Inside Protonation of 1,8-Diazabicyclo[6.6.*n*]alka-4,11-diynes

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Protonation of 1,8-diazabicyclo[6.6.3]heptadeca-4,11-diyne (**4a**), 1,8-diazabicyclo[6.6.4]octa-deca-4,11-diyne (**4b**), 1,8-diazabicyclo[6.6.5]nonadeca-4,11-diyne (**4c**), and 1,8-diazabicyclo[6.6.6]eicosa-4,11-diyne (**4d**) was achieved by treatment of **4a**–**4d** with strong acids. Monoprotonation products were isolated in all cases, while for **4b** and **4c** diprotonation products were also obtained. X-ray investigations show inside protonation for the mono- and diprotonation products.

Introduction

In 1968, Simmons and Park showed that bicyclic systems with nitrogen atoms at the bridgeheads and with medium-sized rings may exist in three isomeric forms: the *out*/*out*, *out*/*in*, and *in*/*in* isomers.[1,2] These isomers are shown schematically in Figure 1. If the chain lengths in 1,(k+2)diazabicyclo[$k.l.m$]alkanes is small (i.e., k, l, and m are between one and three atoms or groups), the *out*/*out* conformation is the most stable one. For larger chains (i.e. k, l, m = 3−6, we expect the *in*/*in* conformer to be more stable than the other two isomers.[3−5]

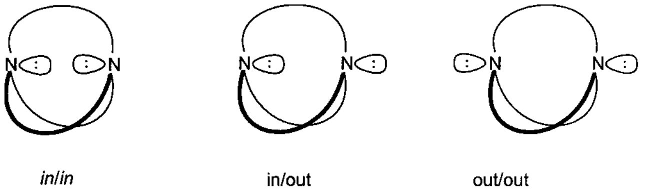

Figure 1. Schematic representation of the *in*/*in*, *in*/*out*, and *out*/*out* conformations of bicyclic 1,(k+2)diazabicyclo[k,l,m]alkanes

This anticipation is supported by the observation that 1,4-diazabicyclo[2.2.2]octane (**1**) exists only in the *out*/*out* conformation and the [1.1.1]cryptand (**2**) in the *in*/*in* conformation.[6,7]

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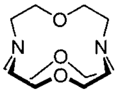

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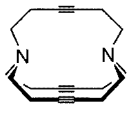

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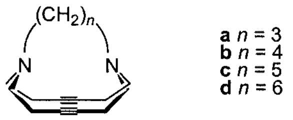
The bicyclic amines with medium-sized rings deserve special interest; they can act as proton sponges.[4] If some of the CH_2 groups in the bridges are replaced by functional groups that provide lone pairs or π electrons, they can act as complexing agents.[6,8] Examples include the [1.1.1]cryptand **2**, for which the mono- and diprotonated forms show the *in*/*in* conformation,[6,7] the 1,6-diazabicyclo[4.4.4]tetradecane,[8] in which both the outside and inside protonated salts were isolated, and the 1,8-diazabicyclo[6.6.6]eicosa-4,11,17-triyne (**3**).[9] In the last case, X-ray analyses of the diprotonated cage and its silver(I) and copper(I) complexes in all three cases showed the *in*/*in* conformation.[9] Common to all three examples is a cage structure with a relatively constant N···N distance.

We have recently synthesized a series of compounds in which the 14-membered ring of 1,8-diazacyclotetradeca-4,11-diyne is bridged by propano-, butano-, pentano-, and hexano-tethers (**4a**−**4d**). All four of them provide a rigid cage system with the *in*/*in* conformation of the lone pairs at the bridgeheads. They were therefore good candidates from which to expect stable protonation products. In this paper we describe our protonation studies on **4a**−**4d**.



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Results

The synthesis of **4b**−**4d** was as described in the literature.[10] The preparation of **4a** was achieved by treatment of 1,3-diaminopropane with two equivalents of 1,6-dibromohex-3-yne in a three-component condensation in the pres-

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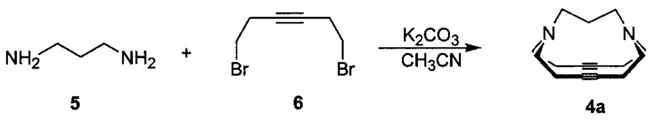
ence of potassium carbonate as base (Scheme 1). The yield was low (3.5%), probably because of the short bridge between the nitrogen atoms.



