medium-ring systems for the creation of simple but unusual bonding situations.

References and Notes

(1) A chemical reaction or structural interaction (e.g., hydrogen bonding) may be studied in unconstrained (intermolecular, i) or singly (intramolecular, ii), doubly (transannular, iii,) or triply constrained (intrabridgehead, iv) systems.

$\mathrm{Me_3\overset{+}{N}{-}H{:}NMe_3}$

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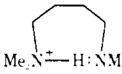

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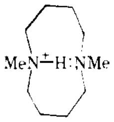

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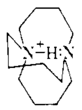

iv

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(9) We are indebted to Professor F. Gerson (Basel) for this spectrum.

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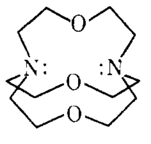
Inside- and Outside-Protonated Ions from 1,6-Diazabicyclo[4.4.4]tetradecane

Sir:

Inside, outside isomerism[1] and encapsulation[2] are two interesting features of the chemistry of macrobicyclic compounds, and it is important to establish size limitations for these phenomena. In particular, what is the smallest system which can encapsulate the smallest ion, the proton? The smallest known cryptand, **1**, can encapsulate two protons or one lithium ion.[4] We report that 1,6-diazabicyclo[4.4.4]tetradecane (**2**)[3] can form an inside-monoprotonated ion, but that the proton can neither be inserted nor removed by simple proton-transfer reactions.



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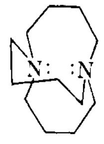

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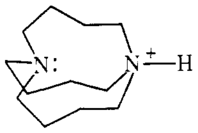

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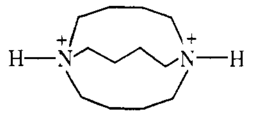

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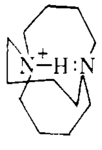

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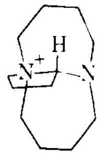

6

Outside protonation of **2** is characterized by $pK_{a1} = 6.5 \pm 0.5$,[5] $pK_{a2} = -3.25$.[6] These values are about 4 and 10 log units lower respectively than those for normal diamines with comparable N–N distances, and surely reflect the strain introduced by outward pyramidalization of the nitrogens of **2**.[7] 1,5-Diazabicyclo[3.3.3]undecane has pK_a values of 10.3 and 6.5,[8] while those for 1,4-diazabicyclo[2.2.2]octane are 8.82 and 2.97.[9] The salt **3**·BF_4[10] has ^{13}C resonances at −58.0, −51.4, −27.3, and −23.5 ppm (D_2O solution) and ^1H absorption ($CDCl_3$ solution) at δ 7.9 (NH), 3.54 (CH_2-N^+H, J_{HCNH} = 5 Hz), 2.62 (CH_2-N), and 2.00 and 1.85 (β-CH_2 groups). Slow proton transfer between equivalent nitrogens of a monoprotonated diamine is unusual, but reflects the large ΔpK_a for **2**. The ion **4** in HSO_3F solution has ^{13}C resonances at −52.2 and −20.3 ppm (unchanged at −90 °C) and ^1H absorption at δ 7.15 (NH), 3.58, and 2.43. Methylene group protons become nonequivalent below −70 °C. A C_{3h} or, more likely, D_3 structure for **4** is suggested.

Inside protonation of **2** might be thermodynamically favorable but kinetically difficult, based on analogy with **1**[3] and with 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene.[11] In practice we cannot *insert* a solvent proton into **2** at all. Thus heating **2** with an equivalent of *p*-toluenesulfonic acid in H_2O at 200 °C does not lead to **5**. However, when solutions of **2** in moderately strongly acidic media (40–70% H_2SO_4, CF_3SO_3H in CH_3CN, $Et_2OH^+BF_4^-$ in CH_2Cl_2) are left for a week or more, the NMR spectrum due to the **3** $\rightleftharpoons$ **4** equilibrium is replaced by that of **5**, accompanied by variable amounts of **6**.[4] The inside protonated ion, isolated as **5** BF_4,[10] was recognized from the extremely deshielded NH proton at δ 17.4 and the inertness of this proton to exchange, even after 3 h at 100 °C in 1 M NaOD/D_2O. Ion **5** shows ^{13}C absorption at −52.0 and −26.2 ppm (unchanged at −30 °C) and ^1H absorption at δ 2.70 and 1.92 for α- and β-CH_2. The protons of these CH_2 groups are nonequivalent at −30 °C, and a D_3 conformation for **5** seems likely. IR absorption for N—H···N is at 1400 cm^{-1} (broad).

