

Synthesis, Crystal Structure, and H/D Exchange of the Inside Protonated Form of the Cage Imine 4,8,12-Triaza-1-azoniatricyclo[6.6.3.2^{4,12}]nonadec-1(15)-ene. A Model for Proton Transfer through an Aliphatic Membrane

Johan Springborg,*[†] Bente Nielsen,[†] Carl Erik Olsen,[†] and Inger Søtofte[‡]

Contribution from the Chemistry Department, Royal Veterinary and Agricultural University, Thorvaldsensvej 40, DK-1871 Frederiksberg C, Denmark, and Department of Chemistry, Technical University of Denmark, DTU 207, DK-2800 Lyngby, Denmark

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Abstract: The reaction of the inside protonated form of the tricyclic amine 1,4,8,12-tetraazatricyclo[6.6.3.2^{4,12}]nonadecane (**1**) with iron(III) affords the inside monoprotonated form of the corresponding imine 4,8,12-triaza-1-azoniatricyclo[6.6.3.2^{4,12}]nonadec-1(15)-ene (**2**), which was isolated as the tetrabromozincate salt (**2a**) in a yield of 78%. The crystal structure of **2a** has been solved by X-ray diffraction at $T = 120$ K. In the imine cation the acidic hydrogen atom and the lone pairs of the nitrogen atoms are oriented toward the inside of the cavity. The acidic hydrogen atom is bound to a nitrogen atom belonging to the triazacyclononane entity. The imine double bond is situated between the N-atom of the triazacyclononane entity and the C-atom belonging to one of the three trimethylene bridges. The imine **2** is stable in acidic solution and the inside coordinated proton is very robust in acidic solution. In basic solution the imine reacts fast to give a quantitative formation of the inside protonated form of the hemiaminal 1,4,8,12-tetraazatricyclo[6.6.3.2^{4,12}]nonadecan-5-ol (**3**). The equilibrium constant $K_m = [3][H^+]/[2]$ was determined at three different temperatures from potentiometric measurements, which gave $K_m = 1.57(1) \times 10^{-5}$ M at 25 °C, $\Delta S^\circ = -83(1)$ J mol⁻¹ K⁻¹, and $\Delta H^\circ = 2.6(3)$ kJ mol⁻¹ at $I = 1.0$ M (NaCl). The inside coordinated proton in **3** is labile in basic solution and the rate for NH/ND exchange was determined by ¹H NMR at three different temperatures. The reaction followed the expression $k_{obs} = k_{ex}[OD^-]$ with $k_{ex} = 0.0978(30)$ dm³ mol⁻¹ s⁻¹ at 25 °C, $\Delta S^\ddagger = 87(4)$ J mol⁻¹ K⁻¹, and $\Delta H^\ddagger = 104.9(11)$ kJ mol⁻¹ at $I = 1.0$ M (NaCl). The exchange rate is more than 5×10^6 times faster than that of the parent saturated cage **1**. This extreme enhancement of reactivity is explained by an intramolecular proton transfer reaction mediated by hydroxy and oxy groups flipping in and out of the cavity, which mechanistically has resemblance to the transport of ions in a biological system.

Introduction

Several new tricyclic amines, so-called cage adamanzanes, have been reported recently.^{1–15} These compounds are cyclic

tetraamines strapped by two alkylene chains connecting two nonadjacent nitrogen atoms as illustrated for some adamanzanes in Chart 1.

The smallest members [1⁶]adamanzane (hexamethylenetetramine) and [1^{4,2}]adamanzane have long been documented in the literature.¹⁶ Previously Schmidtchen¹ has synthesized and studied the largest analogues having hexamethylene or octamethylene bridges, [6⁶]adamanzane and [8⁶]adamanzane. Later Ichikawa and co-workers^{2–4} reported adamanzanes having pentamethylene and hexamethylene bridges. Recently, Miyahara et al. and Springborg et al. have presented the syntheses and X-ray crystal structures of the small tricyclic tetraamines [2⁶]adamanzane,⁵ [2^{4,3}]adamanzane,⁶ [(2,3)³]adamanzane⁷ (**1**), and [3⁶]adamanzane.^{8,9} Contrary to the smallest and largest members these cage molecules have all four nitrogen lone-pairs pointing into the cavity and all have been obtained as inside monoprotonated forms.^{5–11} Along with similar molecules they have been the subject of recent studies discussing properties such as basicity and strain energy.^{12–15} The small adamanzanes are all

* Corresponding author. E-mail: josp@kvl.dk.

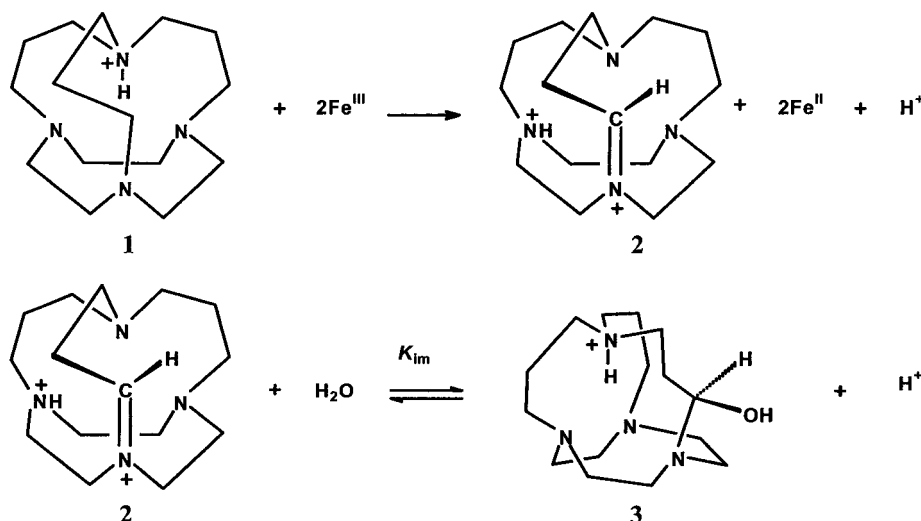
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[‡] Department of Chemistry, Technical University of Denmark.