Scheme 1

For the protonation experiments we added 1−3 equivalents of the acid to a solution of **4** in degassed dichloromethane. The protonation of **4a**−**4d** occurred fairly rapidly, the reactions being complete ten minutes after the addition of acid. The isolated yields of the ammonium ions varied between 67% and 91%. For [**4a**·H]$^+$, [**4b**·H]$^+$, [**4c**·H]$^+$, and [**4d**·H]$^+$ we used trifluoroacetic acid. To obtain the diprotonated forms we used 50−54% solutions of HBF_4 in diethyl ether for **4b**, and trifluoromethanesulfonic acid for **4c**.

For [**4a**·H]$^+$ to [**4d**·H]$^+$ and for [**4b**·2H]$^{2+}$ and [**4c**·2H]$^{2+}$ we isolated single crystals, which allowed a detailed structural study. The most relevant bond lengths and angles of the ammonium salts are summarized in Table 1. Figures 2 and 3 display the molecular structures of [**4a**·H]$^+$, [**4d**·H]$^+$ and [**4b**·2H]$^{2+}$, [**4c**·2H]$^{2+}$, respectively.

Our special interest was focused on the structures of [**4a**·H]$^+$ and [**4b**·H]$^+$. The ^{1}H and ^{13}C NMR spectra are in line with structures of C_{2v} symmetry, but the X-ray structure (Figure 2) clearly shows that the proton in each structure is associated with one bridgehead atom only. Thus, the NMR results are due to a fast equilibrium, as shown in Scheme 2 for [**4a**·H]$^+$.

Comparison between the structural data (Table 1) shows that the transannular distances between the bridgeheads increase from 3.2 Å ([**4a**·H]$^+$) to 4.4 Å ([**4d**·H]$^+$). In all cases the *in*/*in* conformation prevails in the solid state. The X-ray structures and also the chemical shifts of the NH protons show that there is no significant hydrogen bonding to the other bridgehead nitrogen atom in the monoprotonated ions. The N···N distances increase when two protons are in the cavity (cf. [**4b**·H]$^+$/[**4b**·2H]$^{2+}$ and [**4c**·H]$^+$/[**4c**·2H]$^{2+}$). Comparison between mono- and diprotonation also shows a larger sum of the C−*N*−C angles for the diprotonated species. Comparison between the structural parameters of **4c**,[10] [**4c**·H]$^+$, and [**4c**·2H]$^{2+}$ shows that the N···N dis-

Table 1. Most relevant distances [Å] and angles [°] for the mono- and diprotonated species of **4a**−**4d**

	[**4a**·H]$^+$	[**4b**·H]$^+$	[**4b**·2H]$^{2+}$	[**4c**·H]$^+$	[**4c**·2H]$^{2+}$	[**4d**·H]$^+$
N···N	3.197	3.721	4.092	4.088	4.322	4.405
ΣC−NH−C	332	332	338 (338)	328[a]	337 (337)	333.1
ΣC−N−C	335	335	−	328[a]	−	331.6
α[b]	168	174.8	175.6	176.2	175.8	176.4
Θ[c]	17	8.9	26.6	8.7	24.9	17.9

[a] Low precision due to disorder. [b] Average value of the C(sp^3)−C(sp)−C(sp) angle. [c] Torsion between triple bonds.

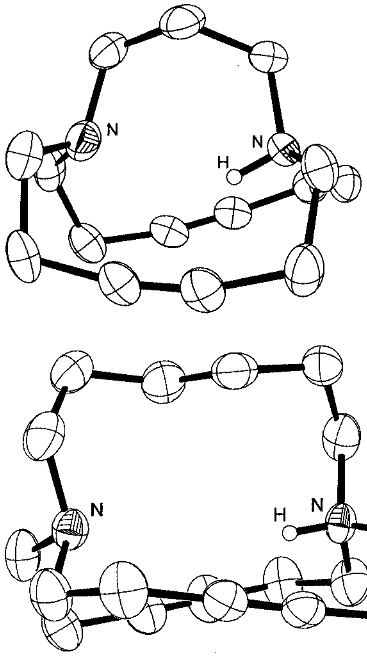


Figure 2. Molecular structures of [**4a**·H]$^+$[$(CF_3CO_2]_2H$]$^-$ (top) and [**4d**·H]$^+$[$(CF_3CO_3)_2H$]$^-$; most of the hydrogen atoms and the anions have been omitted for the sake of clarity

