearity.[5] The formation of a trinuclear palladium complex was attributed to the presence of traces of water during purification.[6] Trinuclear, mixed-metal complexes were obtained by reaction between hydroxopalladium and metal hydride complexes.[7] Larger clusters of Pd with predominantly carbon monoxide ligands are known, and non-hydroxo palladium clusters of catalytic interest have been studied.[8] A mixed metal cluster (Pd/Cu) with an adamantanoid Pd-oxygen substructure (hexanuclear in Pd) but without organic ligands on the palladium has been described.[9]

In this communication, we report the first example of an organometallic, homonuclear hydroxo(π-allyl-Pd) cluster **1**, [(1,3-η^3-propenyl-Pd)$_6$(μ_3-OH)$_4$](CF$_3$SO$_3$)$_2$, without further heteroatom (P or N) ligands. The cluster has a distorted adamantanoid geometry and the crystal lattice consists of clusters, linked by hydrogen bonds via bridging counter ions into double strands.

Cluster **1** was obtained during a an attempted complexation of the sterically hindered bispidine ligand *N*,*N*'-bis(diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonane **2** with a (π-

allyl)palladium species, where we expected to obtain complex **3** (Figure 1). The formation of **3** was proven by ^{1}H NMR spectroscopy.[10] However, when trying to isolate solid **3** from acetone solution, we observed initial formation of colorless, needle-shaped crystals of the protonated ligand salt, **2**·CF_3SO_3H. Upon further undisturbed standing, the precipitation of yellow, rhomboid crystals was observed in experiments using technical grade solvent. Under dry conditions, Pd black precipitated. These crystals were stable for several days at refrigerator temperature (below +4 °C) while covered by the crystallisation solvent. Isolated crystals were reasonably stable in air at ambient temperature for several hours. To our surprise, the yellow crystals were not of the expected complex **3**, but of an adamantanoid (π-allyl)Pd(II) cluster **1** with bridging hydroxo ligands. To the best our knowledge, this is the first example of an organometallic cluster of palladium of this type.[11,14]

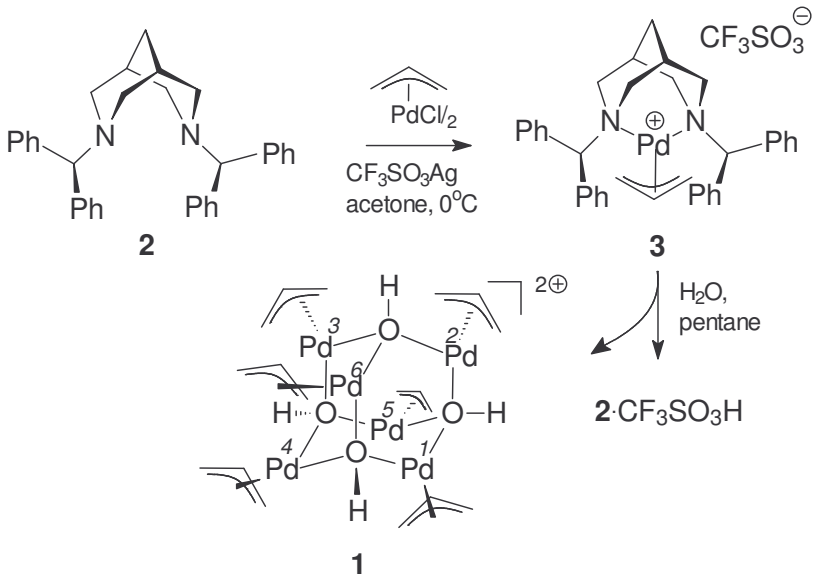

Figure 1. Ligand-induced formation of cluster **1**, hexa(1,3-η^3-propenyl)tetra(μ$_3$-hydroxo)-palladium bistrifluorosulfonate, via complex **3**. The $Pd_6(OH)_4$ subunit is emphasized. Trifluorosulfonate anions omitted for clarity.

The Pd-C distances in cluster **1** vary between 2.048 – 2.082 Å (propenyl C-2) and 2.093 – 2.115 Å (propenyl C-1 and C-3). This is shorter than in the chloro dimer bis[(1,3-η^3-propenyl)palladium chloride] (2.121 Å for C-2, 2.108 – 2.123 Å for C-1 and C-3),[12] and in (1,3-η^3-propenyl)palladium-(*N*,*N*'-diphenyl-1,5-dimethyl-3,7-diazabicyclo[3.3.1]-nonane-9-one)trifluoromethanesulfonate (2.128 Å for C-2 and 2.125 – 2.126 Å for C-1 and C-3),[15] most likely due to the small trans influence of μ$_3$-hydroxo ligands on the Pd-C bond compared to that of Cl or N ligands.

The Pd-O distances in cluster **1**, ranging from 2.133 to 2.179 Å, are shorter than in the only other reported Pd-(μ_3-OH) cluster, {[Pd(8-methylquinoline)]$_3$(μ_3-$Ph_2PCHCOO$-C_2H_5)(μ_3-OH)}PF_6, which are between 2.144 to 2.281 Å.[4] In comparison with a series of μ_2-OH complexes, the Pd-(μ_3-OH) distances in **1** are similar[16a] or significantly longer[4,16b-e] than in the μ_2-OH complexes, where a common feature is that the Pd-μ_2-O bond experiences significantly less trans influence from other ligands than is exerted by the (η^3-propenyl) ligands in **1**.

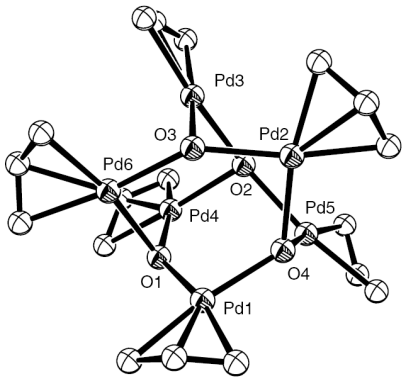

Figure 2. Molecular structure of cluster **1** (counter-ions omitted for clarity)

The dicationic clusters of complex **1** are grouped into pairs, linked by two $CF_3SO_3^-$ anions hydrogen-bonded to the hydroxy ligands (connecting O3↔O4' and O4↔O3'). These pairs are then linked into double strands of clusters via two more $CF_3SO_3^-$ anions connecting O1↔O2' and O2↔O1', respectively (Figure 3). Hydrogen bond lengths are shorter between pairs than in the chains of clusters, with CF_3SO_3···(μ_3-HO) distances at 2.839 Å and 2.872 – 2.921 Å, respectively. Thus, each cluster is surrounded by four shared anions, leading to a regular crystal lattice composed of double strands.

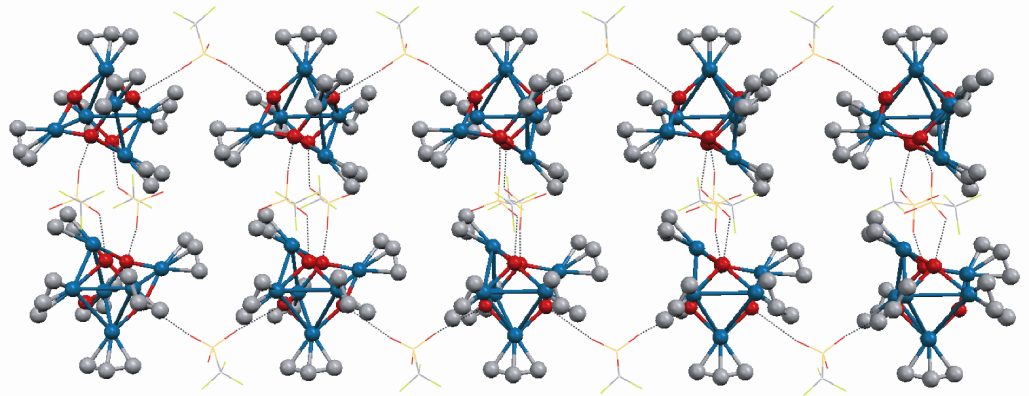

Figure 3. Double strands of clusters of **1**. Cluster pairs bonded via two $CF_3SO_3^-$ anions (between O3↔O4' and O4↔O3') are linked into strands via $CF_3SO_3^-$ anions connecting O1↔O2' and O2↔O1', respectively. Hydrogen bonds are indicated (·····, hydrogens omitted for clarity). The lattice contains one acetone molecule per cluster (not shown).

Hydroxo complexes of transition metals usually form by ligand exchange with water.[5b,17] We propose that this is the case also in formation of cluster **1**. The sequence of steps leading to **1** is coupled to the dynamic process of apparent π-allyl rotation observed in (π-allyl)Pd complexes with chelating dinitrogen ligands.[18] The initial steps leads to the formation of complex **3**, in which steric strain between the organic ligands is released by dissociation of one of the chelating nitrogen atoms. The resulting coordinatively unsaturated complex is then stabilized by hydroxyl ions, generated by deprotonation of water by the strongly basic ligand 2.[19] In conclusion, ligand **2**, although itself not part of the cluster **1**, appears to be responsible for the formation of this new type of palladium complex.

References

[1] a) R. G. Bergman, *Polyhedron* **1995**, *14*, 3227, b) J. W. Gilje, H. W. Roesky, *Chem.Rev.* **1994**, *94*, 895.

[2] V. V. Grushin, H. Alper, *Organometallics* **1993**, *12*, 1890.

[3] C.W. Kohlpaintner, M. Beller, *J. Mol. Catal. A: Chemical* **1997**, *116*, 259.

[4] a) A. Klein, A. Dogan, M. Feth, H. Bertagnolli, *Inorg. Chim. Acta* **2003**, *343*, 189; b) G. Lopez, J. Ruiz, G. Garcia, C. Vicente, J. Casabo, E. Molins, C. Miravitlles, *Inorg.Chem.* **1991**, *30*, 2605.

[5] a) V.V. Grushin, H. Alper, *Organometallics* **1996**, *15*, 5242; b) M. C. Pilon, V.V. Grushin, *Organometallics* **1998**, *17*, 1774.

[6] P. Braunstein, J. Fischer, D. Matt, M. Pfeffer, *J. Am. Chem. Soc.* **1984**, *106*, 410.

[7] V. F. Kuznetsov, C. Bensimon, G. A. Facey, V. V. Grushin, H. Alper, *Organometallics* **1997**, *16*, 97.

[8] P. D. Harvey, Y. Mugnier, D. Lucas, D. Evrard, D. F. Lemaître, A. Vallat, *J. Clust. Sci.***2004**, *15*, 63.

[9] T. Hosokawa, M. Takano, S.-I. Murahashi, *J. Am. Chem. Soc.* **1996**, *118*, 3990.

[10] Full characterization of 3 will be presented in a separate paper.

[11] Formation of **1** and **2**·CF_3SO_3H. In a small test tube *N*,*N*'-bis(diphenylmethyl)-3,7-diaza-bicyclo[3.3.1]nonane[12] (7.6 mg, 16.6 μmol) was dissolved in a mixture of acetone (0.3 mL) and $CHCl_3$ (0.2 mL). After cooling to 0 °C a solution of bis[(1,3-η^3-propenyl)palladium chloride][13] (3.1 mg, 8.5 μmol) in acetone (0.2 mL) was added, followed by a solution of $AgCF_3SO_3$ (4.3 mg, 16.7 μmol) in acetone (0.2 mL). After stirring (30 seconds), the precipitated AgCl was centrifuged to the bottom of the test tube. The clear, slightly yellow solution was transferred with a Pasteur pipette into a screw cap vial, and carefully layered with the same volume of cold hexane, which became slightly cloudy. The closed vial was stored at 4 °C. After one day, colourless needles of **2**·CF_3SO_3H had formed. After two days, yellow rectangular crystals of **1** had appeared.

