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Conformation of 3,7,10-Trimethyl-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecane: a Potential Bifunctional Catalyst for [1,3]-Hydron Transfer Reactions

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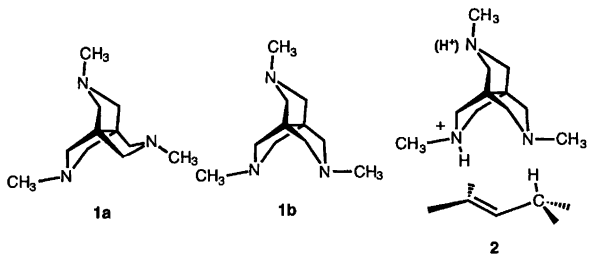
The neutral title compound (**1**) shows only one conformation consistent with C_{3h} symmetry. The compound exhibits C_3-inversion barriers of 10.2 and 10.9 kcal mol^{-1} in dimethyl ether-d_6 and methanol-d_4, respectively. ^{1}H and ^{13}C{^{1}H} NMR have been recorded down to −90 °C in the pD range 1–9 in various methanol–water mixtures. In the pD interval 3–7 low temperature, ^{1}H NMR spectra show a complex and pD- and temperature-dependent pattern. In very acidic solution (pD = 1), where the molecule is trihydronated, C_{3h} symmetry is evidenced. The rate of hydron exchange was shown to be slow in the pD range 5–7.5 below −60 °C thus allowing for distinction between hydronated and unhydronated rings in the NMR spectrum. The combination of various results indicates that **1** assumes conformation **1a** over the whole pD range studied. Catalytic amounts of the conformation **1b**, which is required for bifunctional [1,3]-hydron transfer catalysis could not be excluded. Computations employing molecular mechanics (MM2) and semiempirical quantum chemical methods (PM3) predict neutral **1a** to be 1.4 kcal mol^{-1} more stable than **1b**. However, the calculations indicate that the hydronated form **1bH**$^+$ is favoured in the gas phase.

The title triazapropellane (**1**) has been suggested as a bifunctional catalyst for [1,3]-hydron transfer reactions in solutions of appropriate acidity.[1] In this work the conformational requirements for catalysis are analysed. The conformations and the barrier to conformational interchange have been investigated by dynamic NMR spectroscopy, molecular mechanics (MM2) and semi-empirical quantum mechanical methods (PM3). There are two conformations conceivable for **1**, as shown in **1a** and **1b**, possessing C_{3h} and C_s symmetry, respectively. In the transition state for a catalysed [1,3]-hydron transfer the molecule must be mono- or di-hydronated and have the conformation as shown in **2**, in other words of the type **1b**. We have investigated the static and dynamic stereochemistry of **1** in various methanol–water mixtures and at various pH-values.



Results

Dynamic NMR. The neutral molecule dissolved in dimethyl ether-d_6 showed, as expected, a simple ^{1}H NMR spectrum consisting of two singlets (δ 2.21 and 2.39; intensity 3:4) at room temperature. On lowering the temperature, the low field signal (CH_2) broadened and decoalesced ($T_c = -45$ °C) to a single AB spectrum ($\Delta\delta = 0.96$; $J = 8.8$ Hz), which was unchanged at temperatures down to at least −130 °C. The methyl signal remained unchanged over the whole temperature region. The kinetic data are shown in Table 1. The barriers are comparatively high, in *N*-methylpyrrolidine $\Delta G^{\ddagger}$ for nitrogen inversion is only ca. 8 kcal mol^{-1}.[2] Compound **1** behaved similarly in methanol-d_4 and the low temperature spectrum is shown in Fig. 1a. The barrier was 0.7 kcal mol^{-1} higher in methanol, though. The signific-

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Table 1. Experimental results from dynamic NMR experiments of **1**. Energies in kcal mol^{-1}, entropy in cal mol^{-1} K^{-1}.