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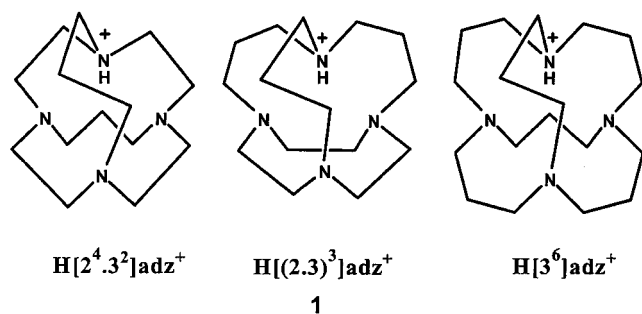
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Scheme 1 The Position of the Inside Coordinated Proton in **1** and **2** Is Based upon Crystallographic Data in This Study and the Literature (Ref 7)^a



^a In **3** the site of protonation is tentative, based upon the structural similarity between **1** and **3** as discussed further in the text.

Chart 1. Inside Protonated Small Cage Adamanzanes^a



^a The site of protonation is based upon crystallographic data.^{6,7,9}

very inert with respect to the inside coordinated proton and in this and other respects they possess features common to the small bi- and tricyclic amines studied by Lehn, Alder, and others.^{10,11,17}

In the present paper we report the synthesis and crystal structure of the new imine cage **2**, the inside protonated form of 4,8,12-triaza-1-azoniatricyclo[6.6.3.2^{4,12}]nonadec-1(15)-ene, obtained by oxidation of **1** by iron(III). The unusual properties of **2** with respect to its very stable imine group and its exorbitantly increased reactivity of the inside coordinated proton in basic solution have been studied.

Results and Discussion

Synthesis and Solution Properties of the Imine Cage.

Oxidation of **1** with iron(III) in aqueous, acidic solution leads to the formation of one imine bond per tetraamine as shown in Scheme 1, and pure **2** was isolated as a tetrabromozincate (**2a**) in a yield of 78%. From this salt a pure diperchlorate **2b** salt was synthesized. From NMR measurements it was established that the reaction mixture contains approximately 95% **2**, and the remaining 5% was identified as one of the two other possible imine isomers.

The ¹³C NMR spectrum of **2** exhibits three resonance lines in the region δ 20–32 ppm for the three different C–CH₂–C

methylene carbon atoms, eleven lines in the region δ 48–59 ppm for the eleven different CH₂–N methylene carbon atoms, and one resonance line at 185.2 ppm for the CH=N methine carbon. The ¹H NMR spectrum has a complex pattern in the region δ 1.5–5.0 ppm for the 28 methylene protons, a doublet ($J = 11$ Hz) at 8.9 ppm for the CH=N proton and at 10.2 ppm a broad singlet for the inside coordinated proton. The observation that the imine proton gives rise to a doublet and not a doublet of doublets means that only coupling to one of the nonequivalent hydrogen atoms of the neighboring methylene groups CH_aH_b–CH=N is important. Following the Karplus relation¹⁸ this suggests that one of the dihedral angles is in the region of 90°, but from the crystallographic data (see following section) it is calculated that the dihedral angle for H_aC–CH is 166° and that for H_bC–CH is 46°. This suggests that the conformation in solution differs from that in the crystal.

The reaction between **1** and iron(III) was followed spectrophotometrically in the visible region. With an excess of iron(III) the reaction could be monitored by following the decrease in the absorption of the intensely colored yellow complex FeCl₄[–]. The decrease in the absorbance could be taken as a measure of the consumption of iron(III), which within experimental error was found to be two moles of iron(III) per mole of tetraamine. The overall half-life of the redox reaction is 17 min at 25 °C ($C_{\text{Fe(III)}} = 0.05$ M, $C_{\text{amine}} = 0.017$ M, and $C_{\text{HCl}} = 0.1$ M). It seems probable that the redox reaction occurs via an amine radical cation, though at present no experimental evidence for this proposal has been obtained.

Crystal Structure of 8,12-Diaza-1,4-diazoniatricyclo[6.6.3.2^{4,12}]nonadec-1(15)-ene Tetrabromozincate Monohydrate (2a**).** The compound consists of **2** and ZnBr₄^{2–} ions and water molecules. The labeling of the atoms in **2** is shown in Figure 1. Bond lengths and angles are as found in similar compounds.⁷ In the present structure the C–N bond lengths average 1.483(6) Å and the C–C single bond lengths 1.516(6) Å. Around N(2) the bond angles C(3)–N(2)–C(4), C(3)–N(2)–C(14), and C(4)–N(2)–C(14) are 117.9(5), 125.2(5), and 116.9(5)°, respectively. The larger angles found are due to the

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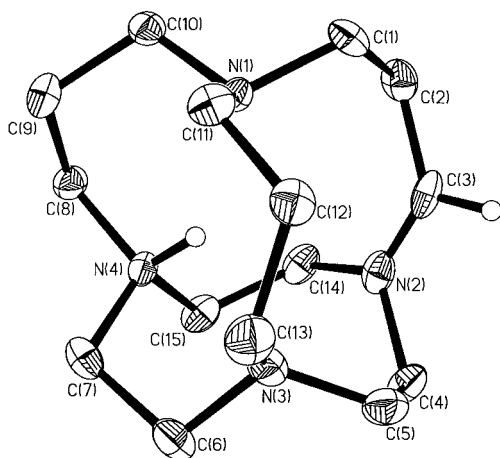


Figure 1. View of the cation **2**. The thermal ellipsoids are drawn at the 50% probability level. With the exception of H(4) bound to N(4) and H(3) bound to C(3) the hydrogen atoms have been omitted for clarity.