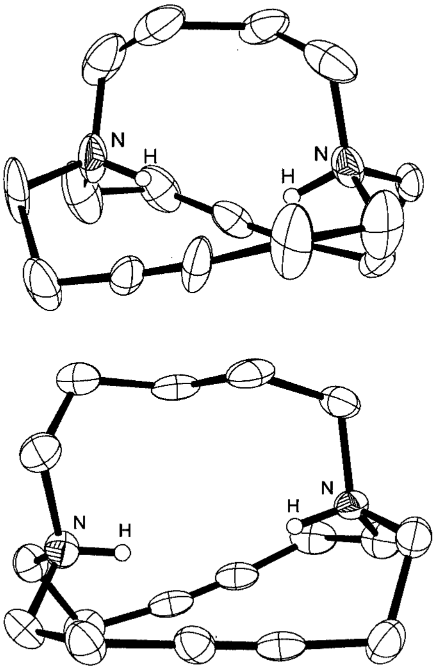
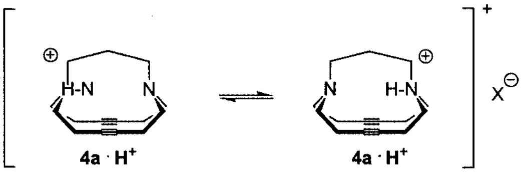


Figure 3. Molecular structures of [**4b**·2H]$^{2+}$[BF_4]$_2$ (top) and [**4c**·2H]$^{2+}$[CF_3SO_3]$_2$; most of the hydrogen atoms and the anions were omitted for the sake of clarity



Scheme 2

tances decrease from **4c** [4.662(2) Å] to [**4c**·H]$^+$ [4.088(2) Å], and even in [**4c**·2H]$^{2+}$ the N···N distance is shorter [4.322(2) Å]. This corresponds to a change in the C−*N*−C angles at the bridgeheads. In **4c** these sums amount to 341.3(2)° and 341.0(2)°, respectively.[10] From Table 1 it can also be seen that the average deviation from linearity of the $CH_2-C{\equiv}C-CH_2$ unit decreases from [**4a**·H]$^+$ to [**4c**·H]$^+$. This is due to the increase of the length of the alkane bridge between the nitrogen centers.

Conclusion

The rigid cages of **4a**−**4d** allow the isolation and structural characterization of the corresponding monoprotonated ammonium salts. In two cases, **4b** and **4c**, we were even able to isolate the bis-ammonium salts.

Experimental Section

General Methods: Moisture- and oxygen-sensitive reactions were conducted in oven-dried glassware under argon. Solvents were distilled and dried under argon before use. Melting points are uncorrected. Materials used for column chromatography were silica gel 60 and Alox III (Merck, Macherey−Nagel). The ^{1}H and ^{13}C NMR spectra were measured with a Bruker AS 300 spectrometer (^{1}H at 300 MHz and ^{13}C at 75 MHz). The chemical shifts are quoted in ppm on the δ scale, with the residual protonated solvent as the internal standard. Mass spectrometry was performed with a JEOL IMS-700 double focusing sector mass spectrometer (JEOL, Tokyo, Japan). The FAB spectra were taken in 3-nitrobenzyl alcohol (NBA) matrix. Elemental analyses were carried out by the Mikroanalytisches Labor der Chemischen Institute der Universität Heidelberg.

Preparation of 1,8-Diazabicyclo[6.6.3]heptadeca-4,11-diyne (4a): 1,6-Dibromohex-3-yne (**6**, 5.0 g, 21 mmol) and 1,3-diaminopropane (**5**, 0.6 g, 8 mmol) were added to a suspension of potassium carbonate (17 g, 0.12 mol) in dry acetonitrile (500 mL). After the mixture had been heated under reflux for 18 h, the potassium carbonate was removed by filtration. The residual solvent was purified by chromatography (ALOX III) with $CHCl_3/CH_3OH$ (10:1) as eluent. After removal of the solvent the residue was recrystallized from ethyl acetate, yielding 70 mg (4%) of colorless, air- and moisture-sensitive crystals, m.p. 99 °C. ^{1}H NMR ($CDCl_3$): δ = 1.90, (m, 2 H), 2.35−2.70 (m, 8 H), 3.15−3.35 (m, 12 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 18.0, 22.0, 55.6, 57.2, 82.4 ppm. HRMS(EI) calcd. ($C_{15}H_{22}N_2$) 230.1783; found 230.1786.

General Procedure for Protonation: One to three equivalents of the acid were added to one equivalent of **4** in dry degassed dichloromethane under argon atmosphere and the mixture was stirred for 3 h. The solvent was removed in vacuo and the remaining solid was recrystallized from chloroform/petroleum ether.