Species	Solvent	pD	*T*/K	k/s^{-1}	$\Delta G^{\ddagger}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
1	$(CD_3)_2O$		224	470	10.2(1)	11.7(5)	6.3(4.0)
1	Methanol-d_4	9.5	224	90	11.0(1)	13.4(5)	10.5(4.0)
1·H+	Methanol-d_4+20% D_2O	7.7	235	300	11.0(2)		
1·H_2^{2+}	Methanol-d_4+20% D_2O	3.8	235	450	10.8(2)		
1·H_3^{3+}	Methanol-d_4+40% D_2O	1.0	291	70	14.5(2)		

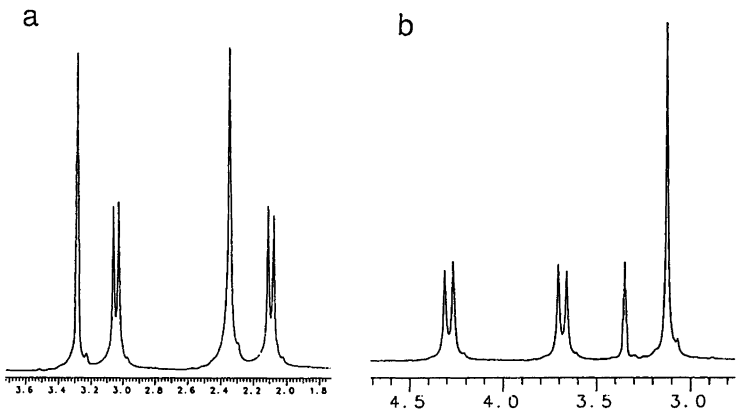


Fig. 1. ^1H NMR spectra of **1** (the peak at ca. δ 3.3 comes from residual protons in the solvent): (a) neutral molecule dissolved in CD_3OD, −83 °C; (b) solvent CD_3OD–D_2O (3:2 v/v); pD 1.0, −72 °C.

antly higher barrier and the slightly higher entropy of activation found in methanol is probably due to hydrogen-bond breakage required prior to conformational inversion. The spectral behaviour of **1** in both dimethyl ether and methanol is consistent with conformation **1a**. The ^1H NMR experiments were repeated in CD_3OD–D_2O (4/1 v/v) with added DCl in D_2O covering the pD-range 9–1. Some spectra are shown in Fig. 2. Decoalescence was observed in the same temperature region as without acid addition but the low temperature (< −60 °C) spectra were more complex. In the pD range 5.5–7.5 five broad and partly overlapping signals from **1** were observed at δ 2–4. At pD 1.0 and −61 °C a spectrum, similar to the spectra in neutral methanol but with downfield shifts of 0.8–1.6 ppm, was obtained (Fig. 1b). Owing to the broad, partly overlapping signals, double resonance experiments failed to indicate both decoupling and saturation transfer. Changing the solvent to CD_2Cl_2 with 1.1 equiv. CF_3COOH gave similar spectral features to those in methanol–water.

$^{13}C\{^1H\}$NMR spectra in methanol-d_4–D_2O consisted of three signals due to methyl, methylene and quaternary carbons. The methyl and methylene ^{13}C signals broadened on cooling but remained unresolved down to

