

Naked Fluoride Ion Sources: Synthesis, Characterization, and Coupling Reaction of 1-Methylhexamethylenetetramine Fluoride

Robert Z. Gnann,¹ Ross I. Wagner,¹ Karl O. Christe,^{*,1,2} Robert Bau,¹ George A. Olah,¹ and Wiliam W. Wilson²

Contribution from the Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089-1661, and Hughes STX, Propulsion Directorate, Phillips Laboratory, Edwards Air Force Base, California 93524

Received September 9, 1996[⊗]

Abstract: Anhydrous 1-methylhexamethylenetetramine (also referred to as *N*-methylurotropinium or methylhexaminium) fluoride was prepared by either halogen exchange between the corresponding iodide and AgF or by a single-step, one-pot, self-assembling synthesis from aqueous CH₃NH₂, HF, formaldehyde, and NH₃. It was characterized by NMR and vibrational spectroscopy. Its hydrate undergoes at 70 °C a Sommelet-type ring opening and coupling reaction to form a potential cryptand system consisting of two bicyclic triazine groups that are connected through a methylene bridge and contain eight ternary nitrogen atoms. The compound was characterized by multinuclear NMR and vibrational spectroscopy, and its structure was determined from single-crystal X-ray diffraction data.

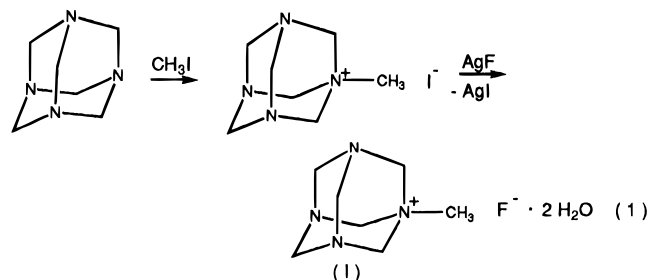
Introduction

The free fluoride anion is a very strong Lewis base and is of significant interest in inorganic^{3,4} and organic⁵ synthesis. The first preparation of anhydrous tetramethylammonium fluoride³ as a source of “naked” fluoride anions with appreciable solubility in common solvents, such as CH₃CN, gave rise to the synthesis of numerous new compounds.⁶ Among these are highly coordinated complex fluoride ions that are the key for studying molecules with coordination numbers >6.⁷

In [(CH₃)₄N]⁺F⁻, the concept of large counteranions was used³ to overcome the solubility limitations of the alkali-metal fluorides. In 1993, Harmon et al. reported⁸ the preparation of anhydrous *N,N,N*-trimethyl-1-adamantylammonium fluoride but gave no properties such as stability, reactivity, or solubility. The anhydrous 1,1,3,3,5,5-hexamethylpiperidinium fluoride⁹ has significant solubility in CH₃CN and was used to synthesize fluoride anions, such as [BrF₆]⁻, [SeF₆]⁻, and [XeF₇]⁻.

Recently, Clark et al. reported¹⁰ the synthesis of the 1-methylhexamethylenetetramine (frequently also referred to in the literature as methylurotropinium¹¹ or methylhexaminium¹²)

fluoride dihydrate and its use as a fluorodenitrating reagent. In their study, urotropine was quarternized with methyl iodide to 1-methylhexamethylenetetramine iodide, which was converted to the corresponding fluoride by a metathesis reaction with AgF in aqueous solution (eq 1).



Since this compound has no β-hydrogen atoms, it is not susceptible to Hofmann (E2) elimination and possesses relatively high thermal stability. Furthermore, the large size of its cation renders it a good candidate for a useful F⁻ ion source. In this paper, we wish to report the results of our independent study of this compound, including a simple, single-step, one-pot, self-assembling synthesis, isolation of the anhydrous fluoride, and an unexpected and novel coupling reaction.

Experimental Section

General Methods. Commercially available urea (Polarchem Corp.), CH₃I, methylamine, CH₃OH (Aldrich), and hydrofluoric acid 49% (Fisher Chemistry) were used as received. AgF (Cationics) was used as a filtered, aqueous solution. All other solvents were purified and dried according to common methods. All air-sensitive and hygroscopic materials were handled in the dry nitrogen atmosphere of a glove box.