[12] F. Binnig, L. Friedrich, H. P. Hofmann, H. Kreiskott, M. Raschack, C. Müller, *Ger.Offen.*, **1978**, DE2726571.

[13] A. E. Smith, *Acta Cryst.* **1965**, *18*, 331.

[14] Crystal data for **1**: $C_{23}H_{40}F_6O_{11}Pd_6S_2$, M_r = 1309.07, yellow rhomboeders, 0.20 × 0.18 × 0.16 mm, triclinic, space group P1, a = 10.321 Å, b = 13.86770(10) Å, c = 14.531 Å, α= 99.0800(10)°, β= 107.3650(10)°, γ = 94.5410(10)°, V = 1942.494(14) Å^3, Z = 2, ρ_{calcd} = 2.238 g/cm^3, absorption coefficient = 2.901 mm^{-1}, θ = 2.09° to 32.89°, F(000) = 1256, T = 173(2) K, R_1 = 0.0334, wR_2 = 0.0780. Independent reflections = 13422 [R(int) = 0.0274], restraints = 240, parameters = 435.

Crystal data for **2**·CF_3SO_3H: $C_{34}H_{35}F_3N_2O_3S$, M_r = 608.70, colorless needles, 1.00 × 0.04 × 0.04 mm, monoclinic, space group $P2_1/n$, a = 9.1585(2) Å, b = 14.3750(3) Å, c = 23.3428(5) Å, α=90°, β= 90.073(1)°, γ = 90°, V = 3073.16(11) Å^3, Z = 4, ρ_{calcd} = 1.316 g/cm^3, absorption coefficient = 0.161 mm^{-1}, θ = 0.87° to 25.12°, F(000) = 1256, T =173(2) K, R_1 = 0.0519, wR_2 = 0.1078. Independent reflections = 5418 [R(int) = 0.0823], restraints = 0, parameters = 424. Siemens SMART CCD area-detector diffractometer, Mo K_α radiation, wavelength = 0.71073 Å, multiscan, SADABS (Sheldrick, 2002). The structures were solved using direct methods, refined with Shelx software package and refined with full-matrix leastsquares on F^2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned idealized positions and were included in structure-factor calculations. The authors acknowledge Dr. V. Langer, Department of Environmental Inorganic Chemistry, Chalmers University of Technology, Gothenburg University, for the data collection. CCDC−264283 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] A. Gogoll, H. Grennberg, A. Axén, *Organometallics* **1997***, 16*, 1167.

[16] a) V. V. Grushin, H. Alper, *Organometallics* **1993**, *12*, 1890; b) C. Pisano, G. Consiglio, A. Sironi, M. Moret, *Chem.Commun.* **1991**, 421; c) G. Pieri, M. Paasquali, P. Leoni, U. Englert, *J.Organomet. Chem.* **1995**, *491*, 27; d) Schnebeck, R.-D. Freisinger, E. Lippert, B. Eur. J. Inorg. Chem. **2000**, 1193; e) U. Thewalt, S. Müller, Z. Naturforsch., B: Chem. *Sci.*, **1989**, *44*, 1206.

[17] T. G. Appleton, J. A. Bailey, D. R. Bedgood, J. R. Hall, *Inorg. Chem.* **1994**, *33*, 217.

[18] a) A. Gogoll, J. Örnebro, H. Grennberg, J.E. Bäckvall, *J. Am. Chem. Soc.* **1994**, *116*, 3631; b) A. Gogoll, C. Johansson, A. Axén, H. Grennberg, *Chem. Eur. J.* **2001**, *7*, 396; c) A. Gogoll, H. Grennberg, A. Axén *Organometallics* **1998**, *17*, 5248.

[19] The pK_a of (**2**·H)$^+$ in acetonitrile is 17.81: L. Toom, A. Kütt, I. Kaljurand, I. Leito H. Grennberg, A. Gogoll, *in preparation*.

II

N,N'-DIBENZHYDRYLBISPIDINE AS A HOST CANDIDATE FOR (π-ALLYL)-PALLADIUM COMPLEXES – SYNTHESIS, STRUCTURE AND BEHAVIOUR AS A STERICALLY DEMANDING BASE

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Experimental section

General experimental details

Melting points were determined in open capillaries using a Stuart Scientific melting point apparatus SMP10 and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300, 400 or 500 MHz (^{1}H) and 75.4, 100.6 or 125.7 MHz (^{13}C) on a Varian XL-300, Varian Unity 400 or Varian Inova 500 spectrometers. Chemical shifts (^{1}H and ^{13}C) were indirectly referenced to tetramethylsilane via the residual solvent signal ($CDCl_3$, 7.26 and 77.0; acetone-d_6, 2.05 and 206.0 ppm; DMSO-d_6, 2.50 ppm). ^{15}N NMR chemical shifts were obtained from ^{1}H detected ^{1}H-^{15}N gHMBC spectra on a Varian Inova 500 spectrometer. The chemical shift was referenced to an external reference (a 0.6 M solution of CH_3NO_2 (0.0 ppm) in $CDCl_3$). NMR signals were assigned from gHSQC,[1] gHMBC,[2] gNOESY[3] and TOCSY[4] spectra. IR spectra were recorded on a Perkin-Elmer 1760 FT-IR spectrometer. Analytical TLC was performed using precoated Merck Silica 60 F_{254} or Merck neutral aluminium oxide 60 F_{254} plates, and compound visualisation was achieved with UV-light (254 nm), or by developing the plates with a 1% $KMnO_4$ basic solution in water or a 5% phosphomolybdic acid solution in ethanol, followed by heating. For column chromatography Matrex silica gel (60 Å, 35-70 μm) or neutral activated γ-Al_2O_3 (60 mesh) from Strem Chemicals were used. Commercial reagents were purchased from Sigma-Aldrich and Cortec.

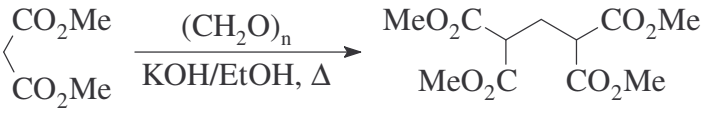
Crystallographic analysis

The X-ray crystallographic analysis was done by Doc. Vratislav Langer, Department of Environmental Inorganic Chemistry, Chalmers University of Technology, Göteborg. Measurements were made on a CCD detector based SMART diffractometer (Siemens) using Mo Kα radiation (λ = 0.71073 Å) (sealed tube at 50 kV and 45 mA). The measurements reported here were conducted at 173 K. The structure solution and full-

matrix least-squares refinement were performed with the programs SHELXS-86[5] and SHELXL-93[6] on F^2. Crystal data, data collection parameters, and results are listed in Tables 1 - 4.

Synthesis

Propane-1,1,3,3-tetracarboxylic acid tetramethylester **(1)**[7]

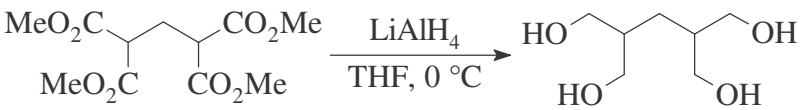


1

Paraformaldehyde (1.10 g, 36.6 mmol) and dimethylmalonate (19.0 g, 143.8 mmol) were weighed into a dry 25 mL round-bottomed flask equipped with a condenser. The flask was placed in an oil bath, the oil was heated to 60 °C and then 12 drops of 10% KOH solution in EtOH were added. The solution turned transparent. The temperature of the oil-bath was increased to 90 °C. Heating was stopped after 9 hours, and after cooling to r.t. the reaction mixture was extracted with toluene (100 mL) and acidified water (100 mL, pH=2-3). The aqueous phase was re-extracted with toluene (2 × 30 mL) and with diethyl ether (30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The excess of dimethylmalonate was recovered (5.30 g) by vacuum distillation (ca. 3 mbar, 50-54 °C), and the title product was obtained by distillation at 151-155 °C, ca. 3 mbar (9.45 g, 34.2 mmol, 93% yield, white crystalline solid).

Its spectroscopic and analytical data were in full agreement with those reported in the literature.[7]

2,4-Bis(hydroxymethyl)pentane-1,5-diol **(2)**[7]



1 **2**

$LiAlH_4$ (5.5 g, 145 mmol) was weighed into a dry 3-neck 250 mL round-bottomed flask equipped with a stir-bar, a condenser and an addition funnel. The flask was cooled to 0 °C and 90 mL of dry THF was added. A solution of propane-1,1,3,3-tetracarboxylic acid tetramethylester (**1**, 16.0 g, 57.9 mmol) in 50 mL of dry THF was slowly (40

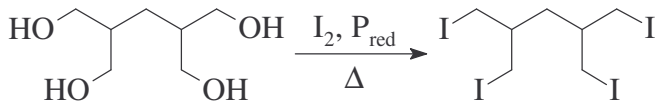
minutes) added to the cooled suspension of $LiAlH_4$. The reaction mixture was stirred at r.t. overnight, then an additional amount of $LiAlH_4$ (4.1 g, 108 mmol) was added, and stirring was continued for 6 hours. The flask was cooled to 0 °C, and water (9.7 mL), 15% NaOH aqueous solution (9.7 mL) and water (28 mL) were slowly added one after another, and the reaction mixture was let to stir at r.t. for 1 hour. The solvent was evaporated under vacuum, and the white solid residue was extracted with THF in a Soxhlet extractor for 60 hours. Recrystallisation from 2-propanol yielded 8.9 g of the title product as flake-like crystals (54.2 mmol, 94% yield).

t_m=131-132 °C (reported 130 °C)[7]

^{1}H NMR (CD_3OD, +25°C, 400 MHz) δ: 3.57 (m, 8H, C*H*$_2$-O), 1.75 (m, 2H, C*H*), 1.29 (m, 2H, C*H*$_2$).

^{13}C NMR ($CDCl_3$, +25°C, 100.6 MHz) δ: 64.0 (*C*H_2-O), 41.9 (*C*H), 27.5 (*C*H_2).

1,5-Diiodo-2,4-bis(iodomethyl)pentane **(3)**[7,8]



2 **3**

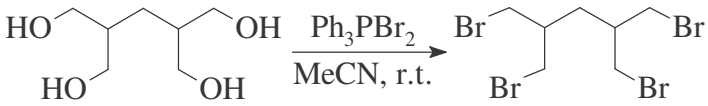
2,4-Bis(hydroxymethyl)pentane-1,5-diol (**2,** 4.00 g, 24.4 mmol) was weighed into a 100 mL round-bottomed flask. Red phosphorous (1.4 g, 45.2 mmol) and coarse-grained iodine (14.4 g, 56.7 mmol) were added to the flask. The temperature was raised very carefully to 120 °C and the reaction mixture was stirred at that temperature for 5 hours. After cooling to r.t., CH_2Cl_2 (30 mL) was added and stirred for a few minutes. Then water (20 mL) was added, the layers were separated, and the water phase was extracted with CH_2Cl_2 (4×20 mL). The organic phase was concentrated yielding a slightly brown powder. Washing the powder with MeOH and recrystallisation from CCl_4 yielded 11.6 g (19.2 mmol, yield 79%) of the title product as white crystals.

t_m=106-107 °C (reported 103-103.5 °C)[8]

^{1}H NMR ($CDCl_3$, +25°C, 400 MHz) δ: 3.41 (m, 4H, CH_2-I), 3.18 (m, 4H, CH_2-I), 1.51 (m, 2H, CH_2), 1.38 (m, 2H, CH).