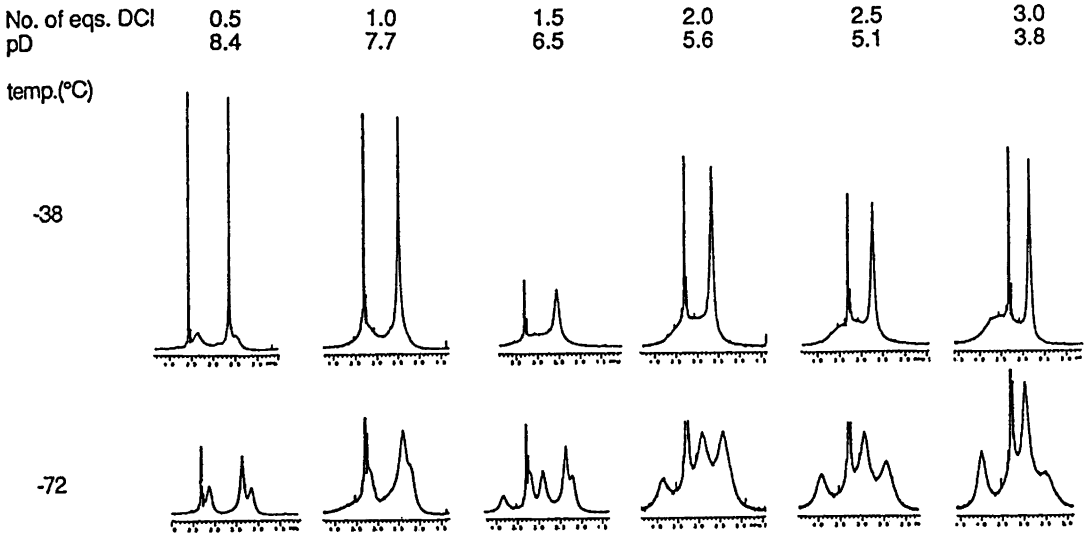


Fig. 2. pD dependence of the low-temperature spectra of **1** in CD_3OD–D_2O (4:1 v/v).

−90 °C. The quaternary carbon signal remained sharp in all experiments. Experiments with the conjugate acid of diazabicyclo[2.2.2]octane (DABCO) in methanol-d_4 (pD = 7.5) revealed similar behaviour. The signal from the methylene carbon atoms broadened at low temperature but remained unresolved at −90 °C.

The ensemble of the spectral features could be understood in terms of two different interpretations. (i) The spectra originate from hydronated **1a** showing different subspectra for hydronated and unhydronated pyrrolidine rings in the pD region where the more complex spectral features are observed. This implies that *hydron jump is slow on the NMR timescale.* (ii) The spectra can alternatively be understood in terms of a mixture of the two conformations **1a** and **1b**, *provided that hydron jump is fast on the NMR timescale.*

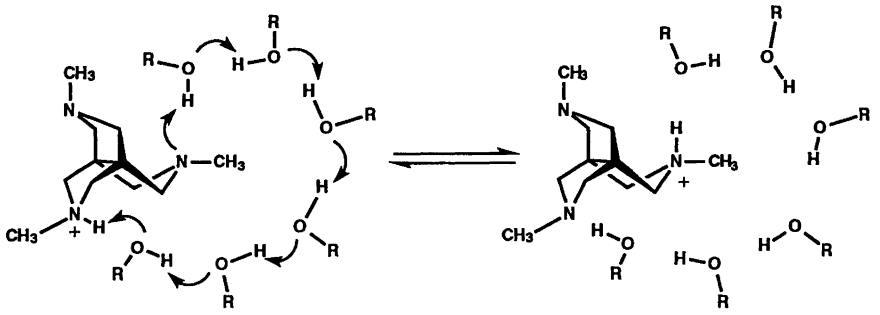
In order to distinguish between the two alternatives, the rate of solvent-assisted hydron exchange as pictured in Scheme 1 is obviously of crucial importance. Fast hydron exchange, which in the cases of the mono- and di-hydronated **1a** leads to fast scrambling of all methyl and methylene groups, respectively, is not consistent with the low temperature spectra in the intermediate pD interval (5.6–7.5). The rates of solvent-assisted hydron exchange for various alkylammonium ions are catalysed by both acid and base,[3] as is the rate of proton transfer between water and methanol[4] [eqn. (1)].

$$CD_3OH + D_2O \rightleftharpoons CD_3OD + DOH \quad (1)$$

Actually, the temperature dependence of the OH residual ^{1}H NMR signal from the solvent is informative (Fig. 3). This signal is a singlet at room temperature but decoalesces into two singlets at lower temperature. This phenomenon is pD-dependent and some derived first order rate constants at various pD values are shown in Table 2. Thus, the rates of propellane inversion and hydron transfer can be studied in the same solution. An analysis of the rate constants and the spectral features shows that the ^{1}H NMR spectrum only shows the complex set of signals for the propellane in the pD range and at temperatures where hydron transfer is slow on the NMR timescale. At lower pD, where the hydron transfer is acid-catalysed, only three signals are obtained, as expected for fast scrambling of the type shown in Scheme 1 of both mono- and di-hydronated species. The pK_a values of $\mathbf{1H^+}$ and $\mathbf{1H_2^{2+}}$ in methanol–water (4:1 v/v) were determined by titration as 7.9 and 5.5, respectively. The corresponding values in methanol have been reported as 8.4 and 6.8.[5] The pK_a for the trication is much lower and could not be determined. As seen in Fig. 2 the spectra at −72 °C are broad in the pD range 5.6–5.1 and the signals at δ 3.9 and 2.9 increase in intensity at the expense of the signal at δ 2.4. We ascribe the former signals to methylene and methyl groups of the hydronated pyrrolidine ring and the high-field signal

Table 2. Experimental results from dynamic NMR experiments of the proton transfer between methanol and water in a 4:1 v/v mixture containing **1** (25 mM).

pD	*T*/K	k/s^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1}
8.0	216	52	10.8(2)
6.7	210	80	10.3(2)
5.7	210	68	10.4(2)
3.7	210	52	10.5(2)
2.4	199	50	9.9(2)



Scheme 1.