The ¹H, ¹³C, and ¹⁹F NMR spectra were recorded using a Bruker AM 360 spectrometer at 360.13, 90.56, and 338.81 MHz, respectively. TMS (¹H and ¹³C) and CCl₃F (¹⁹F) were used as internal standards with positive shifts being to high frequency of the reference compounds. Infrared spectra were recorded in the range 4000–400 cm⁻¹ on either a Midac FT-IR or a Perkin-Elmer Model 283 spectrophotometer. Spectra of solids were obtained by using dry powders pressed between AgCl windows. Spectra of gases were obtained by using a glass cell of 5 cm path length equipped with AgCl windows. Raman spectra were recorded on either a Cary Model 83 or a Spex Model 1403

[⊗] Abstract published in *Advance ACS Abstracts*, December 15, 1996.

(1) University of Southern California.

(2) Hughes STX.

(3) Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J. J. *Am. Chem. Soc.* **1990**, *112*, 7619.

(4) Seppelt, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 292.

(5) Schwesinger, R.; Link, R.; Thiele, G.; Rotter, H.; Honert, D.; Limbach, H. H.; Männle, F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1372 and references cited therein.

(6) Christe, K. O.; Dixon, D. A.; Mercier, H. P. A.; Sanders, J. C. P.; Schrobilgen, G. J.; Wilson, W. W. *J. Am. Chem. Soc.* **1994**, *33*, 2850 and references cited therein.

(7) Christe, K. O.; Curtis, E. C.; Dixon, D. A.; Mercier, H. P. A.; Sanders, J. C. P.; Schrobilgen, G. J.; Wilson, W. W. In *Inorganic Fluorine Chemistry Toward the 21st Century*; Thrasher, J. S., Strauss, S. H., Eds.; ACS Symposium Series 555; American Chemical Society: Washington, DC, 1994.

(8) Harmon K. M.; Southworth B. A.; Wilson K. E.; Keefer P. K. *J. Org. Chem.* **1993**, *58*, 7294.

(9) Mahjoub A. R.; Zhang X.; Seppelt, K. *Chem. Eur. J.* **1995**, *1*, 261.

(10) Clark J. H.; Nightingale D. J. *J. Fluorine Chem.* **1996**, *78*, 91.

(11) See, for example: Ribar, B.; Meszaros, C.; Vladimirov, S.; Zivanov-Staki, D.; Golic, L. *Acta Crystallogr.* **1991**, *C47*, 1987.

(12) See, for example: Blazevic, N.; Kolbah, D.; Belin, B.; Sunjic, V.; Kajfez, F. *Synthesis*, **1979**, 161. Schnekenburger, J.; Kaufmann, R. *Arch. Pharm.* **1971**, *304*, 254 and 259.

spectrophotometer using the 488-nm exciting line of an Ar ion laser or the 647.1-nm exciting line of a Kr ion laser, respectively.

Water contents were measured by the Karl Fischer method¹³ in methanol which was dried over molecular sieves.

Synthesis of 1-Methylhexamethylenetetramine Fluoride (I). Originally, this compound was prepared in a manner similar to that reported by Clark and Nightingale,¹⁰ except for the following modifications. In the metathesis reaction of 1-methylhexamethylenetetramine iodide and AgF in aqueous solution, the AgF was used in a slight deficiency, the AgI was filtered off, and the clear solution was titrated with a diluted aqueous AgF solution until no further AgI precipitation was obtained. While the water was being distilled off, there was no precipitation of brown silver salts. The conversion to the 1-methylhexamethylenetetramine fluoride dihydrate was quantitative. 1-Methylhexamethylenetetramine fluoride (1.79 g) was suspended in 5 mL of 2-propanol (H₂O < 0.03%) and stirred for 30 min. The solvent was removed at ambient temperature under vacuum, and the residue was dried for 5 more h. This process was repeated twice, and the white solid was pumped on overnight. Azeotroping off the water was continued by using 10 mL of 2-propanol with a water content of <0.005% (twice) and additional evacuation overnight. The amount of water in the resulting product was determined by Karl Fischer titration in methanol and resulted in 0.006 wt % (= 60 ppm) of H₂O.