^{13}C NMR ($CDCl_3$, +25°C, 100.6 MHz) δ: 39.1 (*C*H_2), 37.7 (*C*H), 13.0 (*C*H_2-I).

1,5-Dibromo-2,4-bis(bromomethyl)pentane **(4)**[9]



2 **4**

Bromine (8.56 g, 53.6 mmol) was dissolved in dry CH_2Cl_2 (60 mL) in a 100 mL round-bottomed flask, cooled down to at 0 °C, and Ph_3P (14.07 g, 53.6 mmol) was added in 3 portions. After stirring at r.t. for 1 hour, the solvent was evaporated under vacuum. To the obtained Ph_3PBr_2 dry acetonitrile (60 mL) and 2,4-bis(hydroxymethyl)pentane-1,5-diol (**2,** 2.00 g, 12.18 mmol) were added. The yellowish solution was stirred at r.t. under argon atmosphere for 15 hours. Then the solvent was evaporated yielding viscous yellow oil. A dry-column chromatography on silica with pentane-CH_2Cl_2 (1:1 mixture) and further recrystallisation from CCl_4 yielded transparent crystals (3.65 g, 8.78 mmol, 72% yield).

R_f=0.86 (pentane-CH_2Cl_2 1:1 mixture)

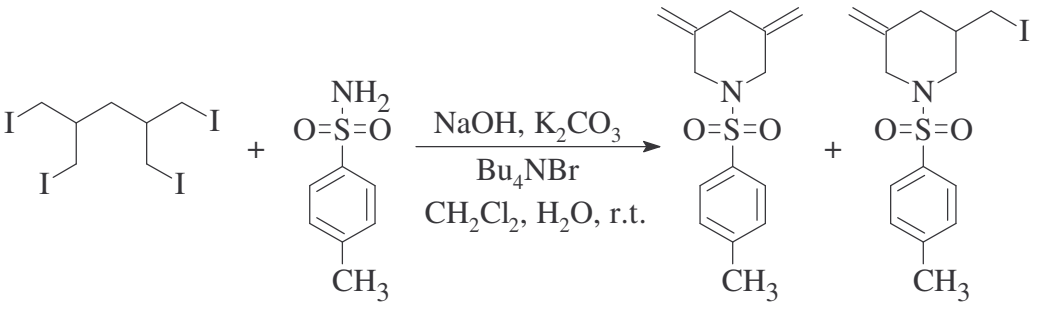
t_m=42-43 °C (reported 45-46 °C)[9]

^{1}H NMR ($CDCl_3$, +25°C, 400 MHz) δ: 3.61 (m, 4H, CH_2-Br), 3.18 (m, 4H, CH_2-Br), 2.08 (m, 2H, CH), 1.51 (m, 2H, CH_2).

^{13}C NMR ($CDCl_3$, +25°C, 75.4 MHz) δ: 38.8 (*C*H), 35.5 (*C*H_2-Br), 33.5 (*C*H_2).

IR (neat film) ṽ: 2960, 1438, 1289, 1247, 796, 669, 618 cm^{-1}.

3,5-Bis(methylene)-1-[(4-methylphenyl)sulphonyl]piperidine **(5)** *and 3-(iodomethyl)-5-methylene-1-[(4-methylphenyl)sulphonyl]piperidine* **(6)**



3 **5** **6**

p-Toluenesulphonamide (0.120 g, 0.70 mmol) was dissolved in a 1:1 mixture (3 mL) of CH_2Cl_2 and water. Fine-grained NaOH (0.185 g, 4.63 mmol), K_2CO_3 (0.395 g, 2.86 mmol), Bu_4NBr (16 mg, 0.05 mmol) and 1,5-diiodo-2,4-diiodometylpentane (**3**, 0.200 g, 0.33 mmol) were added. After stirring at r.t. for 48 hours, the reaction mixture was partitioned between water (10 mL) and CH_2Cl_2 (3 × 10 mL). The aqueous phase was extracted additionally with EtOAc (8 mL) and the combined organic phases were washed with brine (2 × 2 mL) and dried over $MgSO_4$, filtered and the solvent was evaporated under vacuum. Purification by flash chromatography (toluene-CH_2Cl_2 1:4) yielded two products **6** (R_f=0.35, 25 mg, 0.06 mmol, 19% yield) and **5** (R_f=0.30, 65 mg, 0.25 mmol, 75% yield).

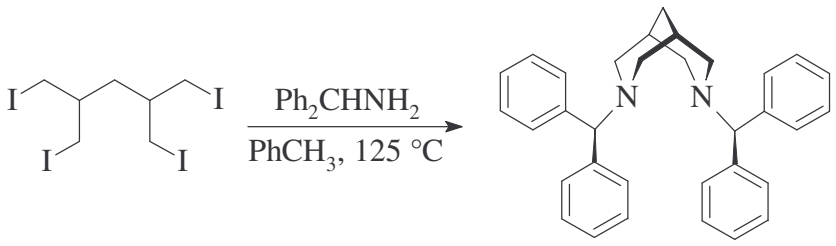
5: ^{1}H NMR ($CDCl_3$, +25°C, 300 MHz) δ: 7.66 (AA' part of AA'BB', 2H, ortho-C*H*), 7.30 (BB' part of AA'BB', 2H, meta-C*H*), 4.86 (m, 2H, =C*H*), 4.81 (m, 2H, =C*H*), 3.66 (s, 4H, 2-CH_2), 2.81 (m, 2H, 4-CH_2), 2.43 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, +25°C, 75.4 MHz) δ: 143.5 (para-*C*), 139.1 (3-*C*), 133.3 (ipso-*C*), 129.5 (meta-*C*H), 128.0 (ortho-*C*H), 111.7 (=*C*H_2), 51.7 (2-*C*H_2), 40.3 (4-*C*H_2), 21.6 (*C*H_3).

6: ^{1}H NMR ($CDCl_3$, +25°C, 300 MHz) δ: 7.66 (AA' part of AA'BB', 2H, ortho-CH), 7.33 (BB' part of AA'BB', 2H, meta-C*H*), 4.99 (m, 1H, =C*H*), 4.91 (m, 1H, =C*H*), 3.63 (d, J=12.2 Hz, 1H, 6-C*H*), 3.39 (dddd, J=11.7, 3.4, 1.1, 1.1 Hz, 1H, 2-C*H*), 3.36 (d, J=12.2 Hz, 1H, 6-C*H*), 3.13 (d, J=6.5 Hz, 2H, CH_2-I), 2.80 (dd, J=11.7, 7.7 Hz, 1H, 2-C*H*), 2.44 (s, 3H, CH_3), 2.34 (dd, J=13.2, 4.0 Hz, 1H, 4-C*H*), 2.01 (dd, J=13.2, 8.3 Hz, 1H, 4-C*H*), 1.93 (m, 1H, 3-C*H*).

^{13}C NMR ($CDCl_3$, +25°C, 75.4 MHz) δ: 143.7, 138.0, 133.0, 129.7 (meta-*C*H), 127.7 (ortho-*C*H), 113.6 (=*C*H_2), 52.0 (6-*C*H_2), 50.8 (2-*C*H_2), 38.2 (4-*C*H_2), 37.6 (3-*C*H), 21.6 (*C*H_3), 8.1 (*C*H_2-I).

3,7-Bis(1,1-diphenylmetyl)-3,7-diazabicyclo[3.3.1]nonane (**7**)[10]



3 **7**

1,5-Diiodo-2,4-bis(iodomethyl)pentane (**3,** 1.00 g, 1.66 mmol) and benzhydrylamine (2.00 g, 10.9 mmol, 6.6 eq.) were weighed into a glass ampoule, dry toluene (6 mL) was added and the ampoule was sealed. After heating at 125 °C for 100 hours, and cooling to r.t., the ampoule was opened and the formed crystals were separated, extracted with 10% NaOH solution (15 mL), re-extracted with CH_2Cl_2 (4 × 15 mL), the combined organic phases were extracted with brine (4 mL) and dried over anhydrous Na_2SO_4. The resulting oil was treated with a mixture of pentane and ether and left in a refrigerator to crystallise. Crystals were separated and the mother liquid was concentrated and purified by column chromatography using pentane-ether-TEA (50:7:3) as the solvent. The total amount of the bispidine derivative separated was 345 mg (0.75 mmol, 45% yield). Additional 310 mg was obtained as a by-product **8**.

R_f=0.64 (pentane-ether-TEA 50:5:3 mixture)

t_m=174-175 °C (reported 170°C)[10]

^{1}H NMR ($CDCl_3$, +25°C, 500 MHz) δ: 7.70 (m, 8H, ortho-C*H*); 7.40 (m, 8H, meta-C*H*), 7.27 (m, 4H, para-C*H*), 4.19 (s, 2H, benzylic C*H*), 2.99 (dm, J=11.1 Hz, 4H, equatorial CH_2), 2.20 (dd, J=11.1, 3.1 Hz, 4H, axial CH_2), 1.84 (m, 2H, bridgehead C*H*), 1.55 (m, 2H, 9-CH_2).

^{1}H NMR ((CD_3)$_2$SO, +25°C, 500 MHz) δ: 7.64 (m, 8H, ortho-C*H*); 7.38 (m, 8H, meta-C*H*), 7.21 (m, 4H, para-C*H*), 4.12 (s, 2H, benzylic C*H*), 2.81 (dm, J=10.7 Hz, 4*H*, 2-CH_2), 2.07 (dm, J=10.7 Hz, 4H, 2-CH_2), 1.79 (m, 2H, bridgehead C*H*), 1.44 (m, 2H, 9-CH_2).

^{13}C NMR ($CDCl_3$, +25°C, 100.6 MHz) δ: 143.5 (ipso-*C*), 128.34 (*C*H), 128.28 (*C*H), 126.6 (para-*C*H), 78.0 (benzylic *C*H), 57.0 (2-*C*H_2), 32.6 (9-*C*H_2), 30.7 (1-*C*H).

^{15}N NMR ($CDCl_3$, +25 °C, 50.7 MHz) δ: -326.4.

IR (neat film) ṽ: 3021, 2890, 2748, 1597, 1491, 1267, 995, 748, 700 cm^{-1}.