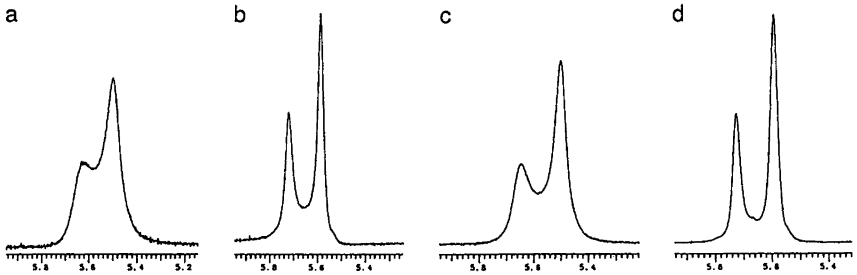


Fig. 3. ^{1}H NMR spectrum of the residual protons in CD_3OH–DOH (4:1 v/v): (a) pD 6.7, −61 °C; (b) pD 6.7, −72 °C; (c) pD 3.7, −61 °C; (d) pD 3.7, −72 °C.

to those of unhydronated pyrrolidine ring. Partial dihydronation at pD 5.6–5.1 is consistent with the observed pK_a of 5.5.

In a 500 MHz ROESY experiment of **1** in CD_3OD–D_2O (4:1 v/v; pD 6.5) at −60 °C both NOE and exchange interactions were observed (Fig. 4). Three exchange correlations were obtained, one from the methyl groups (δ 2.40 and 2.95) and two from geminal exchange in hydronated and unhydronated pyrrolidine rings, respectively. The NOE correlations [2.25 and 3.25; 2.25 and 3.90; 2.95 and 3.25 (weak)] were in agreement with the assignment but could not be used to distinguish between the conformations **1a** and **1b.**

Investigation of the copper(II) complex of **1**. When **1** in CD_3OD (35 mM) was supplied with increasing amounts of $CuCl_2 \cdot 2H_2O$ two new signals appeared from the methyl and methylene groups [δ 2.05 and 3.12(broad)] in addition to the two from free **1**. All the signals were singlets at room temperature. The signals from free **1** disappeared when a little more than one equivalent of $CuCl_2$ had been added. When the temperature was lowered for a sample containing 0.85 equiv. of $CuCl_2$, decoalescence of the signals from the Cu complex occurred at ca. 0 °C and below −30 °C further broadening was observed. These experiments indicate, that a 1:1 complex is formed, that the Cu-exchange is slow and that the conformational change of **1** is still fast on the NMR timescale at room temperature. The conformational exchange is slower for the complex than for free triazapropellane. Owing to the broad and overlapping signals at low temperature it was, however, not possible to gain information of the exact nature of the complex.

Investigation of an N,N′*-trimethylene bridged derivative* (**3**). This dication assumes conformation **1b** of its propellane skeleton and thus should provide information about chemical shifts and dynamics of the unsubstituted ring. The temperature-dependent 300 MHz NMR spectrum of **3** is shown in Fig. 5. Only one rate process affected the spectrum in the temperature range −25 to +40 °C. The process exchanged the following pairs: H_a and H_b, H_c and H_d, H_e and H_g, H_f and H_h, and could be ascribed to the conformational inversion of the trimethylene bridge. The methylene protons of the free