NMR: ¹H NMR (D₂O) δ 2.4 (s, NCH₃), 4.3 (d, 3 × NCH₂N), 4.6 (3 × NCH₂N); ¹³C{¹H} NMR (D₂O) δ 43.2 (NCH₃), 70.1 (3 × NCH₂N), 80.1 (3 × NCH₂N). In DMSO solution, anhydrous 1-methylhexamethylenetetramine fluoride was not detectable by ¹³C NMR spectroscopy due to its limited solubility.

IR (cm⁻¹, intens): 446.6 (w), 481.5 (w), 503.4 (vs), 588.4 (m), 651.0 (vs), 714.8 (m), 785.8 (s), 823.8 (vs), 849.6 (m), 959.3 (s), 994.4 (s), 1014.9 (s), 1044.7 (s), 1150.3 (m), 1244.3 (s), 3003.8 (vw).

Raman (cm⁻¹, intens): 445 (s), 480 (s), 500 (m), 589 (m), 649 (m), 716 (vs), 790 (m), 827 (m), 961 (s), 998 (w), 1024 (w), 1151 (w), 1350 (w), 2980 (m).

One-Step Synthesis of 1-Methylhexamethylenetetramine Fluoride. CH₃NH₂ was bubbled slowly into a tared 100 mL Teflon bottle, containing 18 mL of CH₃OH and a Teflon-coated stirring bar, while the solution was cooled intermittently in an ice bath. To the resulting methanolic solution of 3.647 g of CH₃NH₂ (117.4 mmol) were added 4.911 g of 48% HF (117.9 mmol), 57.192 g of 37.2% HCHO (707.5 mmol), and 24.916 g of 28% NH₃ (409.6 mmol) sequentially (the NH₄-OH dropwise) as aqueous solutions. The resulting clear solution was transferred to a 300 mL round-bottom flask, and volatiles were removed on a rotary vacuum evaporator while keeping the temperature below 60 °C to obtain approximately 25 g of a slurry of crystals. Rapid treatment with 13 25 mL portions of 2-propanol (0.04% H₂O) on the rotary evaporator produced 19.3 g of a solid product. Final azeotropic water removal was accomplished using two 25 mL portions of 2-propanol (H₂O < 0.005%), which was added to the solid in a drybox and removed on a vacuum line. The resulting 15.135 g of dry product contained 0.005 wt % H₂O (Karl Fischer titration). Vibrational spectra (IR and Raman) of the solid and ¹H NMR in D₂O solvent matched those of 1-methylhexamethylenetetramine fluoride prepared by the metathesis of 1-methylhexamethylenetetramine iodide and AgF but indicated the presence of urotropine as an impurity. Extraction with dry, ethanol-free chloroform was used to remove the urotropine, resulting in an analytically pure product, identical to that obtained by the multistep synthesis described above.

Synthesis of Bis(7-N-methyl[3.3.1]-1,3,5,7-tetraazanone-3-N-yl)-methane (II). 1-Methylhexamethylenetetramine iodide (2.003 g) was converted to the corresponding fluoride as described above. After most of the water was distilled off in the rotary evaporator at 70 °C, the remaining thick oil was transferred to a sublimation apparatus. After the formation of 0.12 g of clear and colorless crystals on the cooling finger (yield ~6%), no further sublimation was observed after 2 days at 70 °C in a dynamic vacuum. The remaining residue was pure 1-methylhexamethylenetetramine fluoride, as shown by IR, ¹H NMR, and ¹⁹F NMR.

A sublimation experiment was repeated with 0.947 g of anhydrous 1-methylhexamethylenetetramine fluoride at 70 °C under a dynamic

vacuum. After 4 days only 0.011 g of a yellow/white solid sublimate was obtained, which in the ¹³C-NMR showed only traces of II.