presence of the N=C bond (the N(2)–C(3) bond length is 1.251(8) Å). The N(2)–C(3)–C(2) angle of 128.1(6)° and the C(3)–C(2)–C(1) angle of 105.5(5)° are also influenced by the double bond. All the other bond angles are in the range of 108.2–(5)–115.2(5)°. The C(3)–N(2)–C(4)–C(14) group is planar with the hydrogen atom, H(3), attached to C(3) 0.20 Å above and C(2) 0.26 Å below the plane. The C(2) atom is twisted from this plane, the torsion angle C(2)–C(3)–N(2)–C(14) being 13.9(9)°. This unusual twisting is undoubtedly caused by strain in the tricyclic skeleton and is significantly more pronounced than that reported for, e.g., 8-acetamido-2,4,4,8-tetramethyl-3-azoniabicyclo[3.3.1]non-2-ene perchlorate,²² which has six-membered-ring systems and where a torsion angle of 4.1(10)° is found. The acidic hydrogen atom and the lone pairs of the nitrogen atoms are oriented toward the inside of the cavity. The distances between the bridgehead nitrogen atoms in **2** are 3.158(7) Å for N(1)···N(3) and 2.958(7) Å for N(2)···N(4). The N(2)···N(1) and N(2)···N(3) distances of 3.340(7) and 2.854(7) Å, respectively, are influenced by the N=C bond and therefore longer than the corresponding distances N(4)···N(1) and N(4)···N(3) of 2.848(6) and 2.703(7) Å, respectively. The acidic hydrogen atom H(4) is attached to N(4) and is hydrogen bonded to the other three nitrogen atoms with H(4)···N distances in the range 2.04–2.46 Å. The four nitrogen atoms form a rather distorted tetrahedron with N(2) 0.11(2) Å and N(4) 1.45(1) Å above and N(1) 0.54(2) Å and N(3) 1.02(2) Å below the least-squares plane through the atoms. In the crystal packing the water molecule is hydrogen bonded to ZnBr₄²⁻ ions.

Stability of 2 in Acidic Solutions. The imine is stable in acidic solutions as the ¹H and ¹³C NMR spectra of **2a** in 0.1 M D₂SO₄ show no sign of formation of other products within 14 days at room temperature. Likewise, no outside protonation of the amine groups was observed as shown by the identity of the ¹H NMR spectra of solutions of **2a** in D₂O and in 1 M D₂SO₄, respectively. In contrast the parent amine **1** was previously shown to undergo outside protonation of one or more of the

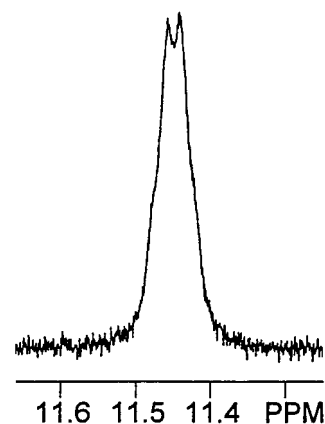


Figure 2. The resonance band of the inside coordinated proton in **3** exhibits a small splitting (6 Hz) due to coupling with neighboring methylene protons. The shown spectrum was measured using a 400 MHz instrument.

amine groups in strongly acidic solutions ([H⁺] ≥ 0.1 M).⁷ Probably protonation of the monocharged cation **1** is favored relative to protonation of the doubly charged cation **2** due to electrostatic factors. The inside coordinated proton does not exchange in acidic solutions as was also found for the amine **1**.⁷

Hydrolysis of the Imine Bond in 2. Aqueous solutions of **2a** are slightly acidic (pH ca. 2) and this is explained by the formation of the hemiaminal **3** (Scheme 1) as shown in the following equilibria (eqs 1 and 2).



The reactions are fast and addition of excess hydroxide gives quantitative formation of the hemiaminal **3**, which is very stable in basic solutions (pH 10–14); e.g. ¹³C NMR spectra of a solution of **3** in 0.01 M NaOD showed no significant change within hours at room temperature. In more concentrated base, however, the compound does react as described at the end of this section. The hemiaminal **3** was not isolated as a salt but its structure in solution was characterized unambiguously by its ¹³C NMR spectrum, which exhibits three resonance lines in the region δ 21–28 ppm for the three different C–CH₂–C methylene carbon atoms, eleven lines in the region δ 42–58 ppm for the eleven different CH₂–N methylene carbon atoms, and one resonance line at 88.3 ppm for the CH(OH)–N carbon atom.

The ¹H NMR spectrum of freshly prepared (see below) solutions of **3** shows a broad peak at 11.45 ppm for the inside coordinated proton as shown in Figure 2. The signal has a small splitting of 0.015 ppm (using a 400 MHz instrument) corresponding to 6.0 Hz. This splitting could be due either to coupling of the NH hydrogen or to its being located at different nitrogen atoms. To clarify this ambiguity the spectrum was also measured using a 200 MHz instrument, which gave a splitting of 0.029 ppm corresponding to 5.8 Hz. It therefore follows that the splitting cannot be due to different sites of protonation. This was further confirmed by the COSY spectrum, which showed coupling between the NH proton and protons in the region δ 2.45–2.72 ppm, which from a HSQC spectrum were shown to

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Table 1. Thermodynamic Data for $K_{\text{im}} = K_{\text{H}_2\text{O}}K_{\text{a}}$ (Scheme 1 and Eqs 1 and 2) at $I = 1.0$ M (NaCl)

$T/^\circ\text{C}$	$K_{\text{im}}^{\text{obs}}/\text{M}$	$K_{\text{im}}^{\text{calc}}/\text{M}^2$
5.65	1.47×10^{-5}	1.46×10^{-5}
25.0	1.56×10^{-5}	1.57×10^{-5}
39.4	1.66×10^{-5}	1.65×10^{-5}

^a $K_{\text{im}}^{\text{calc}}$ are calculated values using the parameters. $\Delta S^\circ = -83(1)$ J mol⁻¹ K⁻¹ and $\Delta H^\circ = 2.6(3)$ kJ mol⁻¹.

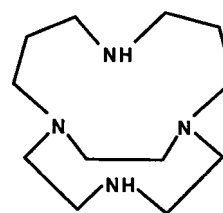
belong to methylene groups bound to nitrogen (coupling with carbon atoms positioned in the region δ 45–58 ppm). The C–CH₂–C methylene protons in the ¹H NMR spectrum are positioned in the region δ 1.4–2.4 ppm. It is therefore concluded that the observed splitting is due to coupling between the NH proton and the neighboring methylene protons. The COSY spectrum showed no coupling between NH and CH(OH) (δ 4.75 ppm), thus indicating that the nitrogen adjacent to the latter group is not the site of protonation. Due to the electron-withdrawing effect of oxygen this nitrogen is also expected to be the least basic site of the four nitrogen atoms.