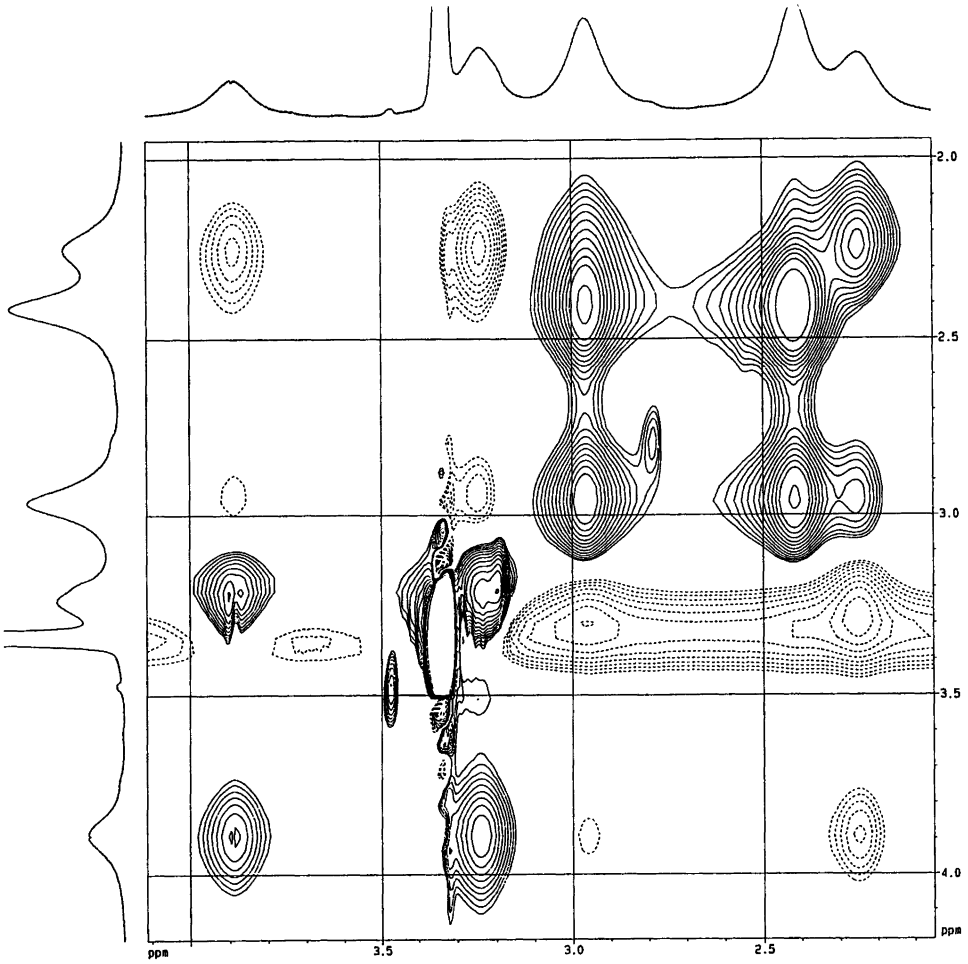


Fig. 4. ROESY spectrum of **1** 500 MHz in CD_3OD–D_2O (4:1 v/v), −60 °C.

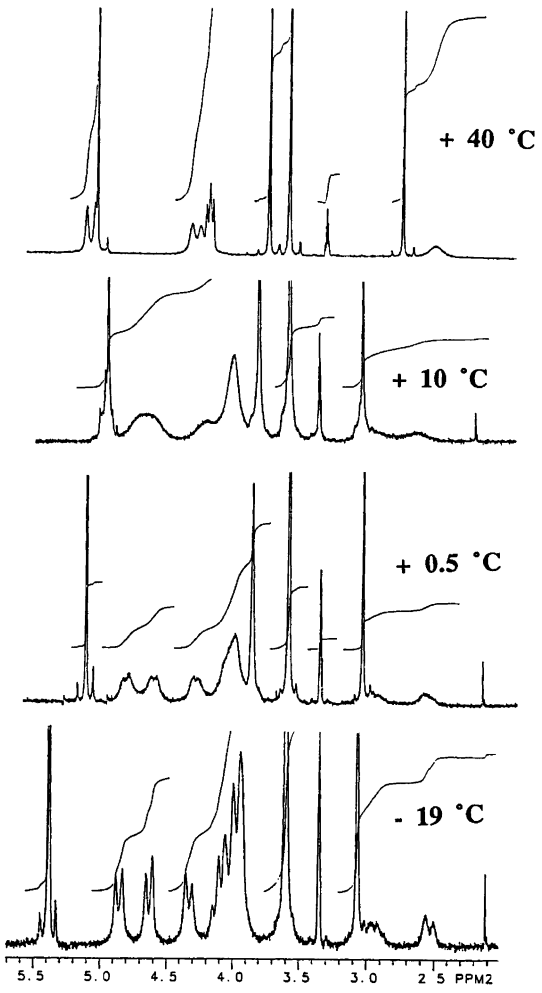
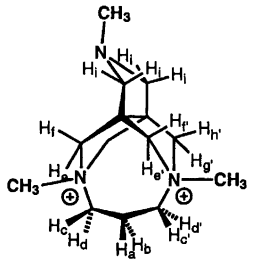