Table 1: X-ray crystal structure data for 3,7-dibenzhydryl-3,7-diazabicyclo[3.3.1]nonane (**7**)

Empirical formula	$C_{33}H_{34}N_2$	
Formula weight	458.62	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 8.95580(10) Å	
	b = 22.6588(3) Å	β= 109.2400(10)°
	c = 13.5142(2) Å	
Volume	2589.23(6) $Å^3$	
Z	4	
Density (calculated)	1.177 Mg/m^3	
Absorption coefficient	0.068 mm^{-1}	
F(000)	984	
Crystal size	0.60 × 0.50 × 0.30 mm^3	
Theta range for data collection	2.40 to 30.52°.	
Index ranges	-12≤h≤12, -32≤k≤32, -19≤l≤19	
Reflections collected	40127	
Independent reflections	7851 [R(int) = 0.0344]	
Completeness to θ = 30.52°	99.2 %	
Absorption correction	multiscan, SADABS (Sheldrick, 2002)	
Max. and min. transmission	0.9799 and 0.9604	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7851 / 0 / 350	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2σ(I)]	R_1 = 0.0507, wR_2 = 0.1167	
R indices (all data)	R_1 = 0.0699, wR_2 = 0.1283	
Largest diff. peak and hole	0.291 and -0.235 e·$Å^{-3}$	

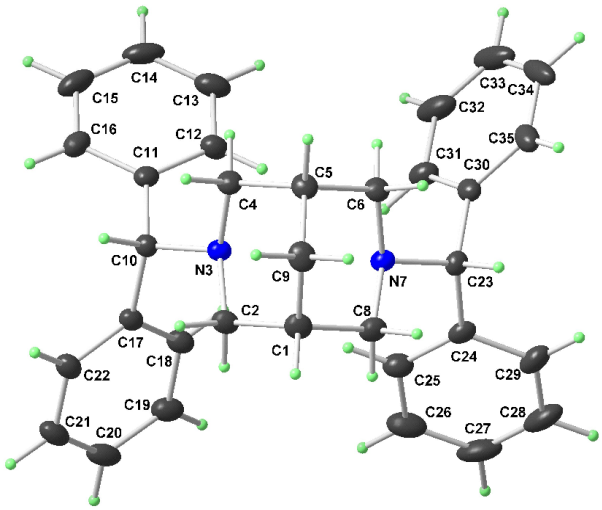
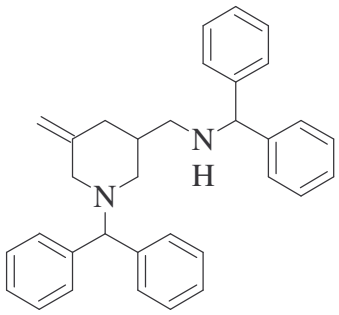


Figure 1. Numbering scheme for **7**. Atomic displacement parameters shown at 30% probability

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C-1	7721(1)	1255(1)	5740(1)	34(1)
C-2	7566(1)	1899(1)	5360(1)	33(1)
N-3	8074(1)	1990(1)	4438(1)	28(1)
C-4	9674(1)	1745(1)	4634(1)	33(1)
C-5	9775(1)	1096(1)	4964(1)	33(1)
C-6	8657(1)	688(1)	4139(1)	31(1)
N-7	6967(1)	809(1)	3953(1)	27(1)
C-8	6633(2)	823(1)	4951(1)	34(1)
C-9	9432(2)	1048(1)	5994(1)	38(1)
C-10	8020(1)	2616(1)	4140(1)	29(1)
C-11	8332(1)	2690(1)	3101(1)	30(1)
C-12	7985(2)	2242(1)	2351(1)	37(1)
C-13	8240(2)	2326(1)	1396(1)	48(1)
C-14	8821(2)	2857(1)	1173(1)	55(1)
C-15	9146(2)	3306(1)	1901(1)	53(1)
C-16	8914(2)	3226(1)	2866(1)	41(1)
C-17	6421(1)	2892(1)	4049(1)	29(1)
C-18	5038(1)	2689(1)	3296(1)	34(1)
C-19	3572(2)	2933(1)	3215(1)	40(1)
C-20	3482(2)	3395(1)	3871(1)	43(1)
C-21	4842(2)	3602(1)	4615(1)	43(1)
C-22	6305(2)	3347(1)	4711(1)	36(1)
C-23	5966(1)	370(1)	3231(1)	29(1)
C-24	4206(1)	510(1)	2941(1)	32(1)
C-25	3645(2)	1082(1)	2924(1)	41(1)
C-26	2014(2)	1192(1)	2576(1)	55(1)
C-27	955(2)	728(1)	2239(1)	61(1)
C-28	1502(2)	159(1)	2254(1)	57(1)
C-29	3116(2)	49(1)	2607(1)	44(1)
C-30	6367(1)	329(1)	2218(1)	31(1)
C-31	6027(1)	797(1)	1504(1)	38(1)
C-32	6366(2)	755(1)	573(1)	58(1)
C-33	7029(2)	249(1)	335(1)	72(1)
C-34	7369(2)	-215(1)	1030(2)	71(1)
C-35	7049(2)	-179(1)	1975(1)	48(1)

By-product: *Benzhydryl-(1-benzhydryl-5-methylene-piperidin-3-ylmethyl)-amine* **(8)**



8

The oil from the ampoule was washed with 10% NaOH solution (15 mL) and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic phases were washed once with brine (4 mL) and dried over anhydrous Na_2SO_4. The oily residue was passed through a silica column using pentane-CH_2Cl_2-ether-TEA (42:5:5:2) as the solvent. Additional purify-cation of the piperidine derivative by using silica gel as the stationary phase and pentane-ether-TEA (9.5:0.3:0.2) as the eluent, gave 310 mg of the piperidine derivative (0.66 mmol, 40% yield).

R_f=0.53 (pentane-ether-TEA 50:5:3)

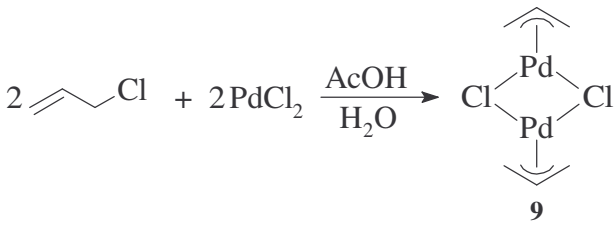
^{1}H NMR ($CDCl_3$, +25 °C, 500 MHz) δ: 7.14–7.45 (m, 20H), 4.77 (s, 1H, NH-C*H*-Ph), 4.76 (m, 1H, =CH_2(*E*)), 4.67 (m, 1H, =CH_2(*Z*)), 4.35 (s, 1H, N-C*H*-Ar), 3.07 (d, J=12.0 Hz, 1H, N-CH_2(eq)-C=), 2.83 (dm, J=11.5 Hz, 1H, N-CH_2(eq)-CH), 2.74 (d, J=12.0 Hz, 1H, N-CH_2(ax)-C=), 2.55 (dd, J=11.7, 6.8 Hz; 1H, CH-CH_2-NH), 2.48 (dd, J=11.7, 6.8 Hz; 1H, CH-CH_2-NH), 2.45 (dd, J=13.0, 4.2 Hz; 1H, =C-CH_2(eq)-CH), 2.07 (dd, J=11.5, 8.5 Hz; 1H, CH-CH_2(ax)-N), 1.96 (m, 1H, CH_2-C*H*-CH_2), 1.88 (dddd, J=13.0, 9.3, 1.0, 1.0 Hz; 1H, =C-CH_2(ax)-CH), 1.42 (bs, 1H, N*H*).

^{13}C NMR ($CDCl_3$, +25 °C, 100.6 MHz) δ: 144.3, 143.9 (*C*=CH_2), 142.7 (ipso-*C*), 142.6, 128.4, 127.9 (ortho-*C*H), 127.23, 127.21, 126.8, 109.6 (=*C*H_2), 75.7 (N-*C*H-Ar), 67.2 (NH-*C*H-Ar), 58.9 (N-*C*H_2-C=), 55.6 (CH-*C*H_2-N), 51.1 (NH-*C*H_2), 37.5 (=C-CH_2-CH), 36.7 (CH_2-*C*H-CH_2).

^{15}N NMR ($CDCl_3$, +25 °C, 50.7 MHz) δ: -320.1 (*N*), -325.6 (*N*H).

IR (neat film) ν̃: 3061, 3024, 2791, 1597, 1452, 909, 704 cm^{-1}.

Bis[(1,3-η³-propenyl)palladium(II) chloride] **(9)**



9

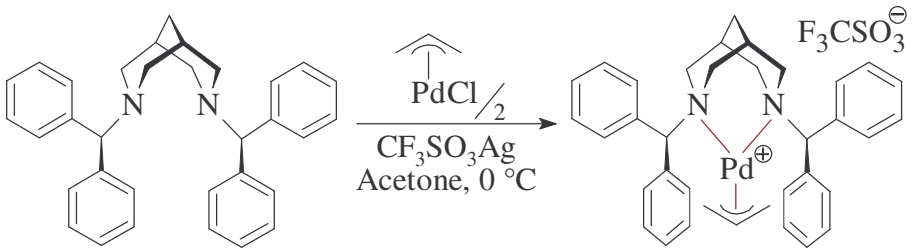
This compound was prepared according to a literature procedure.[11]

t_m=decomposed at 156 °C (reported t_m=160 °C).

^{1}H NMR ($(CD_3)_2CO$, +25°C, 500 MHz) δ: 5.59 (tt, J=12.0, 6.8 Hz; 1H, meso-CH), 4.02 (ddd, J=6.8, 0.7, 0.7 Hz; 2H, syn-C*H*), 3.04 (ddd, J=12.0, 0.7, 0.7 Hz; 2H, anti-C*H*).

^{13}C NMR ($(CD_3)_2CO$, +25°C, 100.6 MHz) δ: 112.3 (CH), 63.0 (CH_2).

{N,N'-Bis(diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonane}(1,3-η³)-propenyl palladium trifluoromethanesulphonate (isomers **10a** and **10b)**



7 **10**

In a small test tube *N,N'*-bis(diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonane (**7,** 7.6 mg, 16.6 µmol) was dissolved in a mixture of acetone-d_6 (0.3 mL) and $CDCl_3$ (0.2 mL). After cooling to 0 °C a solution of bis((1,3-η³-propenyl)palladium chloride) (**9,** 3.1 mg, 8.5 µmol) in acetone-d_6 (0.2 mL, slightly yellow solution) was added. At 0 °C, a solution of $AgCF_3SO_3$ (4.3 mg, 16.7 µmol) in acetone-d_6 (0.2 mL), was added, resulting in an appearance of white precipitate. The mixture was stirred briefly (30 seconds), then the precipitate was centrifuged to the bottom of the test tube. For the NMR spectroscopic investigations, the slightly yellow solution was evaporated under vacuum, dissolved in 0.7 mL of acetone-d_6 and transferred into an NMR tube.

For the crystallisations, the clear, slightly yellow solution was transferred with a Pasteur pipette into a screw cap vial, layered carefully with the same volume of cold hexane.

The upper (hexane) layer got slightly cloudy. The vial was closed and stored in a refrigerator. After one day, colourless needles (**11b**) had formed in the clear solution. After two days, yellow rectangular crystals had appeared that decomposed within a week.

The ratio between the two isomers in acetone at -70 °C was 2.8:1.

MAJOR ISOMER **10a**:

^{1}H NMR (acetone-d_6, -70 °C, 500 MHz) δ: 6.8-8.0 (several multiplets), 5.91 (s, 2H, benzylic C*H*), 4.84 (tt, J=11.8, 6.9 Hz; 1H, allyl 2-C*H*), 4.63 (d, J=12.2 Hz, 2H, equatorial 2-CH_2), 4.07 (d, J=12.5 Hz, 2H, equatorial 4-CH_2), 3.29 (d, J=12.2 Hz, 2H, axial 2-CH_2), 3.29 (d, J=11.8 Hz, 2H, allyl anti-CH_2), 2.69 (dd, J=12.5, 2.2 Hz, 2H, axial 4-CH_2), 2.51 (m, 1H, 1-C*H*), 2.43 (d, J=6.9 Hz, 2H allyl syn-CH_2), 2.30 (m, 1H, 5-C*H*), 1.16 (m, 2H, 9-CH_2).

^{13}C NMR (acetone-d_6, -70 °C, 125.7 MHz, chemical shifts from 2D experiments) δ: 126-146 (aromatic signals), 118.8 (allyl 2-*C*H), 80.2 (benzylic *C*H), 66.8 (allyl CH_2), 60.3 (2- and 8-*C*H_2), 51.4 (4- and 6-*C*H_2), 32.6 (9-*C*H_2), 31.6 (1-*C*H), 28.6 (5-*C*H).