It is noted that a similar splitting in the ¹H NMR spectrum for the inside coordinated proton has not been observed in **1** or **2** or in other reported inside protonated tetraamine cages related to **1**.^{5–9} However, in the case of H[2⁶]adz⁺ evidence for a coupling between NH and the methylene protons has been presented⁵ and was shown to cause a small (1 Hz) splitting of the signal from the 28 identical methylene protons. In the present study additional measurements of the COSY spectra unambiguously showed that the adamantanes H[2⁴.3²]adz⁺ and H[3⁶]adz⁺ (Chart 1) and the imine **2** all exhibit a distinct coupling between the NH proton and methylene protons of the type CH₂–N, whereas the COSY spectrum of H[(2.3)³]adz⁺ (**1**) gave no evidence for such a coupling. It still remains to be answered why the coupling only in the case of **3** causes a splitting of the NH proton signal and also why **1** does not exhibit coupling.

The formation of **3** is reversible and addition of excess strong acid very fast reforms the imine as shown by NMR and also by isolation of a pure salt of reformed **2**. The concentration equilibrium constant $K_{\text{im}} = K_{\text{H}_2\text{O}}K_{\text{a}}$ was determined potentiometrically by measuring $\text{pH} = -\log([\text{H}^+]/\text{M})$ in solutions of **2b** with added sodium hydroxide. The equilibration is fast as seen by the fact that during the titration a constant pH reading after each addition of base was obtained within the response time of the glass electrode, i.e. 15–30 s, and during the titration no other reactions interfere. K_{im} was determined at three temperatures (Table 1) and this gave $K_{\text{im}} = 1.57(1) \times 10^{-5}$ M at 25 °C, $\Delta S^\circ = -83(1)$ J mol⁻¹ K⁻¹, and $\Delta H^\circ = 2.6(3)$ kJ mol⁻¹ at $I = 1.0$ M (NaCl).

From the ¹H and ¹³C NMR spectra it is estimated that $K_{\text{H}_2\text{O}} < 0.01$ since solutions of **2a** in 0.1 M D₂SO₄ do not exhibit signals for **3H⁺** (or other species). From the composite expression $K_{\text{im}} = K_{\text{H}_2\text{O}}K_{\text{a}}$ it follows that the acid dissociation constant for the diprotonated species **3H⁺** must be greater than 10⁻³ M. This lower limit estimate seems reasonable since the diprotonated form of **1** is a relatively strong acid with an acid dissociation constant of about 0.1 M.⁷

The ¹³C NMR spectra of solutions of **2a** in D₂O and 0.1 M D₂SO₄ are essentially identical. However, for the acidic solutions it was observed that the CH=N carbon gives an intense sharp signal at 185.2 ppm whereas in pure D₂O the signal is weak and broad. This line broadening is explained by coalescence between the resonance lines of the CH=N carbon of **2** and the

Chart 2**4**

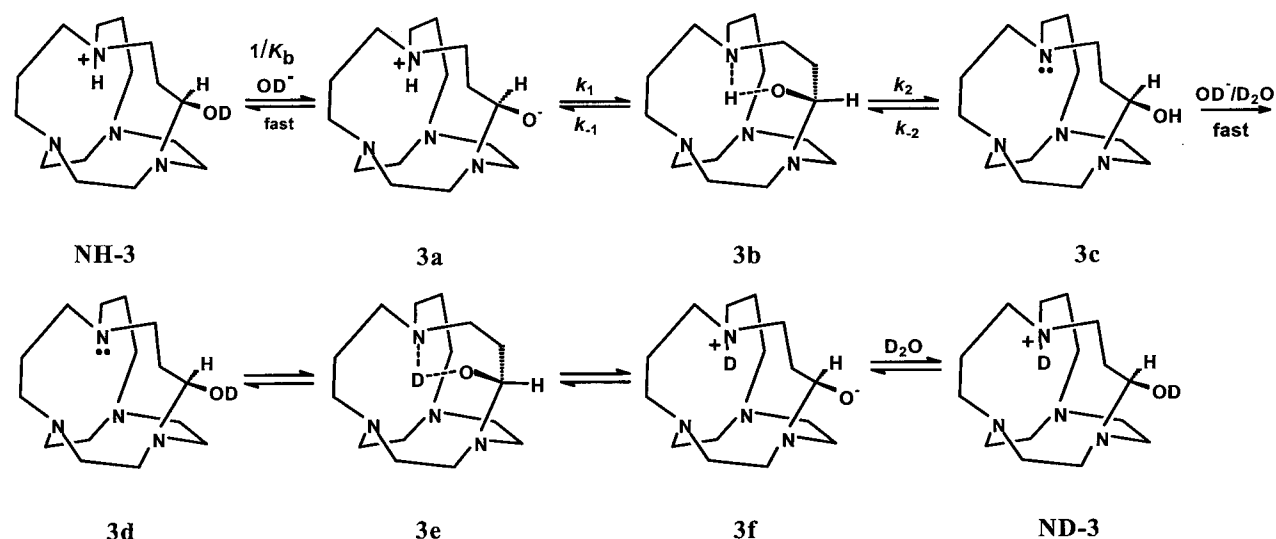
CH(OH) carbon of the hemiaminals (**3** and **3H⁺**) due to a fast equilibration between these species (from the value of K_{im} it is calculated that an aqueous 10⁻¹ M solution of **2a** contains approximately 1% of the hemiaminal in its unprotonated form **3**). This means that the equilibrium between **2** and **3** is fast on the NMR time scale in agreement with the statement given above.

Partially neutralized solutions of **2a** (pH ~4) are stable for at least 30 min at room temperature. At longer periods a series of reactions were detected by NMR measurements. These reactions involve displacement of the imine bond and formation of new hydroxy species and probably also enamines. Unambiguous determination of the structure of any of these species could not be achieved.