Preparation of [4a·H]$^+$[$(CF_3CO_2)_2H$]$^-$: M.p. 71 °C; yield 74%. ^{1}H NMR ($CDCl_3$): δ = 1.90 (m, 2 H), 2.45−2.65 (m, 8 H), 3.20−3.40 (m, 12 H), 7.80 (br. s, NH) ppm. ^{13}C NMR: δ = 17.6, 21.7, 55.5,

Table 2. Crystallographic data for [**4a**·H]+, [**4b**·H]$^+$, [**4b**·2H]$^{2+}$, [**4c**·H]$^+$, [**4c**·2H^2]$^+$, and [**4d**·H]$^+$

	[**4a**·H]$^+$	[**4b**·H]$^+$	[**4b**·2H]$^{2+}$	[**4c**·H]$^+$	[**4c**·2H^2]$^+$	[**4d**·H]$^+$
Empirical formula	$C_{19}H_{24}F_6N_2O_4$	$C_{20}H_{26}F_6N_2O_4$	$C_{16}H_{26}N_2{}^{2+}\cdot 2BF_4{}^-$	$C_{21}H_{28}F_6N_2O_4$	$C_{19}H_{30}F_6N_2O_7S_2$	$C_{20}H_{37}F_3N_2O_6$
Formula mass [$^g/_{mol}$]	458.40	472.43	420.01	486.45	576.57	458.52
Crystal color	colorless	colorless	colorless	colorless	colorless	colorless
Crystal size [mm]	0.36×0.31×0.26	0.25×0.25×0.15	0.34×0.08×0.04	0.40×0.20×0.09	0.40×0.18×0.06	0.50×0.28×0.10
Crystal shape	polyhedron	polyhedron	irregular	polyhedron	polyhedron	polyhedron
Temperature [K]	200(2)	200(2)	100(2)	200(2)	200(2)	200(2)
Crystal system	monoclinic	monoclinic	orthorhombic	triclinic	orthorhombic	triclinic
Space group	$P2_1/c$	$P2_1/c$	$Pna2_1$	$P\bar{1}$	$Pca2_1$	$P\bar{1}$
Z	4	4	4	2	4	2
a [Å]	12.7892(3)	12.892(6)	18.463(5)	7.9596(1)	18.1743(16)	7.905(3)
b [Å]	12.0914(3)	12.092(5)	8.601(2)	12.4372(3)	11.3626(12)	12.942(6)
c [Å]	14.4595(3)	14.781(7)	11.994(3)	12.8151(3)	12.3652(8)	13.026(5)
α [°]	90	90	90	105.431(1)	90	107.80(3)
β [°]	108.284(1)	106.68(5)	90	103.113(2)	90	96.35(2)
γ [°]	90	90	90	99.662(1)	90	103.04(4)
V [Å^3]	2123.12(8)	2207.1(17)	1904.6(9)	1155.29(4)	2553.5(4)	1212.7(8)
$D_{calcd.}$ [g/cm^3]	1.43	1.42	1.46	1.40	1.50	1.37
μ [mm^{-1}]	0.13	0.13	0.14	0.13	0.29	0.12
h_{min}/h_{max}	−16/16	−13/14	−15/15	−10/10	−11/11	−10/9
k_{min}/k_{max}	−15/15	−11/13	−7/5	−16/16	−14/2	−16/16
l_{min}/l_{max}	−18/18	−16/16	−9/9	−16/16	−15/8	0/16
Refl. collected	21638	11874	4114	12148	4864	4191
Refl. unique	4876	3402	1148	5269	3581	4191
Refl. observed	3625	2178	1099	2649	2025	2725
Parameter	346	345	331	418	335	315
S (Gof) on F^2	1.03	1.01	1.05	1.00	0.87	1.07
$R(F)$	0.053	0.043	0.031	0.067	0.043	0.045
$R_w(F^2)$	0.127	0.090	0.078	0.200	0.066	0.118
$(\Delta\rho)_{max}$ [e·Å^{-3}]	0.34	0.18	0.09	0.37	0.28	0.39
$(\Delta\rho)_{min}$ [e·Å^{-3}]	−0.34	−0.19	−0.12	−0.29	−0.25	−0.23

57.0, 82.0 ppm. HRMS (FAB$^+$): calcd. ($C_{15}H_{23}N_2$) 231.1861; found 231.1842, calcd. ($C_{32}H_{46}F_3N_4O_2$) 575.3528; found 575.3611.

Preparation of $[\mathbf{4b}\cdot H]^+[(CF_3CO_2)_2H]^-$: M.p. 72 °C, yield 72%. ^{1}H NMR ($CDCl_3$): δ = 1.90 (m, 4 H), 2.50 (m, 8 H), 2.90−3.10 (m, 12 H), 7.20 (br. s, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.6, 23.8, 54.2, 55.2 ppm. HRMS (FAB$^+$): calcd. ($C_{34}H_{50}F_3N_4O_2$) 603.3886, found 603.3891. $C_{20}H_{26}F_6N_2O_4$ (472.43) calcd. C 50.85, H 5.54, N 5.93; found C 50.98, H 5.83, N 5.91.