Fig. 5. Temperature dependence of the ^{1}H NMR spectrum of **3** in CD_3OD–D_2O (1 : 1).

pyrrolidine ring, H_i, remained unaffected in the temperature range, apart from some broadening at lower temperatures. The barrier was determined by bandshape methods as $\Delta G^{\ddagger} = 13.8$ kcal mol^{-1} at 282 K. The chemical shifts of the propellane moiety are instructive. The pseudo-equatorial protons in the charged pyrrolidine rings appeared at *higher field* than their axial geminals in contrast with their cyclohexane equivalents and $\Delta\delta_{eg}$ was larger than $\Delta\delta_{fh}$. The axial protons α to N^+ resonated at appreciably lower field (δ 4.7) than in dihydronated **1** (δ 4.1), a support for the predominance of conformation $\mathbf{1a}H_2^{2+}$ for the dication. Notably, the geminal protons of the uncharged pyrrolidine ring remained a singlet in the temperature interval.

Computational results. The conformational stability of **1** and its hydronated forms was studied by means of molecular mechanics MM2(1991 force field) and semi-empirical PM3 calculations. The results are shown in Table 3 and PM3-optimized structures of the hydrated monocations in Fig. 6. The neutral conformations **1a** and **1b** were not satisfactorily minimized by PM3 calculations in that they failed to reach acceptable gradient norms and afforded unrealistic geometries. Molecular mechanics predict **1a** to be more stable than **1b** by 1.37 kcal mol^{-1} in agreement with the experimental results. However, both MM2 and PM3 predict $\mathbf{1b}H^+$ to be more stable than $\mathbf{1a}H^+$, both as free ions and as monohydrated ions.



3

Discussion

The conceptually simple question of the conformation of **1** and its cations turned out to be not so straightforward to settle. The following interpretation accounts for the NMR results. Although unequivocal assignment of the signals was not achieved, a judicious analysis of the temperature dependence of the signals from **1** and from the solvent hydroxy hydrons, as well as of the ROESY spectrum and comparison with the bridged analogue **3**, indicates that **1** exists in the conformation **1a** and its mono- and di-hydronated forms. In such an interpretation, the low-temperature spectra should consist of subspectra from hydronated and unhydronated pyrrolidine rings in the pD range (ca. 7.5–5.0) where the hydron flux is slow, and of an average of these spectra at lower pD due to fast hydron flux. Thus, the pD dependence of the ^{1}H NMR spectra at −72 °C are illustrative. At pD 8.4 relatively sharp signals are observed, corresponding to slow conformational inversion of unhydronated **1**. At pD 7.7 the signals are broad due to partial hydronation and intermediate hydron flux, and at pD 6.5 sharp signals from both hydronated and unhydronated rings are seen due to slow hydron flux. The signals at δ 3.85 and 2.90 together with a hidden signal, possibly under the one at δ 2.90, should then come from the hydronated pyrrolidine ring and the remaining signals, with the same pattern, but about twice the intensity, should originate from the unhydronated rings. In more acidic solutions (pD 5.6–5.1) the signals first broaden, and finally, at pD 3.8, sharper signals from averaged spectra due to fast acid-catalysed hydron flux are obtained.

The molecular mechanics results for the neutral molecule are probably reliable, and in agreement with experiment. The computational results are not very helpful in treating the ionic species, though. The calculated conformational stabilities of the monocation, $\mathbf{1}H^+$ and

Table 3. Calculated energy differences between **1a** and **1b**, and their monocations, and hydrated monocations. Energies in kcal mol^{-1}.