The inside protonated ion is extraordinarily inert to deprotonation or further protonation. Deprotonation does not occur under conditions where *n*-Bu_4N^+ undergoes Hoffmann elimination, e.g., 2 h in $NaNH_2/NH_3$ at −33 °C or dry thermolysis of hydroxide salts at 160° for 0.5 h. Formation of an inside, outside diprotonated ion occurs in 1:1 HSO_3F/SbF_5 but not in HSO_3F alone. This dication has ^1H NMR absorptions at δ 7.30 (N–H), 3.9 and 3.60 (α-CH_2), and 2.45 (β-CH_2). Only one NH is observed, but there are no absorptions at very low field, indicating disruption of the N—H···N bond.

The reactions which produce **5** are most unusual and are not simple proton transfers. We have made the following observations for reactions in 40–70% aqueous H_2SO_4. (i) In 60–70% H_2SO_4, **5** is the only product, but in more dilute acid it is accompanied by irreproducibly variable amounts of **6** (up to ~1:1 **5**:**6** ratio). Reaction rates are generally fastest at ~50% acid but are also quite irreproducible. (ii) Reactions are dramati-

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cally accelerated by one-electron oxidants ($K_2S_2O_8$, VO_2^+, (p-$BrC_6H_4)_3N^{+}\cdot$) without serious effect on product composition. Thus in 70% acid addition of 0.1 molar ratio of $K_2S_2O_8$ leads to complete reaction in 1 h. (iii) Reactions in D_2SO_4/D_2O solutions lead to **5** which contains an N–H (always >80% of expected ^1H integral) and which has deuterium incorporated at the α carbon. At least in $K_2S_2O_8$-promoted reactions, there can be extensive α-deuteration. Thus with 0.5 equiv of $K_2S_2O_8$ in 70% D_2SO_4/D_2O, **2** gave **5** with >60% of complete exchange of α-CH_2 groups, the β-CH_2 and N–H of **5** being apparently unaffected. The N–H of **5** therefore comes from an α-CH_2 group by either 1,2 or 1,5 transfer and deuteration at α-CH_2 must occur subsequent to this. The effects of oxidants suggest the involvement of aminium cation radicals, which are known to undergo 1,5-hydrogen atom transfers[12] and also to deprotonate from carbon to form α-amino radicals.[13] The stable radical cation salt, $C_{12}H_{24}N_2BF_4$, from one-electron oxidation of **2**,[4] is quantitatively transformed into a 1:1 mixture of salts **5** and **6** on heating the solid to 130 °C, but is stable in the H_2SO_4 solutions where **5** is formed and indeed acts as an inhibitor of the reaction leading to **5**. The stable radical cation has an *in, in* conformation,[4] whereas models show that the intramolecular transfer of hydrogen inside the cage is only possible from an α-CH_2 next to an outwardly pyramidalized nitrogen. An *in, out* or *planar, out* radical cation is likely to be involved in the thermal decomposition and related intermediates may occur in the reactions in acid solution.

Acknowledgments. We thank the S.R.C. for research studentships for A.C. and R.B.S.

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(5) Approximate value based on UV spectra of 10^{-4} M solutions in aqueous buffer. The extreme water insolubility of **2** and its great ease of oxidation make precise measurement very difficult.
(6) Based on NMR studies in H_2SO_4/H_2O solution. The second protonation is half-complete in 49.5% H_2SO_4. The log I vs. H_0 plot has a slope of 0.9.
(7) For some force field calculations relevant to this point, see W. Parker, R. L. Tranter, C. I. F. Watt, L. W. K. Chang, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **96,** 7121 (1974).
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Cytochrome *c* Models

Sir:

The kinetic features of cytochrome *c* have been intensively studied over the last decade[1] establishing the criteria for its outer-sphere electron transfer mechanism, probably via the exposed heme edge.[2,3] By contrast, the thermodynamic and structural features have received less definitive study. We address three questions: (a) what are the structural changes accompanying the redox reaction, (b) is the intrinsic ligation capacity of methionine to iron modified by the protein, and (c) what determines the high redox potential of the Fe(II/III) couple?