In strong basic solution **3** slowly undergoes cleavage of one of the trimethylene bridges ($t_{1/2} =$ approximately 4 h in 0.5 M NaOH, 25 °C) giving the bicyclic amine 1,5,9,12-tetraazabicyclo[7.5.2]hexadecane (**4**) (Chart 2), which was isolated as the bromide salt of the triprotonated form, **4·3HBr·3H₂O** (yield 29%). The mixed chloride–bromide salt of this amine was recently obtained by hydrolysis of **1** in concentrated hydrochloric acid (yield 40%).⁷

NH/ND Exchange of 3. The ¹H NMR spectrum of freshly prepared solutions of **3** in 0.01 M NaOD exhibits a signal at δ 11.45 ppm, which as mentioned above belongs to the inside coordinated proton. The intensity of the signal decreases with time and vanishes after some hours at 25 °C, while the remaining part of the ¹H NMR spectrum as well as the ¹³C NMR spectrum reveals no changes. Subsequent addition of excess strong acid to the solution affords the ND-form of the imine **2**, i.e. this compound shows no signal in the ¹H NMR spectrum for the inside coordinated proton. The ND-form was isolated as the tetrabromozincate (**ND-2a**). These observations are unambiguously interpreted in terms of an exchange of the inside coordinated protons with deuterons from the solvent as strongly supported by infrared studies. The infrared spectrum of **2a** shows a broad but distinctive band at 2635 cm⁻¹ assigned to the N⁺–H stretching motion. In **ND-2a** this band is shifted to $\nu(\text{N}^+ - \text{D}) = 1974$ cm⁻¹. It is seen that the ratio $\nu(\text{N}^+ - \text{H})/\nu(\text{N}^+ - \text{D}) = 1.33$ is close to the value 1.37 calculated using the approximative equation²¹ $\nu(\text{N}^+ - \text{H})/\nu(\text{N}^+ - \text{D})_{\text{calc}} = \{[m_{\text{D}}/(m_{\text{D}} + m_{\text{N}})]/[m_{\text{H}}/(m_{\text{H}} + m_{\text{N}})]\}^{1/2}$. In this context it should be noted that the series of cage adamantanes such as **1** and its analogues have been the subject of a comprehensive structural and spectroscopic study using density functional theory methodologies by Galasso,¹⁵ and among other data observed and calculated N⁺–H stretching frequencies for inside protonated adamantanes are reported.

Since the H/D exchange at high temperatures and/or high base concentrations is too rapid to be monitored by NMR the kinetics was studied using the method of quenching, i.e. at

Scheme 2. Proposed Reaction Mechanism for the NH/ND Exchange of **3** in Basic Solution^a

^a The site of protonation is discussed in the text.

Table 2. Kinetic Data for the NH/ND Exchange Reaction at $I = 1.0$ M (NaCl)

$T/^\circ\text{C}$	$[\text{OD}^-]/\text{M}$	$k_{\text{obs}}/\text{s}^{-1}$	$k_{\text{calc}}/\text{s}^{-1}$
40.2	0.032	0.0274	0.0256
	0.0078	0.00611	0.00623
25.0	0.0986	0.00940	0.00963
	0.0266	0.00247	0.00260
0.0	0.344	0.000649	0.000641
	0.166	0.000329	0.000309
	0.0989	0.000199	0.000184
	0.00734	0.0000121	0.0000137

^a Calculated using $k_{\text{calc}} = [\text{OD}^-]k_{\text{ex}}$ where $k_{\text{ex}} = 0.0978(30) \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ (25 °C) is defined by the activation parameters. $\Delta S^\ddagger = 87(4) \text{ J mol}^{-1} \text{ K}^{-1}$ and $\Delta H^\ddagger = 104.9(11) \text{ kJ mol}^{-1}$.

different times excess acid (DCl) was added to samples of the basic solutions of **3** resulting in quantitative reformation of the imine **2**, which is stable and does not undergo H/D exchange under these conditions. From the ^1H NMR spectra of these quenched solutions the degree of exchange was estimated from the relative area of the signal for the inside coordinated proton of **2**. The kinetics was studied at three temperatures and the concentration of OD^- was varied from 0.007 to 0.3 M. In all experiments the exchange reaction followed the expression for a first-order reaction giving the k_{obs} values in Table 2. The dependence of k_{obs} on the OD^- concentration followed the expression $k_{\text{obs}} = [\text{OD}^-]k_{\text{ex}}$ and this gave $k_{\text{ex}} = 0.0978(30) \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ at 25 °C, $\Delta S^\ddagger = 87(4) \text{ J mol}^{-1} \text{ K}^{-1}$, and $\Delta H^\ddagger = 104.9(11) \text{ kJ mol}^{-1}$ at $I = 1.0$ M (NaCl).

It was recently shown⁷ that the rate constant for the NH/ND exchange reaction of **1** is less than $4 \times 10^{-9} \text{ s}^{-1}$ in 0.01 M NaOD at 25 °C and in the present study new measurements in 1 M NaOD showed that it is less than $2 \times 10^{-8} \text{ s}^{-1}$ at 25 °C. At the latter conditions the exchange rate of **3** is 0.0978 s^{-1} , i.e. at least 5×10^6 times faster than that of **1**.

The inertness of the inside coordinated proton of **1** and of the analogous small adamanzane cages (Chart 1) is explained by encapsulation of the proton by the tricyclic framework.^{5–9} The structural difference between **1** and **3** is that in the latter a hydrogen atom is substituted with the much larger hydroxy group meaning that from a steric point of view **3** should exchange its proton slower than **1**, which is contrary to the fact.

Therefore, the most likely explanation is that the enhanced reactivity is due to a specific involvement of the hydroxy/oxy groups in **3** as outlined in Scheme 2. It is proposed that the oxy group assists in the transportation of H^+ out of the cavity and that the hydroxy group assists in taking D^+ into the cavity. First, it is assumed that the OH to OD exchange (in **3** and **3c**) occurs much faster than the NH/ND exchange. Second, it is assumed that a small percentage of the hydroxy group is deprotonated. The first step in the exchange sequence is transportation of the inside coordinated proton to the outside via the oxy group (**3a–c**). A fast OH/OD exchange (**3c** to **3d**) is then followed by the reverse reaction sequence resulting in the insertion of an inside coordinated deuteron giving **ND-3**. The formation of **3c** is considered the point of no return since the rate constant k_{-2} (**3c** to **3b**) undoubtedly is smaller than the rate constant for the OH/OD exchange (**3c** to **3d**). The rate expression is thus determined by the relative magnitudes of k_1 , k_{-1} , and k_2 . It is assumed that the concentration of all intermediates (**3a** to **3f**) is negligible from a stoichiometric point of view and therefore $[\mathbf{3a}] = [\text{NH-3}][\text{OD}^-]/K_b$. Applying the steady-state approximation, $d[\mathbf{3b}]/dt = 0$, gives the rate law in eq 3, which is in