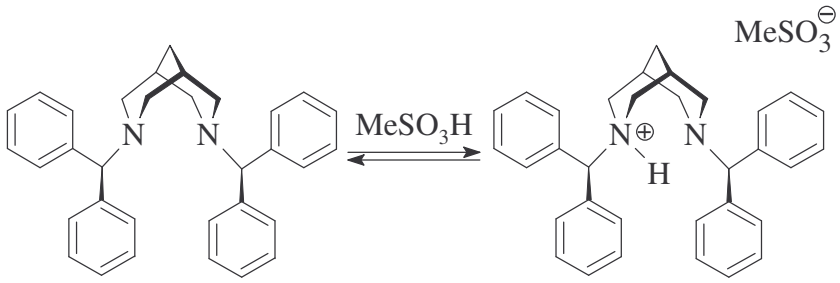
MINOR ISOMER **10b**:

^{1}H NMR (acetone-d_6, -70 °C, 500 MHz) δ: 6.8-8.0 (several multiplets), 5.89 (s, 2H, benzylic C*H*), 5.72 (tt, J=12.2, 6.8 Hz; 1H, allyl 2-C*H*), 4.33 (d, J=12.2 Hz, 2H, equatorial 4-CH_2), 4.23 (d, J=12.2 Hz, 2H, equatorial 2-CH_2), 3.51 (d, J=6.8 Hz, 2H, allyl syn-CH_2), 3.16 (d, J=12.2 Hz, 2H, axial 2-CH_2), 2.66 (dd, J=12.2 Hz, 2H, axial 4-CH_2), 2.32 (m, 1H, 1-C*H*), 2.24 (m, 1H, 5-C*H*), 1.41 (d, J=12.2 Hz, 2H, allyl anti-CH_2), 1.12 (m, 2H, 9-CH_2).

^{13}C NMR (acetone-d_6, -70 °C, 125.7 MHz, chemical shifts from 2D experiments) δ: 126-146 (aromatic signals), 116.0 (allyl 2-*C*H), 79.0 (benzylic *C*H), 64.7 (allyl *C*H_2), 60.9 (2- and 8-*C*H_2), 52.2 (4- and 6-*C*H_2), 31.6 (1-*C*H), 29.2 (5-*C*H), 28.5 (9-*C*H_2).

^{15}N NMR (acetone-d_6, -70 °C, 50.7 MHz) δ: -340.9 (indistinguishable signals for the major and minor isomers).

N,N'-Bis(diphenylmethyl)-7-aza-3-azoniabicyclo[3.3.1]nonane methylsulphonate **(11a)** and *N,N'-Bis(diphenylmethyl)-7-aza-3-azoniabicyclo[3.3.1]nonane trifluoromethyl-sulphonate* **(11b)**



7 **11a**

Procedure 1 in $CDCl_3$. A solution of methanesulphonic acid (14.7 mg, 0.153 mmol) in CH_2Cl_2 (1.0 mL) was added to a solution of *N,N'*-bis(diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonane (**7,** 70.0 mg, 0.153 mmol) in CH_2Cl_2 (1.0 mL), stirred and evaporated to dryness under vacuum, giving 84.7 mg of white powder.

Procedure 2 in $CDCl_3$. To a solution of *N,N'*-bis(diphenylmethyl)-3,7-diazabicyclo-[3.3.1]nonane (**7,** 7.2 mg, 15.7 μmol) in $CDCl_3$ (ca. 0.7 mL) small amounts of methanesulphonic acid solution (ca. 150mM) in $CDCl_3$ were added. The titration was followed using the 500 MHz NMR spectrometer, and was stopped after full conversion to the mono-protonated form.

Procedure 3 in DMSO-d_6. To a suspension of *N,N'*-bis(diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonane (**7,** 6.2 mg, 13.5 μmol) in $(CD_3)_2SO$ (ca. 0.7 mL) small amounts of methanesulphonic acid solution (ca. 300mM) in $(CD_3)_2SO$ were added. The substrate dissolved completely during the addition of the acid solution. The titration was followed using the 500 MHz NMR spectrometer, and was stopped after full conversion to the mono-protonated form.

Procedure 4. A crystals suitable for X-ray analysis were obtained as a byproduct **11b** in an attempt to produce crystals of **10a** or **10b** (see above).

^{1}H NMR ($CDCl_3$, +25°C, 500 MHz) δ: 10.0 (bs, 1H, N*H*), 7.60 (m, 8H, ortho-C*H*), 7.45 (m, 8H, meta-C*H*), 7.38 (m, 4H, para-C*H*), 5.28 (s, 2H, benzylic C*H*), 3.32 (dm, J=11.8 Hz, 4H, axial CH_2), 3.17 (dm, J=11.8 Hz, 4H, equatorial CH_2), 2.89 (s, 3H, CH_3), 2.19 (m, 2H, bridgehead C*H*), 2.01 (m, 2H, 9-CH_2).

^{1}H NMR ($(CD_3)_2SO$, +25°C, 500 MHz) δ: 10.3 (bs, 1H, N*H*), 7.58 (m, 8H, ortho-C*H*), 7.53 (m, 8H, meta-C*H*), 7.43 (m, 4H, para-C*H*), 5.05 (s, 2H, benzylic C*H*), 3.16 (dm, J=11.8 Hz, 4H, 2-C*H*), 2.85 (dm, J=11.8 Hz, 4H, 2-C*H*), 2.33 (s, 3H, CH_3), 2.21 (m, 2H, 1- and 5-C*H*), 1.69 (m, 2H, 9-CH_2).

^{15}N NMR ($CDCl_3$, +25°C, 50.7 MHz) δ: -314.2.

Table 3. X-ray crystal structure data for 3,7-dibenzhydryl-3,7-diazabicyclo[3.3.1]nonane·CF_3SO_3H **(11b)**

Empirical formula	$C_{34}H_{35}F_3N_2O_3S$	
Formula weight	608.70	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 9.1585(2) Å	α = 90°
	b = 14.3750(3) Å	β = 90.073(1)°
	c = 23.3428(5) Å	γ = 90°
Volume	3073.16(11) Å^3	
Z	4	
Density (calculated)	1.316 Mg/m^3	
Absorption coefficient	0.161 mm^{-1}	
F(000)	1280	
Crystal size	1.00 × 0.04 × 0.04 mm^3	
Theta range for data collection	0.87 to 25.12°.	
Index ranges	-10≤h≤10, -17≤k≤17, -27≤l≤27	
Reflections collected	32643	
Independent reflections	5418 [R(int) = 0.0823]	
Completeness to theta = 25.12°	99.0 %	
Absorption correction	multiscan	
Max. and min. transmission	0.9936 and 0.8557	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5418 / 0 / 424	
Goodness-of-fit on F^2	1.063	
Final R indices [I>2σ(I)]	R_1 = 0.0519, wR_2 = 0.1078	
R indices (all data)	R_1 = 0.0795, wR_2 = 0.1212	
Largest diff. peak and hole	0.250 and -0.267 e·Å^{-3}	

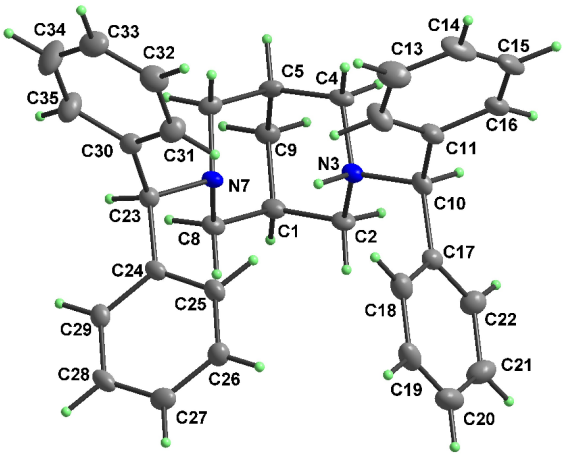


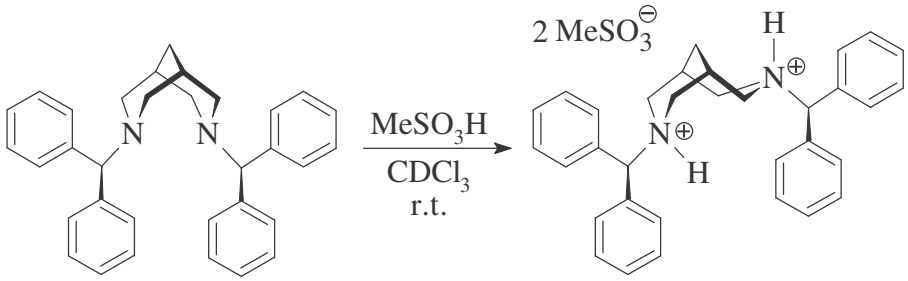
Figure 2. Numbering scheme for **11b**. Atomic displacements shown at 30% probability level.

Table 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **11b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S-1	3191(1)	-2182(1)	-611(1)	36(1)
F-1	4221(4)	-3814(2)	-350(2)	103(1)
F-2	1902(4)	-3754(2)	-392(2)	116(1)
F-3	3069(5)	-3150(2)	327(1)	122(1)
O-1	3266(3)	-2457(2)	-1204(1)	48(1)
O-2	1869(3)	-1717(2)	-459(1)	60(1)
O-3	4498(3)	-1756(2)	-395(1)	53(1)
N-3	-4725(3)	336(2)	-1339(1)	26(1)
N-7	-2357(3)	1211(2)	-1798(1)	25(1)
C-1	-2533(4)	-522(2)	-1689(1)	31(1)
C-2	-4190(4)	-531(2)	-1641(1)	30(1)
C-4	-3957(4)	446(2)	-764(1)	32(1)
C-5	-2309(4)	449(2)	-838(1)	29(1)
C-6	-1742(4)	1252(2)	-1207(1)	30(1)
C-8	-1983(4)	285(2)	-2055(1)	30(1)
C-9	-1823(4)	-479(2)	-1094(1)	32(1)
C-10	-6381(4)	352(2)	-1281(1)	32(1)
C-11	-6910(4)	1210(2)	-962(1)	34(1)
C-12	-6331(5)	2092(2)	-1050(2)	47(1)
C-13	-6930(6)	2856(3)	-768(2)	54(1)
C-14	-8084(5)	2747(3)	-407(2)	57(1)
C-15	-8658(4)	1872(3)	-312(2)	50(1)
C-16	-8050(4)	1105(2)	-586(1)	40(1)
C-17	-7122(4)	228(2)	-1862(1)	31(1)
C-18	-7269(4)	973(3)	-2243(2)	42(1)
C-19	-7910(4)	836(3)	-2781(2)	48(1)
C-20	-8429(5)	-28(3)	-2936(2)	55(1)
C-21	-8319(5)	-756(3)	-2555(2)	53(1)
C-22	-7680(4)	-630(3)	-2023(2)	42(1)
C-23	-1681(4)	1936(2)	-2172(1)	29(1)
C-24	-2449(4)	1968(2)	-2758(1)	28(1)

C-25	-3949(4)	1990(2)	-2801(1)	35(1)
C-26	-4641(4)	2091(2)	-3325(1)	37(1)
C-27	-3819(4)	2162(2)	-3817(2)	36(1)
C-28	-2322(4)	2130(2)	-3789(1)	35(1)
C-29	-1625(4)	2028(2)	-3256(1)	31(1)
C-30	-1627(4)	2896(2)	-1894(1)	31(1)
C-31	-2859(4)	3387(2)	-1753(2)	42(1)
C-32	-2745(5)	4255(3)	-1486(2)	46(1)
C-33	-1432(5)	4640(3)	-1379(2)	49(1)
C-34	-192(5)	4163(3)	-1521(2)	67(1)
C-35	-296(5)	3294(3)	-1776(2)	52(1)
C-36	3093(7)	-3285(3)	-242(2)	68(1)

N,N'-Bis(diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonane · 2MeSO$_3$H **(12)**



7 **12**

To a solution of *N,N'*-bis(diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonane (**7,** 7.2 mg, 15.7 µmol) in $CDCl_3$ (ca. 0.7 mL) small amounts of methanesulphonic acid solution (ca. 300 mM) in $CDCl_3$ were added. The titration was followed using the 500 MHz NMR spectrometer, and was stopped after full conversion to the di-protonated form **12**.