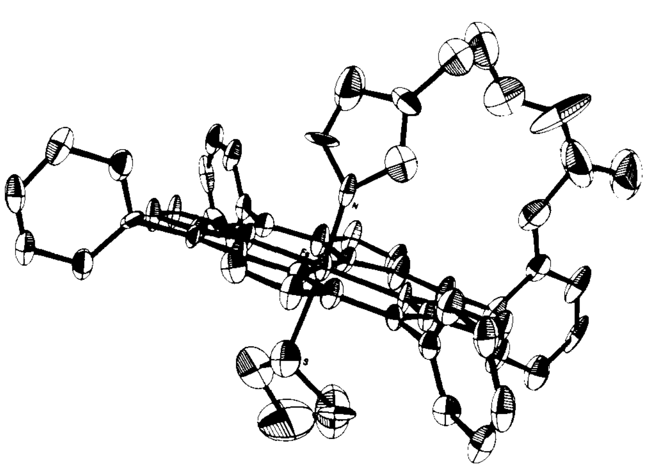

Figure 1. An ORTEP Plot of the Fe($\overline{\text{C}_5\text{-Im})(\text{TPP}}$)(THS) molecule **4**. Atoms are represented by their vibrational ellipsoids contoured to enclose 25% of the electron density.

Since the crystal structures of various ferro- and ferricytochromes *c* reveal only very minor protein reorganization upon redox,[2-4] we shift our focus of attention to changes in bond lengths to iron. If small, these can in part rationalize rapid electron transfer (the Franck-Condon principle).[5] Our first goal was to synthetize and structurally characterize a redox pair of low-spin thioether liganded hemes which were identical except for the oxidation state of the iron. The diamagnetic ferrous complex $Fe^{II}(THT)_2(TPP)\cdot THT$ (**1**) was isolated by anaerobic treatment of Fe(TPP)[6] with tetrahydrothiophene (THT).[7] Its exact one-electron oxidation product $[Fe^{III}(THT)_2(TPP)]^+$ can be prepared electrochemically or by treatment of $Fe(OClO_3)(TPP)$[8] with excess THT and isolated as a low-spin perchlorate salt $[Fe(THT)_2(TPP)]ClO_4\cdot 2CHCl_3$ (**2**). That thioethers bind sufficiently strongly to form a six-coordinate complex and that their ligand field strength is sufficiently high to yield a low-spin complex (μ_{eff} = 2.1 BM) is notable. We believe that the notion of methionine as an intrinsically poor ligand to ferric hemes has been exaggerated.[9] In ferricytochrome *c* only moderately strong field and strongly binding ligands (cyanide, imidazole, etc.) displace methionine[10] suggesting that incomplete[11-13] or nonexistent[9] thioether ligation in earlier ferricytochrome *c* models is the result of unrecognized, but recently emphasized,[8] competition from coordinating anions.

The X-ray structures of **1**[14] and **2** have been determined, but crystallographic difficulties forced us to abandon **2** in favor of an analogous pentamethylene sulfide derivative $[Fe(PMS)_2(TPP)]ClO_4\cdot 3CHCl_3$ (**3**).[15] Comparison of the Fe–N bond lengths [Fe^{II}_{av} 1.996 (6); Fe^{III}_{av} 1.982 (6)] reveals distances entirely consistent with expectations based on other low-spin ferrous and ferric hemes.[16] Quite unexpectedly, however, there is virtual parity of the Fe–S bonds in the two oxidation levels (Fe^{II}–S = 2.34 Å; Fe^{III}–S = 2.33, 2.35 Å). Apparently the expected increase in Fe–S upon oxidation due to poor compatibility of the "hard" Fe(III) for the "soft" thioether is offset by the increased charge attraction of Fe(III) for its ligands. This suggests that the same lack of substantial nuclear motion upon redox might also obtain in cytochrome *c*, implying that the choice of methionine as a ligand is beneficial to rapid electron transfer.

More satisfying than the above models is a true synthetic analogue of cytochrome *c* whose synthesis exploits the "tail

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