$$k_{\text{calc}} = [\text{OD}^-]k_{\text{ex}} = \frac{[\text{OD}^-]k_1k_2}{(k_{-1} + k_2)K_b} \quad (3)$$

agreement with the observed first-order dependence of $[\text{OD}^-]$. In the following it is attempted to obtain a rough order of magnitude estimate for k_1 . It is assumed that $K_b \sim 10^2$ M corresponding to the acidity of secondary alcohols²⁰ (probably K_b is somewhat smaller due to the inductive effect from the neighboring N-group). The rate constants k_{-1} and k_2 refer to similar reactions. The constant k_2 refers to a reaction involving N–H bond breaking, which probably is favored over O–H bond breaking (k_{-1}) as the latter reaction involves charge separation. On the other hand, considering steric effects, k_2 refers to the passage of a hydroxy group through the cavity membrane while k_{-1} refers to the passage of the smaller (estimated on the basis of van der Waals radii) oxy group and this might favor the latter reaction. It is possible that the electrostatic effect ($k_2 > k_{-1}$) is more pronounced than the steric effect ($k_{-1} > k_2$), and our best

estimate is therefore that $k_2 \geq k_{-1}$ yielding the approximation $k_{ex} \sim 1/2k_1/K_b \sim k_1/10^2 \text{ M}^{-1}$, which gives $k_1 \sim 10 \text{ s}^{-1}$. It follows that k_{-1} and k_2 are both significantly greater than 10 s^{-1} .

In Schemes 1 and 2 the site of protonation in **3** has been chosen as the apical nitrogen atom based upon the structural similarity between **1** and **3**. Protonation at the N-CH(OH) site is unlikely as discussed above, whereas protonation at any of the two other sites belonging to the triazacyclononane entity is possible and in neither case does this change the essential features of the proposed mechanism.

Finally, it should be mentioned that alternative mechanisms for the NH/ND exchange involve rapid C–N cleavage leaving one bridge temporarily open followed by NH/ND exchange with subsequent fast ring closure back to the original structure. One such mechanism could be deprotonation of the iminium group to generate an enamine followed by C–N cleavage. This mechanism would predict H/D exchange at the carbon atom α to the iminium group. Another alternative mechanism involves ring opening of **3a** (Scheme 2) to generate an aldehyde. In this case an exchange of the methylene hydrogen atoms adjacent to the aldehyde group should occur. However, the ¹H and ¹³C (dept) NMR spectra of the reformed imine **2** unambiguously show that no CH/CD exchange takes place during the treatment with base and both mechanisms can therefore be excluded.

Concluding Remarks

The chemical and physical properties of small adamanzanes are quite different from those of the larger members of this type of tetraamines. The small amines are formed with a proton encapsulated in the cage (Chart 1). Until now, attempts to extract the proton have failed and for these compounds the term proton prison may seem more descriptive than the usually used term proton sponge.¹¹ Although yet unreported the unprotonated cages should be stable and have, like their protonated forms, all four lone pairs pointing inward as shown on the basis of DFT calculation by Galasso.¹⁵ While the small cages thus seem inert with respect to substitution reactions involving the inside coordinated proton, the larger members with their more open structures have been reported to encapsulate inorganic as well as organic anions, although these studies have mainly been focused on the N-alkylated ammonium cages.¹ The oxidation of **1** to form a stable imine (**2**) in high yield is interesting but follows well-known trends in organic chemistry. The same may be said about the surprisingly large kinetic stability of the hemiaminal **3**. The rate of NH/ND exchange **1** is increased by a factor of at least 5×10^6 when one hydrogen atom is substituted with a hydroxy group (**3**) and this has led to the mechanism depicted in Scheme 2. The essence of this mechanism—a flipping in to and out of the cavity of oxy/hydroxy groups—may serve as a very simple model for passive proton transfer through membranes in biological systems.

Experimental Section

Abbreviations and Nomenclature. The simplified nomenclature suggested for adamanzanes has been discussed recently^{7–9} and is illustrated in Chart 1 for cage adamanzanes. The IUPAC names for the present compounds are the following: **1** = H[(2.3)³]adz⁺ = 1,4,12-triaza-8-azoniatricyclo[6.6.3.2^{4,12}]nonadecane = inside monoprotonated form of [(2.3)³]adz = 1,4,8,12-tetraazatricyclo[6.6.3.2^{4,12}]nonadecane; **2** = 4,12-diaza-1,8-diazoniatriacyclo[6.6.3.2^{4,12}]nonadec-1(15)-ene = inside monoprotonated form of 4,8,12-triaza-1-

azoniatricyclo[6.6.3.2^{4,12}]nonadec-1(15)-ene; **2a** = 4,12-diaza-1,8-diazoniatriacyclo[6.6.3.2^{4,12}]nonadec-1(15)-ene tetrabromozincate monohydrate; **2b** = 4,12-diaza-1,8-diazoniatriacyclo[6.6.3.2^{4,12}]nonadec-1(15)-ene diperchlorate; **ND-2a** = [8-²H]4,12-diaza-1,8-diazoniatriacyclo[6.6.3.2^{4,12}]nonadec-1(15)-ene tetrabromozincate monohydrate; **3** = 5-hydroxy-1,4,12-triaza-8-azoniatricyclo[6.6.3.2^{4,12}]nonadecane = inside protonated form of 1,4,8,12-tetraazatricyclo[6.6.3.2^{4,12}]nonadecan-5-ol; **3H⁺** = 15-hydroxy-4,12-diaza-1,8-diazoniatriacyclo[6.6.3.2^{4,12}]nonadecane; **4** = [(2.3)².2¹]adz = 1,5,9,12-tetraazabicyclo[7.5.2]hexadecane.

Materials. H[(2.3)³]adz]Br was prepared by the published method.⁷ Deuterated solutions were purchased from Dr. Glaser AG Basel. All other chemicals were of analytical grade.

Caution. Mechanical handling or heating of perchlorates represents a potential hazard. In our hands, however, explosions with the present compound have never occurred.