^{1}H NMR ($CDCl_3$, +25°C, 500 MHz) δ: 9.16 (bs, 1H, chair-side N*H*), 8.01 (bs, 1H, boat-side N*H*), 7.73-7.83 (several multiplets), 7.36-7.52 (several multiplets), 5.96 (d, J=9.0 Hz, 1H, boat-side benzylic C*H*), 5.44 (d, J=8.1 Hz, 1H, chair-side benzylic C*H*), 3.64 (m, 2H, boat-side equatorial CH_2), 3.56 (m, 2H, boat-side axial CH_2), 3.40 (m, 2H, chair-side equatorial CH_2), 3.25 (m, 2H, chair-side axial CH_2), 2.77 (m, 2H, bridgehead C*H*), 2.58 (m, 1H, boat-side 9-C*H*), 1.99 (m, 1H, chair-side 9-C*H*),

^{13}C NMR ($CDCl_3$, +25 °C, 100.6 MHz) δ: 133.6, 133.0, 130.0, 129.9, 129.7, 129.1, 128.8, 128.5, 80.2 (chair-side benzylic *C*H), 75.9 (boat-side benzylic *C*H), 56.9 (chair-side *C*H_2), 51.5 (boat-side *C*H_2), 39.5 (*C*H_3), 24.5 (bridgehead *C*H), 20.6 (9-*C*H_2).

^{15}N NMR ($CDCl_3$, +25°C, 50.7 MHz) δ: -322.4 (boat-side *N*H), -325.3 (chair-side *N*H).

Acknowledgments

The Swedish Natural Science Research Council, the Swedish Technical Science Research council, and Magn. Bergvalls Stiftelse are acknowledged for financial support.

References

1. Davis, A.L., Keeler, J., Laue, E.D., Moskau, D. *J. Magn. Reson.*, **1992**, *98*, 207–216.
2. Hurd, R.E., John, B.K. *J. Magn. Reson.*, **1991**, *91*, 648–653.
3. Wagner, R., Berger, S. *J. Magn. Reson., Series A*, **1996**, *123*, 119-121.
4. Braunschweiler, L., Ernst, R.R. *J. Magn. Reson.*, **1983**, *53*, 521-528.
5. Sheldrick, G.M. *Acta Crystallogr., Sect. A*, **1990**, *A46*, 467-473.
6. Sheldrick G.M. SHELXL-93 Program for Crystal Structure Determination; University of Göttingen, Germany; **1993**.
7. Gogoll, A., Johansson, C., Axén, A., Grennberg, H. *Chem. Eur. J.*, **2001**, *7*, 396-403.
8. Zefirov, N.S., Gogozina, S.V. *Tetrahedron*, **1974**, *30*, 2345-2352.
9. Galik, V., Landa, S. *Collect. Czech. Chem. Commun.*, **1973**, *38*, 1101-1103.
10. Binnig, F., Friedrich, L., Hofmann, H.P., Kreiskott, H., Raschack, M., Müller, C. *Ger. Offen.*, **1978**, DE 2’726‘571.
11. Hüttel, R., Kratzer, J., Bechter, M. *Chem. Ber.*, **1961**, *94*, 766-780.

III

STUDIES ON SUBSTITUTED 3,7-DIAZABICYCLO[3.3.1]NONANES

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Experimental section

General experimental details

Melting points were determined in open capillaries using a Stuart Scientific melting point apparatus SMP10 and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 or 500 MHz (^{1}H) and 100.6 or 125.7 MHz (^{13}C) on a Varian Unity 400 or Varian Inova 500 spectrometers. Chemical shifts (^{1}H and ^{13}C) were indirectly referenced to tetramethylsilane via the residual solvent signal ($CDCl_3$, 7.26 and 77.0; acetone-d_6, 2.05 and 206.0 ppm; DMSO-d_6, 2.50 ppm). ^{15}N NMR chemical shifts were obtained from ^{1}H detected ^{1}H-^{15}N gHMBC spectra on a Varian Inova 500 spectrometer. The chemical shift was referenced to an external reference [a 0.6 M solution of CH_3NO_2 (0.0 ppm) in $CDCl_3$]. NMR signals were assigned from gHSQC,[1] gHMBC,[2] gNOESY[3] and TOCSY[4] spectra. IR spectra were recorded on a Perkin-Elmer 1760 FT-IR spectrometer. Analytical TLC was performed using precoated Merck Silica 60 F_{254} or Merck neutral aluminium oxide 60 F_{254} plates, and compound visualisation was achieved with UV-light (254 nm), or by developing the plates with a 1% $KMnO_4$ basic solution in water or a 5% phosphomolybdic acid solution in ethanol, followed by heating. For column chromatography Matrex silica gel (60 Å, 35-70 μm) or neutral activated γ-Al_2O_3 (60 mesh) from Strem Chemicals were used. Commercial reagents were purchased from Sigma-Aldrich and Cortec.

pK_a determination

Chemicals

The synthesis and purification of the reference compounds is described elsewhere.[5-9]

Acetonitrile (Romil, > 99.9%, Super purity Solvent (Far UV), water content < 0.005%) was the same used in previous works[5,6] and was used without further purification. The water content was determined by coulometric Karl Fischer titration to be about 0.004%.

Solutions of methanesulphonic acid ($MeSO_3H$) (Fluka, > 99%) and trifluoromethane-sulphonic acid (TfOH) (Aldrich, 99+%) were used as acidic titrants. Solution of phosphazene base $tBuP_1$(pyrr) (Fluka, ≥ 98%) was used as basic titrant.

Measurements

The spectrophotometric titration method used in this work is the same as described earlier,[5,7,10] *i.e*. the simultaneous titration of two free bases with an acid of comparable basicity was carried out and the UV-VIS spectrum was recorded after each addition of acidic titrant. Also, both bases were titrated separately. A glovebox (MBraun) was used to ensure that the environment is free from humidity and oxygen. A Perkin Elmer Lambda 40 spectrophotometer, connected to an external sample compartment, situated in the glovebox. The cell compartment was connected to the UV-VIS spectrophotometer by means of two quartz fiber optic cables. Glassware used during the experiments was heated at 150 ºC for at least six hours and then cooled in a dessicator over P_2O_5. Concentrations of bases during the titration experiments were in the 10^{-5} M range and never exceeded $14 \cdot 10^{-5}$ M, concentration of acidic and basic titrants were usually in the $5 \cdot 10^{-4}$ M range. The solutions were transferred by means of Pasteur pipettes or Hamilton gas tight syringes.

A solution of $MeSO_3H$ in acetonitrile was used as acidic titrant in most cases. In some experiments (see Table 1), a solution of TfOH was used because of too low acidity of $MeSO_3H$. Two basicity equilibriums were measured using both acids to make sure that the ΔpK_a does not depend on anions of the acids used in this work (Table 1).

The water content of collected titrated waste solutions was determined by coulometric Karl Fischer titration to be about 0.005-0.006%.

Calculation methods

The ΔpK_a values for the pairs of bases, which have good UV-VIS spectra and difference of their UV-VIS spectra of neutral and protonated forms, were obtained from UV-VIS spectra. The details of calculation methods are given previously.[5,7,10,11] From each titration experiment of the mixture of bases, the ΔpK_a was determined as the mean of 10-20 values.

As most of the used bispidines have small differences between UV-VIS spectra of the neutral and the protonated form, in such cases another calculation method[7] was used. This method uses in addition to the available spectra, the exact amount of moles of the compounds in the titration vessel and added titrant (see ref. 5 for details). Not always could a good agreement between these two different approaches ('pure' spectrophotometric and 'based on moles' method) be obtained. In this case, the result with better standard deviation (usually the method based on moles) is reported.

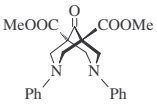
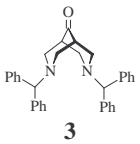
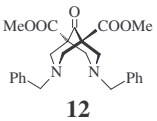
The absolute pK_a values were calculated as in the previous papers[5,10] by minimising the sum of squares of differences between directly measured ΔpK_a values and assigned pK_a values while keeping the pK_a values of other bases constant (Table 1).

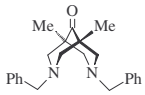
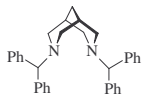
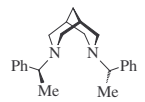
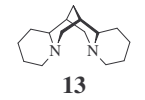
However, it should be stressed, that the absolute pK_a values of bases given in Table 1 are not as accurate as the relative pK_a-s. The precision and the consistency of the results can be assessed using a standard deviation *s* as defined by the following equation:

$$s = \sqrt{\frac{u}{n_m - n_c}}$$

where n_m=35 is the number of measurements, n_c=8 is the number of pK_a values determined. For our results, *s*=0.13 pK_a units.

Table 1. Results of UV-VIS spectrophotometric titration experiments in MeCN solution and assigned pK_a values for the conjugate acid forms of the bispidines

Bispidine	Reference base	pK_a of reference base[a]	C(Bispidine) $\cdot 10^5$ M[b]	C(Reference base) $\cdot 10^5$ M[b]	ΔpK_a [c]	Assigned pK_a value	*s*	Acid[d]	Calculation method[e]
 **10**	3-NO_2-Aniline	7.68	1.59	4.74	0.44		0.10	T	S
	3-NO_2-4-F-Aniline	7.67	2.56	5.67	0.42		0.10	T	S
	2,6-$(MeO)_2$-Pyridine	7.64	2.49	7.11	0.48	**8.11**	0.10	T	S
	2,4-F_2-Aniline	8.39	2.58	8.33	-0.23		0.03	T	S
	2-Cl-Pyridine	6.79	3.29	13.25	1.38		0.05	T	S
 **3**	2,6-Cl_2-4-NO_2-PhP_1(pyrr)	14.43	1.73	3.67	-0.95	**13.47**	0.10	M	NV
	2,6-$(NO_2)_2$-PhP_1(pyrr)	14.12	1.50	5.22	-0.65		0.10	M	NV
 **12**	2,4-$(NO_2)_2$-PhP1(pyrr)	14.88	3.57	3.19	-0.95	**13.79**	0.10	M	NV
	2,6-$(NO_2)_2$-PhP_1(pyrr)	14.12	2.78	7.53	-0.35		0.05	M	NV
	2,6-Cl_2-4-NO_2-PhP_1(pyrr)	14.43	2.74	4.03	-0.62		0.05	M	NV
	3-NH_2-Pyridine	14.17	1.67	6.63	-0.44		0.05	M	NV