Method	1a	1b	1aH$^+$	1bH$^+$	1aH$^+$·bH$_2$O	1bH$^+$·bH$_2$O	1a·H$_2^{2+}$	1b·H$_2^{2+}$
MM2(-91)	39.97	41.34	36.56	36.30	34.89	34.18	33.10	33.73
Relative	0	1.37	0.27	0	0.71	0	0	0.63
PM3	*a*	*a*	145.11	143.46	80.89	79.55	—	—
Relative			1.62	0	1.35	0		

[a]PM3 did not afford acceptable results.

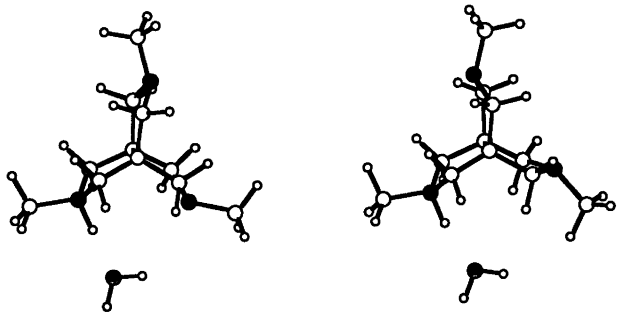


Fig. 6. PM3-optimized structures of hydrated **1a**H$^+$ and **1b**H$^+$.

1H$^+$ · H$_2$O, are the opposite of our interpretation of the experimental results, and solvation by water–methanol not surprisingly has a decisive influence. The calculated energy difference for the monohydrate does not represent the stability in solution, where all nitrogens can be solvated, and where the dielectric constant is high. The counter ion (Cl^-) was also omitted in the calculations.

Conclusions

The triazapropellane **1** prefers a conformation of type **1a** in both aprotic and protic solvents, in the latter case over the pD range 1–9. This interpretation requires that hydron exchange between the nitrogen atoms in the mono- and di-cations is slow below −60 °C, which was verified by measurement of the hydron exchange between methanol and water. Since small amounts of the conformation **1b** may be present, it cannot be excluded that **1** may act as a bifunctional catalyst for [1,3]-hydron transfer reactions.

Experimental

3,7,10-trimethyl-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecane (**1**) was prepared according to known procedures.[6,7]

3,7,10-Trimethyl-7,10-(trimethylene)-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecanium dibromide, (**3**) was prepared from **1** (0.177 g, 0.906 mmol), 1,3-dibromopropane (0.60 ml, 5.9 mmol) in 10 ml acetonitrile. The reaction mixture was stirred at 50 °C for 5 days. After cooling, the crystals were filtered and washed with dry acetonitrile. Yield 75 mg (21%), m.p. >250 °C (decomp.).

General. NMR spectra were recorded on a Varian XL300 or a Bruker ARX500 spectrometer. Dimethyl ether-d_6, for low-temperature NMR, was prepared from methanol-d_4.[8] The sample containing dimethyl ether-d_6 as solvent was degassed by repeated freeze–thawing cycles before being sealed off under high vacuum. Temperature calibration of the NMR spectrometer was performed with methanol according to the method described by van Geet.[9] pD values of the NMR samples were varied by addition of appropriate amounts of 1.2 M DCl in D_2O. The pD measurements were made with a combination pH electrode connected to a Philips PW 9420 pH meter.

The populations and rate constants were evaluated by visual fitting of the experimental spectra to spectra calculated by the McConnell classical formalism[10] and Sutherland's modification for two-site exchange AB systems,[11] and by DNMR5.[12] The evaluations of T_2 and δν values for bandshape calculations were performed as previously described.[13] The enthalpies and entropies of activation are obtained by a linear regression analysis of ln (k/T) versus $(1/T)$ according to the Eyring equation.[14] Errors in activation parameters are given with the assumption that the temperature could be determined to an accuracy of ±0.5 K.[15]

The pK_a values of 3,7,10-trimethyl-3,7,10-triazatricyclo[3.3.3.0^{1,5}]undecane were determined by titration. The substance was dissolved in methanol–water 4:1, with 0.10 M KCl as supporting electrolyte, and titrated with 0.10 M HCl in methanol–water, 4:1.

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