Analyses. Bromide analyses were made by potentiometric titrations with silver nitrate and zinc analyses were performed using atomic absorption spectroscopy with a Perkin-Elmer 2380 atomic absorption spectrophotometer.

Calculations. Nonlinear least-squares calculations were performed with the program PROC NLIN (DUD method) from the SAS Institute INC, Cary, NC.

Spectral Measurements. Infrared spectra were measured on a Perkin-Elmer 2000 FT-IR spectrophotometer and a Cary 3 spectrophotometer was used for spectral measurements in the visible region. ¹H NMR, ¹³C NMR, COSY, and HSQC spectra were measured on a Bruker Avance 400 NMR spectrometer and in one case on a Bruker AC 200 NMR spectrophotometer. ¹H chemical shift values (δ) are reported in ppm and are referenced to internal dioxane ($\delta(\text{dioxane}) = 3.75 \text{ ppm}$) for D₂O solutions. ¹³C chemical shift values (δ) are referenced to internal dioxane ($\delta(\text{dioxane}) = 67.40 \text{ ppm}$) for D₂O solutions. ¹³C DEPT NMR spectra were used to assign CH and CH₂ carbon atoms.

Potentiometric Determinations of K_{im} . The concentration of hydrogen ions was measured with Metrohm equipment and a Radiometer glass electrode combined with a calomel reference electrode (GK2401 B) as described previously.¹⁹ The equilibrium constant K_{im} was determined by titration of solutions of **2b** with sodium hydroxide. The ionic strength was kept at a constant 1.00 M by using the appropriate addition of sodium chloride. The determinations were performed at three different temperatures and the thermodynamic parameters were fitted by minimizing the sum $(K_{obs} - K_{calc})^2$, the values of K_{calc} being defined by $K_{calc} = \exp(\Delta S^\circ/R - \Delta H^\circ/RT)$.

Kinetic Measurement of the NH/ND Exchange Reaction. The kinetics of the NH/ND exchange reaction was monitored by ¹H NMR, using batch methods and quenching with an addition of excess 6 M DCl. In all experiments the ionic strength was kept at a constant 1.00 M by using the appropriate addition of sodium chloride and the perchlorate salt **2b** was used. The degree of exchange was determined by the relative area of the resonance signal for the inside coordinated proton calculated by comparing the integral of this signal with the integral of resonance signals at $\delta 8.85 \text{ ppm}$ for the imine proton (N=CH). The exchange reaction followed the expression for a first-order reaction giving the k_{obs} values in Table 2. The activation parameters were fitted by minimizing the sum $[\ln(k_{obs}) - \ln(k_{calc})]^2$, the values of k_{calc} being defined by $k_{calc} = k_{ex}[\text{OD}^-]$ and $k_{ex} = (k_B T/h) \exp(\Delta S^\ddagger/R - \Delta H^\ddagger/RT)$.

Syntheses: (a) 4,12-Diaza-1,8-diazoniatriacyclo[6.6.3.2^{4,12}]nonadec-1(15)-ene Tetrabromozincate Monohydrate (2a**).** To a mixture of **1a**, [H[(2.3)³]adz]Br (2.20 g, 6.33 mmol), and FeCl₃·6H₂O (4.22 g, 15.6 mmol) was added water (30 mL) and the suspension was stirred at 25 °C for 3 h during which time all solid dissolved to give initially a brown solution, the color of which gradually became less intense. The solution was cooled in ice and solid LiOH (1.3 g, 54 mmol) was added while stirring. After 1 h the black-brown precipitate of iron

hydroxide was removed by filtration using a fine porosity filter and the precipitate was washed with water (two \times 10 mL). To the combined filtrates were added a slight excess of 12 M HCl (approximately 4 mL), and the pale yellow solution was evaporated under reduced pressure (60 °C) to dryness. The solid was dissolved in water (30 mL) and to the filtered solution was added a solution of saturated zinc bromide (10 mL). A white precipitate formed and was filtered off after 10 min, washed with 96% ethanol (two \times 10 mL), and dried in the air. This gave 3.32 g (yield 78%) of a pure product (**2a**). In a few instances the yield was higher (up to 91%) and the product was slightly impure, and a pure product was then obtained by reprecipitation (dissolution in 1 M NaOH and precipitation by addition of 48% hydrobromic acid). Anal. Calcd for $C_{15}H_{30}N_4ZnBr_4 \cdot H_2O$: Zn, 9.77; Br, 47.7. Found: Zn, 9.70; Br, 47.3. ^{13}C NMR data in 0.1 M H_2SO_4 δ /ppm: 185.2 (N=CH), 58.7, 58.2, 57.3, 56.6, 54.5, 52.6, 52.4, 51.7, 51.0, 49.4, 48.8 (CH_2-N), 31.4 (N=CH- CH_2), and 23.5, 20.4 ($CH_2-CH_2-CH_2$). 1H NMR data in 0.1 M H_2SO_4 δ /ppm: 10.15 (NH), 8.85 (doublet, $J = 11.4$ Hz, N=CH), 1.5–5.0 (several multiplets from methylene protons).

(b) [**8- 2H 4,12-Diaza-1,8-diazoniatriacyclo[6.6.3.2 4,12]nonadec-1(15)-ene Tetrabromozincate Monohydrate (ND-2a)**]. A solution of **2a** (0.430 g, 0.642 mmol) in 1 M NaOD (6.4 mL) was kept at 0 °C in a closed bottle for 60 min, $[OD^-] = 0.5$ M. Then a cold solution of 18 M D_2SO_4 (0.4 mL) was added under vigorous stirring followed by addition of a saturated, aqueous solution of zinc bromide (0.5 mL) and a white precipitate instantaneously formed. Filtration, washing with 96% ethanol (two times 2 mL), and drying in the air gave 0.367 g (yield 85%) of product. The ^{13}C NMR spectrum in 0.1 M D_2SO_4 was identical with that of **2a**. Likewise the 1H NMR spectrum in 0.1 M D_2SO_4 was identical with that of **2a** except that the resonance line at 10.15 ppm (NH) had almost disappeared (a minor peak integrating for 0.005 proton is ascribed to the content of HOD in the solvent). The infrared spectrum was measured with use of KBr tablets.