 **11**	2-NO_2-4-CF_3-PhP1(pyrr)	16.53	1.98	3.61	0.96		0.05	M	NV
	2-NO_2-5-Cl-PhP_1(pyrr)	17.27	4.16	1.85	0.19		0.07	M	NV
	4-$N(CH_3)_2$-Pyridine	17.95	1.43	4.50	-0.47	**17.48**	0.10	M	NV
	4-$N(CH_3)_2$-Pyridine	17.95	2.67	5.02	-0.46		0.10	T	NV
	2-NO_2-4-Cl-PhP_1(pyrr)	17.68	1.88	3.87	-0.19		0.10	M	NV
 **9**	2,5-Cl_2-PhP_1(pyrr)	18.52	1.13	1.86	-0.70		0.04	M	NV
	4-Pyrrolidinylpyridine	18.33	1.04	3.23	-0.59	**17.81**	0.04	M	NV
	4-$N(CH_3)_2$-Pyridine	17.95	1.42	3.32	-0.17		0.06	M	NV
	4-NO_2-PhP_1(pyrr)	18.51	1.12	2.85	-0.70		0.06	M	NV
 **4**	PhP_1(dma)	21.25	1.24	2.49	0.03		0.06	M	NV
	4-Br-PhP_1(pyrr)	21.19	1.84	1.14	0.08		0.06	M	NV
	PhP_1(dma)Me	21.03	1.14	2.04	0.23	**21.27**	0.06	M	NV
	4-CF_3-PhP_1(pyrr)	20.16	1.49	1.61	1.01		0.10	M	NV
	PhTMG	20.84	1.54	2.71	0.43		0.05	M	NV
 **14**	2-Cl-PhP_1(pyrr)	20.17	2.34	2.74	1.2		0.10	M	NV
	PhP_1(dma)	21.25	1.79	3.62	0.11		0.05	M	NV
	4-Br-PhP_1(pyrr)	21.19	1.79	2.99	0.21	**21.33**	0.05	M	NV
	$PhP_1(dma)_2$Me	21.03	2.17	2.67	0.36		0.05	M	NV
	PhTMG	20.84	2.05	3.40	0.56		0.05	M	NV
 **13**	PhP_1(pyrr)	22.34	4.39	3.87	-0.55		0.05	M	NV
	PhP_1(dma)	21.25	4.07	3.17	0.41		0.05	M	NV
	PhP_1(dma)	21.25	6.45	3.53	0.42	**21.67**	0.05	T	NV
	4-Br-PhP_1(pyrr)	21.19	3.58	3.14	0.58		0.10	M	NV
	$PhP_1(dma)_2$Me	21.03	4.11	2.67	0.60		0.07	M	NV
	PhTMG	20.84	3.97	4.32	0.77		0.07	M	NV

[a] Reference 9

[b] $\Delta pK_a = pK_a$(Bispidine) – pK_a(Reference base)

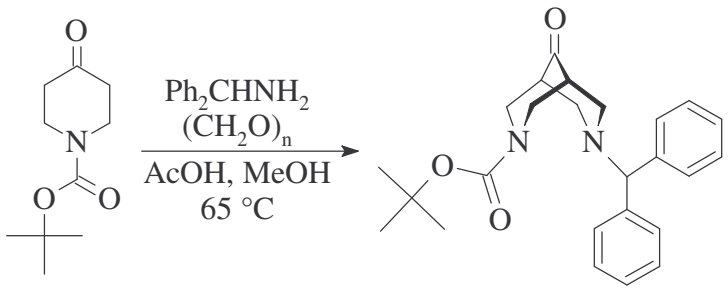
[c] Concentration of bispidine and reference base in mixture

[d] Abbreviation of the acid titrated with: M = CH_3SO_3H, T = CF_3SO_3H

[e] Calculation method: NV – Bispidine as "non-visible", ΔpK_a calculated on molar basis, S – calculated from UV-VIS spectra

Synthesis

3-(tert-Butyloxycarbonyl)-7-(1,1-diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonane-9-one **(1)**



1

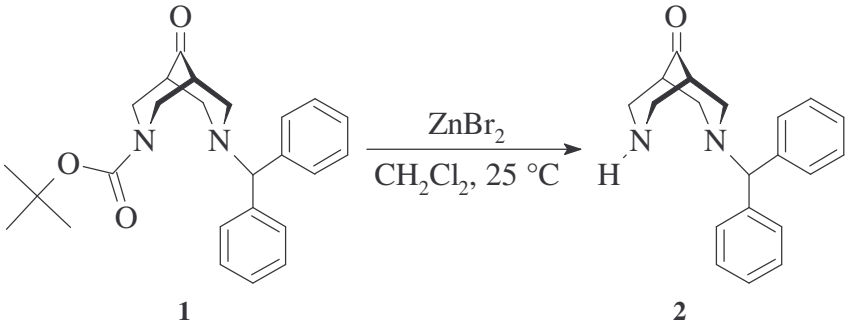
A suspension of coarse-grained paraformaldehyde (1.00 g, 33.3 mmol) in methanol (50 mL) was slowly added to a refluxing solution of 1-Boc-piperidin-4-one (3.00 g, 15.1 mmol), benzhydrylamine (2.98 g, 15.2 mmol) and acetic acid (0.92 g) in methanol (80 mL). During 1 hour another portion of paraformaldehyde (1.00 g, 33.3 mmol) was added and the mixture was refluxed overnight. Water (500 mL) and 1M KOH solution (30 mL) were added and the aqueous phase was extracted with diethyl ether and CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was evaporated. The yellow foamy residue was purified by flash chromatography on silica gel (pentane-CH_2Cl_2-EtOAc 10:3:2) to yield an oil (3.78 g, 9.29 mmol, 62% yield).

R_f=0.40 (pentane-CH_2Cl_2-EtOAc 10:3:2).

^{1}H NMR ($CDCl_3$, +25°C, 500 MHz) δ: 7.48 (m, 4H), 7.29 (m, 4H), 7.19 (m, 2H, para-C*H*), 4.63 (dm, J=13.4 Hz, 1H, C*H*-N-CO), 4.47 (dm, J=13.4 Hz, 1H, C*H*-N-CO), 4.05 (s, 1H, benzylic C*H*), 3.42 (dd, J=13.4, 2.9 Hz, 1H, C*H*-N-CO), 3.32 (dd, J=13.4, 2.9 Hz, 1H, C*H*-N-CO), 3.27 (m, 2H, CH_2-N), 2.52 (dm, J=11.5 Hz, 2H, CH_2-N), 2.40 (m, 1H, bridgehead C*H*), 2.34 (m, 1H, bridgehead C*H*), 1.64 (s, 9H, (CH_3)$_3$C).

^{13}C NMR ($CDCl_3$, +25 °C, 100.6 MHz) δ: 213.9 (9-*C*=O), 154.5 (N-*C*=O), 130.0 (1C, ipso-*C*), 128.8 (2C), 128.6 (2C), 128.2 (1C, ipso-*C*), 127.6 (2C), 127.4 (2C) 127.2 (2C, para-*C*H), 80.3 (*C*(CH$_3$)$_3$), 76.0 (benzylic *C*H), 58.4 (2C, *C*H$_2$-N), 50.2 (*C*H$_2$-N-CO), 49.8 (*C*H$_2$-N-CO), 47.4 (*C*H-CO), 47.3 (*C*H-CO), 28.6 (*C*H$_3$).

3-(1,1-diphenylmethyl)-3,7-diazabicyclo[3.3.1]nonane-9-one **(2)**



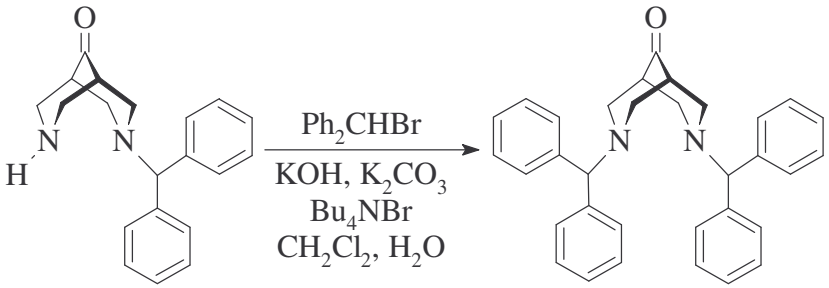
1 **2**

To 3-(*tert*-butyloxycarbonyl)-7-benzhydryl-3,7-diazabicyclo[3.3.1]nonan-9-one (**1**, 4.06 g, 9.98 mmol) and anhydrous $ZnBr_2$ (4.50 g, 20.0 mmol) CH_2Cl_2 (60 mL) was added, and the suspenstion was stirred at r.t. for 13 hours. The mixture was poured into dilute

aqueous NaOH solution, and the aqueous phase was extracted with CH_2Cl_2. The organic phase was concentrated yielding yellow foam (2.58 g, 8.43 mmol, 84% yield).

^{1}H NMR ($CDCl_3$, +25°C, 500 MHz) δ: 7.42 (m, 4H, ortho-C*H*), 7.31 (m, 4H, meta-C*H*), 7.21 (m, 2H, para-C*H*), 4.00 (s, 1H, benzylic C*H*), 3.78 (m, 1H), 3.53 (m, 2H), 3.33 (m, 2H), 3.18 (m, 2H), 2.55 (m, 2H), 2.3 (m, 2H).

3,7-Bis(1,1-diphenylmetyl)-3,7-diazabicyclo[3.3.1]nonane-9-one **(3)**



2 **3**

To a mixture of 3-benzhydryl-3,7-diazabicyclo[3.3.1]nonan-9-one (**2**, 2.00 g, 6.53 mmol), benzhydrylbromide (1.86 g, 7.53 mmol), K_2CO_3 (9.0 g, 65.1 mmol), KOH (1.83 g, 32.7 mmol) and Bu_4NBr (0.4 g, 1.24 mmol), CH_2Cl_2 (100 mL) and water (40 mL) were added. Stirred at r.t. for 45 hours, extracted with CH_2Cl_2 (2×50 mL), dried over Na_2SO_4, filtrated and concentrated yielding 4.2 g of yellow oil. Purification with flash chromatography on silica gel (pentane-EtOAc-CH_2Cl_2-TEA 100:7:20:6) and recrystallisation from acetone gave 2.99 g of colourless crystals (6.33 mmol, 97% yield).

t_m=187-189 °C.

^{1}H NMR ($CDCl_3$, +25°C, 500 MHz) δ: 7.43 (m, 8H, ortho-C*H*); 7.31 (m, 8H, meta-C*H*); 7.22 (m, 4H, para-C*H*); 4.42 (s, 2H, benzylic C*H*); 3.10 (dm, 4H, CH_2); 2.73 (dm, 4H, CH_2); 2.52 (m, 2H, bridgehead C*H*).

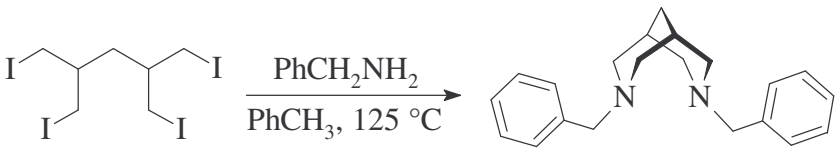
^{13}C NMR ($CDCl_3$, +25°C, 100.6 MHz) δ: 215.0 (*C*=O); 142.0 (ipso-*C*); 128.5 (aromatic *C*H); 127.9 (aromatic *C*H); 127.1 (para-*C*H); 74.7 (benzylic *C*H); 56.6 (4C, CH_2); 47.0 (2C, bridgehead *C*H).

^{15}N NMR ($CDCl_3$, +25°C, 50.7 MHz) δ: -329.6.