Preparation of $[\mathbf{4b}\cdot 2H]^{2+}[BF_4]_2^-$: Waxy material, yield 88%. ^{1}H NMR (DMSO): 1.80 (m, 4 H), 2.50 (m, 8 H), 2.90−3.00 (m, 12 H), 5.80 (br. s, NH) ppm. ^{13}C NMR (DMSO): δ = 17.1, 23.5, 54.1, 54.9, 81.8 ppm. HRMS (FAB$^+$): calcd. ($C_{16}H_{25}N_2$) 245.2018, found 245.2015; calcd. ($C_{16}H_{26}BF_4N_2$) 333.2125; found 333.2128.

Preparation of $[\mathbf{4c}\cdot H]^+[(CF_3CO_2)_2H]^-$: M.p. 75 °C, yield 67%. ^{1}H NMR ($CDCl_3$): δ = 1.55 (m, 2 H), 1.70 (quint. J = 6.6 Hz, 2 H), 1.90 (m, 2 H), 2.40−2.74 (m, 14 H), 3.55 (m, 2 H), 3.65 (m, 4 H), 6.30 (br. s, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.6, 18.4, 20.5, 22.6, 25.9, 52.4, 52.7, 52.9, 53.3, 73.8, 85.8 ppm. HRMS (FAB$^+$): calcd. ($C_{17}H_{27}N_2$) 259.2174, found 259.2172, calcd. ($C_{36}H_{54}F_3N_4O_2$) 631.4199, found 631.4217. $C_{21}H_{28}F_6N_2O_4$ (486.45) calcd. C 51.85, H 5.80, N 5.76; found C 51.80, H 5.82, N 5.80.

Preparation of $[\mathbf{4c}\cdot 2H]^{2+}[CF_3SO_3]_2^-$: M.p. 190 °C (decomp.), yield 72%. ^{1}H NMR (CD_3OD): δ = 1.92 (m, 2 H), 2.10 (m, 4 H), 3.10 (m, 8 H), 3.30 (quint J = 1.7 Hz, 4 H), 3.60 (m, 12 H), 6.20 (br. s, 2 H) ppm. ^{13}C NMR (CD_3OD): δ = 17.1, 23.9, 27.0, 54.7, 56.2, 82.3 ppm. HRMS (FAB$^+$) calcd. ($C_{18}H_{28}F_3N_2O_3S$) 409.3896, found 409.3864; calcd. ($C_{35}H_{54}F_3O_3N_4S$) 667.3859; found 667.3864.

Preparation of $[\mathbf{4d}\cdot H]^+[CF_3CO_2]^-$: M.p. 125 °C, yield 92%. ^{1}H NMR ($CDCl_3$): δ = 1.53−1.55 (m, 2 H), 1.64 (m, 4 H), 1.91 (m, 2 H), 2.30−2.41 (m, 10 H), 2.77 (br. s, 4 H), 3.60 (m, 2 H), 3.66 (m, 4 H), 6.00 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.3, 17.3, 22.3, 23.1, 23.8, 24.7, 50.2, 50.7, 51.1, 51.7, 72.9, 85.4 ppm. HRMS (FAB$^+$) calcd. ($C_{18}H_{29}N_2$) 273.2331; found 273.2339, calcd. ($C_{38}H_{58}F_3N_4O_2$) 659.4512; found 659.4474. $C_{18}H_{29}N_2\cdot CF_3CO_2\cdot 2H_2O$ (422.2) calcd. C 56.86, H 7.87, N 6.63; found C 57.15, H 7.81, N 6.66.

X-ray Diffraction Analyses: The reflections were collected on Bruker Smart CCD and Bruker APEX diffractometers (Mo-K_α radiation, graphite monochromator). Intensities were corrected for Lorentz and polarization effects, no absorption corrections were applied due to the low data redundancy for $[\mathbf{4d}\cdot H]^+$, $[\mathbf{4b}\cdot 2H]^{2+}$, and $[\mathbf{4c}\cdot 2H]^{2+}$; for all the others absorption corrections were applied by use of SADABS.[11] The structures were solved by direct methods. Full matrix, least-squares refinement was carried out against F^2. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were treated by use of appropriate riding models except for the N−H and O−H protons, which were refined isotropically. Structure solution and refinement were carried out with the SHELXTL software package.[12] The crystallographic data are listed in Table 2. CCDC-207932−CCDC-207937 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk /conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IE2, UK [FAX: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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