(c) **4,12-Diaza-1,8-diazoniatriacyclo[6.6.3.2 4,12]nonadec-1(15)-ene Diperchlorate (2b)**. To a solution of **2a** (2.0 g, 2.99 mmol) in 0.1 M H_2SO_4 (70 mL) was added an aqueous saturated solution of sodium perchlorate (10 mL) and a white precipitate formed. The precipitate was filtered off, washed two times with water (10 mL) and one time with 96% ethanol (10 mL), and then dried in the air. This gave 1.13 g (yield 81%) of pure **2b**. The purity was shown by 1H and ^{13}C NMR spectra and by determination of the molar mass by titration with base, which gave 466 g/mol compared to the calculated value of 465.3 g/mol for the anhydrous perchlorate salt. In basic solution **2** forms the hemiaminal **3**. ^{13}C NMR data for solutions of **2b** in 0.01 M NaOD, 1 M NaCl δ /ppm: 88.3 (CH(OH)), 57.2, 56.8, 56.43, 56.40, 53.6, 50.9, 50.2, 50.1, 49.9, 46.9, 42.4, (CH_2-N), 27.4 (CH(OH)- CH_2-CH_2), and 21.5, 21.3 ($CH_2-CH_2-CH_2$). The 1H NMR spectrum exhibits a broad peak at 11.45 ppm for the inside coordinated proton and multiplets in the region δ 1.4–5.0 ppm. The same data were obtained for solutions of **2a** in 1 M NaOD. The salt is slightly soluble in pure water but soluble in 1 M NaCl.

(d) [**(2.3) $^2,2^1$]adz 3 ·3HBr·3H $_2$ O: 1,5,9,12-Tetraazabicyclo[7.5.2]-hexadecane Trihydrobromide Trihydrate (4·3HBr·3H $_2$ O)**]. To a mixture of [H[(2.3) 3]adz]Br (**1a**) (2.50 g, 7.2 mmol) and $FeCl_3 \cdot 6H_2O$ (4.80 g, 17.8 mmol) was added water (68 mL) and the suspension was stirred at 50 °C for 45 min during which time all solid dissolved to give initially a brown solution, the color of which gradually became less intense. The temperature was raised to 80 °C, solid LiOH (1.47 g, 61 mmol) was added, and the mixture was stirred for 1 h at this temperature. The black-brown precipitate of iron hydroxide was removed by filtration using a fine porosity filter and the precipitate was washed with water (two times 25 mL). Filtration combined with centrifugation was at some occasions applied with success. The combined filtrates were evaporated under reduced pressure (80 °C) to

a final volume of 30 mL. To the pale brownish-yellow solution was added 40 w/w % NaOH (15 mL) and the solution was extracted with three portions of chloroform (50 mL). The combined chloroform extracts were evaporated to dryness. The solid (1.96 g) was dissolved in 1 M HBr (12.5 mL) and the solution evaporated under reduced pressure (80 °C) and the procedure was repeated by adding another portion of 1 M HBr (12.5 mL). The brownish solid was dissolved in hot methanol (25 mL), and after cooling in ice acetone (38 mL) was added. A grayish precipitate (approximately 0.3 g) was filtered off and acetone (150 mL) was slowly added to the filtrate while cooling in ice. This gave a white precipitate, which was filtered off and dried at 70 °C. Yield: 1.1 g of pure [(2.3) $^2,2^1$]adz 3 ·3HBr·3H $_2$ O (yield 29%). Anal. Calcd for $C_{12}H_{26}N_4 \cdot 3HBr \cdot 3H_2O$: Br, 45.8. Found: Br, 46.4. ^{13}C NMR data in D_2O δ /ppm: 58.5, 51.5, 50.6, 49.2, and 45.0 (CH_2-N) and 23.4 (C- CH_2 -C) are identical with those values previously reported.⁷

Crystal Structure Determination. The crystals of the compounds are cooled to 120 K using a Cryostream nitrogen gas cooler system. The data were collected on a Siemens SMART platform diffractometer with a CCD area sensitive detector. The structures were solved by direct methods and refined by full-matrix least-squares against F^2 of all data. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms could be located from electron-density difference maps, but all the hydrogen atoms of the cation are at calculated positions using a riding model with C-H = 0.95–0.99 Å and fixed thermal parameters ($U(H) = 1.2U$ for attached atom). The hydrogen atoms of the water molecule were refined isotropically with fixed O-H = 0.87 Å. In electron-density difference maps there were no peaks found around N(1), and around N(3) there were two but with rather wrong angles. Around N(4) there was one peak with the right angles. When calculating the position of the hydrogen atom attached to N(4) the coordinates of H(4) were in agreement with those found in the maps. The calculated position of a hydrogen atom attached to N(3) did not agree with any of the found positions. Therefore, the position of the acidic hydrogen atom was chosen as the hydrogen H(4) attached to N(4). Programs used for data collection, data reduction, and absorption were SMART, SAINT, and SADABS.^{23,24} The program SHELXTL ver. 5.03²⁵ was used to solve the structures and for molecular graphics. PLATON²⁶ was used for molecular geometry calculations. Crystal data: $C_{15}H_{30}N_4ZnBr_4 \cdot H_2O$, $M = 669.46$, triclinic, $a = 8.914(2)$ Å, $b = 10.946(2)$ Å, $c = 11.207(2)$ Å, $\alpha = 86.88(3)^\circ$, $\beta = 88.04(3)^\circ$, $\gamma = 85.24(3)^\circ$, $V = 1087.7(4)$ Å 3 , $T = 120(2)$ K, space group $P\bar{1}$ (no. 2), $Z = 2$, $D_x = 2.044$ g cm $^{-3}$, crystal size = $0.23 \times 0.12 \times 0.10$ mm 3 , $\mu(Mo K\alpha) = 8.488$ mm $^{-1}$, 7603 reflections measured, 5346 unique ($R_{int} = 0.023$) and 4114 reflections with $I > 2\sigma(I)$ which were used in all calculations. The final $R1$ was 0.0482 (observed data) and $wR(F^2)$ was 0.1208 (all data).

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Supporting Information Available: Fractional atomic coordinates, bond lengths and angles, as well as thermal parameters (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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