IR (neat film) ν̃: 3026, 2951, 2793, 1734 (C=O), 1596, 1492, 1450, 985, 757, 708 cm^{-1}.

pK_a^{MeCN} = 13.47

N,N'-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane **(4)**[12]



8 **4**

1,5-Diiodo-2,4-bis(iodomethyl)pentane (**8**, 1.00 g, 1.66 mmol) and benzylamine (1.06 g, 9.89 mmol) were dissolved in 6 mL of dry toluene, and sealed into a glass ampoule. After heating at 125 °C for 3 days, the ampoule was cooled to r.t. The contents were extracted with 10% NaOH solution, followed by re-extraction of the aqueous phase with toluene, evaporation of the organic phase and drying under vacuum. Flash chromatography was carried out by using silica gel and pentane-ether-TEA (7:0.5:0.6) as the mobile phase, resulting in the isolation of the title product as a transparent oil (0.23 g, 0.75 mmol, 45% yield). Additional 103 mg was isolated as a by-product **5**.

4: R_f=0.5 (pentane-ether-TEA 7:0.5:0.6)

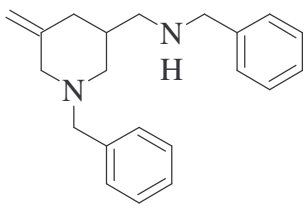
^{1}H NMR ($CDCl_3$, +25°C, 500 MHz) δ: 7.47 (m, 4H, ortho-C*H*); 7.34 (m, 4H, meta-C*H*); 7.27 (m, 2H, para-C*H*); 3.50 (benzylic CH_2); 2.83 (dm, 4H, N-CH_2); 2.36 (dd, 4H, J=10.8, 4.0 Hz, N-CH_2); 1.91 (m, 2H, bridgehead C*H*); 1.58 (m, 2H, 9-CH_2).

^{13}C NMR ($CDCl_3$, +25°C, 100.6 MHz) δ: 139.8 (ipso-*C*); 128.8 (aromatic *C*H); 128.0 (aromatic *C*H); 126.5 (para-*C*H); 63.4 (benzylic *C*H_2); 57.9 (N-*C*H_2); 30.9 (9-*C*H_2); 29.9 (bridgehead *C*H).

^{15}N NMR ($CDCl_3$, +25°C, 50.7 MHz) δ: -335.6.

pK_a^{MeCN} = 21.27

By-product: *N-Benzyl-N-[(1-benzyl-5-methylenepiperidin-3-yl)methyl]amine* **(5)**



5

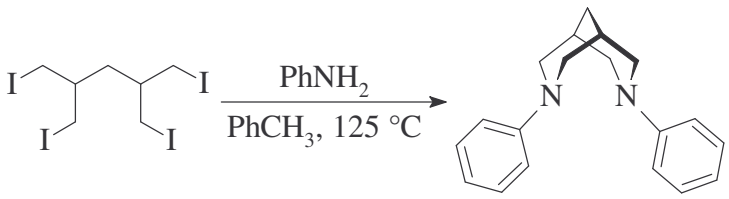
Yield 103 mg (0.34 mmol, 20%).

5: R_f=0.42 (pentane-toluene-TEA 10:2:1)

^{1}H NMR ($CDCl_3$, +25°C, 500 MHz) δ: 7.25-7.38 (m, 10H, aromatic C*H*), 4.79 (m, 2H, =CH_2), 3.78 (s, 2H, NH-CH_2-Ph), 3.61 (d, J=13.1 Hz, 1H, benzylic 1-N-C*H*), 3.54 (d, J=13.1 Hz, 1H, benzylic 1-N-C*H*), 3.16 (d, J=11.7 Hz, 1H, 6-C*H*), 2.88 (dm, J=11.2 Hz, 1H, 2-C*H*), 2.75 (d, J=11.7 Hz, 1H, 6-C*H*), 2.60 (dd, J=11.8, 6.9 Hz, 1H), 2.55 (dd, J=11.8, 6.5 Hz, 1H), 2.44 (dd, J=13.0, 4.0 Hz, 1H, 4-C*H*), 2.06 (dd, J=11.2, 8.9 Hz, 1H, 2-C*H*), 1.94 (m, 1H, 3-CH, 1H), 1.84 (m, 1H, 4-C*H*).

^{13}C NMR ($CDCl_3$, +25°C, 100.6 MHz) δ: 143.5 (=*C*), 140.4 (ipso-*C*), 138.1 (ipso-*C*), 129.0, 128.2, 128.0, 127.9, 126.9, 126.8, 109.6 (=*C*H_2), 62.7 (benzylic 1-N-*C*H_2), 60.1 (6-*C*H_2), 57.1 (2-*C*H_2), 53.8 (NH-*C*H_2-Ph), 52.6 (CH-*C*H_2-NH), 37.3 (4-*C*H_2), 36.6 (3-*C*H).

3,7-Diphenyl-3,7-diazabicyclo[3.3.1]nonane **(6)**[13]



8 **6**

1,5-Diiodo-2,4-bis(iodomethyl)pentane (**8**, 2.00 g, 3.31 mmol) and freshly distilled aniline (1.86 g, 20.0 mmol) were dissolved in 9 mL of dry toluene, and sealed into a glass ampoule. After heating at 125 °C for 3 days, the ampoule was cooled to r.t. The contents were extracted with 10% NaOH solution, followed by re-extraction of the aqueous phase with CH_2Cl_2, evaporation of the organic phase and drying under vacuum. Flash chromatography was carried out by using silica gel and CH_2Cl_2-pentane (2:3) as the mobile phase, resulting in the isolation of the title product as slightly yellow oil (350 mg, 1.25 mmol, 38% yield). Additional 365 mg was separated as a by-product **7**.

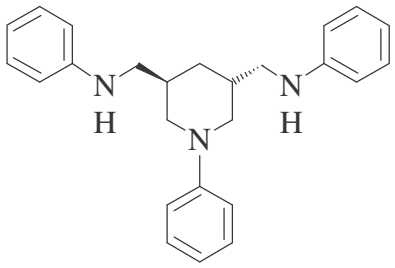
R_f=0.49 (CH_2Cl_2-pentane 2:3)

^{1}H NMR ($CDCl_3$, +25°C, 500 MHz) δ: 7.26 (m, 4H, meta-C*H*), 6.86 (m, 4H, ortho-C*H*), 6.77 (m, 2H, para-C*H*), 3.75 (dm, J=11.3 Hz, 4H, CH_2), 3.15 (dd, J=11.3, 4.0 Hz, 4H, CH_2), 2.34 (m, 2H, bridgehead C*H*), 1.86 (m, 2H, 9-CH_2).

^{13}C NMR ($CDCl_3$, +25°C, 100.6 MHz) δ: 150.9 (ipso-*C*), 128.9, 117.4 (para-*C*H), 113.7, 53.3 (2-*C*H_2), 29.1 (bridgehead *C*H), 28.7 (9-*C*H_2).

^{15}N NMR ($CDCl_3$, +25°C, 50.7 MHz) δ: -315.4.

By-product: *trans-3,5-bis[(phenylamino)methyl]-1-phenylpiperidine* **(7)**



7

Yield: 365 mg (0.99 mmol, 30% yield).

7: R_f=0.40 (CH_2Cl_2-pentane 2:3)

^{1}H NMR ($CDCl_3$, +25°C, 500 MHz) δ: 7.39 (m, 2H, meta-C*H*), 7.33 (m, 4H, meta-C*H*), 7.07 (m, 2H, ortho-C*H*), 7.00 (m, 1H, para-C*H*), 6.86 (m, 2H, para-C*H*), 6.75 (m, 4H, ortho-C*H*), 3.40 (ddm, J=11.6, 3.7 Hz, 2H), 3.36 (dd, J=12.7, 7.7 Hz, 2H), 3.25 (dd, J=12.7, 6.0 Hz, 2H), 3.14 (ddm, J=11.6, 6.7 Hz, 2H), 2.27 (m, 2H, 3-C*H*), 1.76 (dd, J=6.3, 5.7 Hz, 2H, 4-CH_2).

^{13}C NMR ($CDCl_3$, +25°C, 100.6 MHz) δ: 152.3 (1C, ipso-*C*), 148.3 (2C, ipso-*C*), 129.2 (4C, meta-*C*H), 129.0 (2C, meta-*C*H), 119.8 (1C, para-*C*H), 117.24, 117.17, 112.7 (4C, ortho-*C*H), 53.9 (2C, N-*C*H_2), 46.9 (2C, N-*C*H_2), 33.0 (2C, 3-*C*H), 31.5 (1C, 4-*C*H_2).

The following compounds were available from other sources: 1,5-diiodo-2,4-bis(iodomethyl)pentane (**8**) 3,7-dibenzhydrylbispidine (**9**, both prepared as described in Appendix II), 3,7-diphenyl-1,5-dicarbomethoxybispidinone (**10**, prepared by A. Axén[14]), 3,7-dibenzyl-1,5-dimethylbispidinone (**11**, prepared by A. Axén[14]), 3,7-dibenzyl-1,5-dicarbomethoxybispidinone (**12**, prepared by A. Axén[14]), (–)-sparteine (**13**, commercial reagent purchased from Aldrich, distilled under vacuum prior to use), 3,7-diphenethylbispidine (**14**, prepared according to a literature procedure[15]).

Acknowledgments

The Swedish Natural Science Research Council, the Swedish Technical Science Research council, Magn. Bergvalls Stiftelse, and the Estonian Science Foundation Grant 5800 are gratefully acknowledged for financial support.

References

1. Davis, A.L., Keeler, J., Laue, E.D., Moskau, D. *J. Magn. Reson.*, **1992**, *98*, 207–216.
2. Hurd, R.E., John, B.K. *J. Magn. Reson.*, **1991**, *91*, 648–653.
3. Wagner, R., Berger, S. *J. Magn. Reson., Series A*, **1996**, *123*, 119-121.
4. Braunschweiler, L., Ernst, R.R. *J. Magn. Reson.*, **1983**, *53*, 521-528.
5. Kaljurand, I., Rodima, T., Leito, I., Koppel, I., Schwesinger, R. *J. Org. Chem.*, **2000**, *65*, 6202-6208.
6. Inamo, M., Kohagura, T., Kaljurand, I., Leito, I. *Inorg. Chim. Acta*, **2002**, *340*, 87-96.
7. Rodima, T., Kaljurand, I., Pihl, A., Mäemets, V., Leito, I., Koppel, I. *J. Org. Chem.*, **2002**, *67*, 1873-1881.
8. Rodima, T., Mäemets, V., Koppel, I.A. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2637-2644.
9. Kaljurand, I., Kütt, A., Sooväli, L., Rodima, T., Mäemets, V., Leito, I., Koppel, I.A. *J. Org. Chem.*, **2005**, *70*, 1019-1028.
10. Leito, I., Kaljurand, I., Koppel, I.A., Yagupolskii, L.M., Vlasov, V.M. *J. Org. Chem.*, **1998**, 63, 7868-7874.
11. Leito, I., Rodima, T., Koppel, I.A., Schwesinger, R., Vlasov, V.M. *J. Org. Chem.*, **1997**, *62*, 8479-8483.
12. Ruenitz, P.C., Smissman, E.E. *J. Heterocyc. Chem.*, **1976**, *13*, 1111-1112.
13. Zefirov, N.S., Gogozina, S.V. *Tetrahedron*, **1974**, *30*, 2345-2352.
14. Gogoll, A., Grennberg, H., Axén, A. *Organometallics*, **1997**, *16*, 1167-1178.
15. Johansson, C., Axén, A., Grennberg, H., Gogoll, A. *Chem. Eur. J.*, **2001**, *7*, 396–403.