Analytical Data for II. Mp: 80 °C; soluble in DMSO-*d*₆, acetone-*d*₆, and benzene-*d*₆. ¹³C{¹H} NMR in benzene-*d*₆ δ: 39.55 (s, CH₃N, two carbon atoms), 72.20 and 76.28 (s, NCH₂N, four carbon atoms each), 71.07 (s, NCH₂N, two carbon atoms), 75.34 (s, NCH₂N, one bridging carbon atom).

¹H NMR in benzene-*d*₆: 1.71 (s), 3.24 (s), 3.42 (d), 3.83 (m), 4.06 (m).

Raman (cm⁻¹, peaks with a rel intens <5% are not listed): 200 (m), 250 (s), 325 (w), 351 (m), 385 (w), 418 (s), 445 (s), 455 (s), 488 (m), 530 (w), 553 (vw), 610 (w), 640 (s), 730 (vs), 846 (w), 851 (s), 863 (w), 965 (vs), 991 (vw), 1025 (s), 1028 (m), 1039 (w), 1078 (w), 1098 (w), 1115 (w), 1140 (w), 1222 (m), 1310 (m), 1327 (m), 1380 (m) 1449 (s), 1464 (m), 1478 (m), 2785 (s), 2858 (s), 2869 (s), 2877 (s).

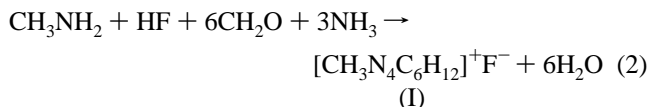
X-ray Structure Determination of II. Data were collected at room temperature on a Siemens P4/RA diffractometer with Cu Kα X-rays. The structure was solved by direct methods and refined to final agreement factor of *R* = 3.6% and *R*_w = 3.9% for 1339 reflections with *F* > 4σ(*F*). Calculated hydrogen positions were included in the structure analysis.

Results and Discussion

Synthesis of Anhydrous 1-Methylhexamethylenetetramine Fluoride. In accord with the procedure of Clark et al.,¹⁰ 1-methylhexamethylenetetramine iodide was converted into the corresponding fluoride using AgF in an aqueous solution. To achieve a complete conversion without having any impurities of silver salts in our product, a titration with a diluted AgF solution was used. The water removal by azeotroping off H₂O from an isopropyl alcohol solution under vacuum is based on the method of Christe et al.³ and lowers the water content to 50 ppm, as shown by a Karl Fischer titration in methanol. In contrast to the corresponding dihydrate,¹⁰ the anhydrous fluoride is nearly insoluble in all common solvents. Only in DMSO solution is the fluoride ion detectable by ¹⁹F NMR spectroscopy as a very weak and broad signal at δ -101 ppm. In solvents such as CH₃CN, CH₂Cl₂, C₂H₅CN, DMF, and CH₃Cl, the HF₂⁻ anion¹⁴ is the only product detectable by ¹⁹F NMR spectroscopy.

The IR spectrum of the anhydrous 1-methylhexamethylenetetramine fluoride agrees well with those given for corresponding heavier halides.¹⁵ The spectra of the dry fluoride show neither absorptions in the HOH stretching regions at about 3300 cm⁻¹ nor absorptions in the HOH bending region at ca. 1700 cm⁻¹.

Direct Synthesis. The cocondensation of aqueous methylamine, HF, ammonia, and formaldehyde resulted in the first direct synthesis of a quarternized hexamethylenetetramine fluoride (eq 2):



This type of self-assembling reaction was previously reported¹⁶ by Morgan and Curtis for the synthesis of 1-alkylhexamethylenetetramine perchlorates, fluoroborates, bromides, and chlorides.

Using inexpensive starting materials, the synthesis can be carried out in a one-pot reaction in aqueous solution. Furthermore, the process is readily scalable and was carried out on a 15 g scale without any problems. Urotropine is the only detectable side product, but can be easily extracted with

(14) Christe, K. O.; Wilson, W. W. *J. Fluorine Chem.* **1990**, *46*, 339.

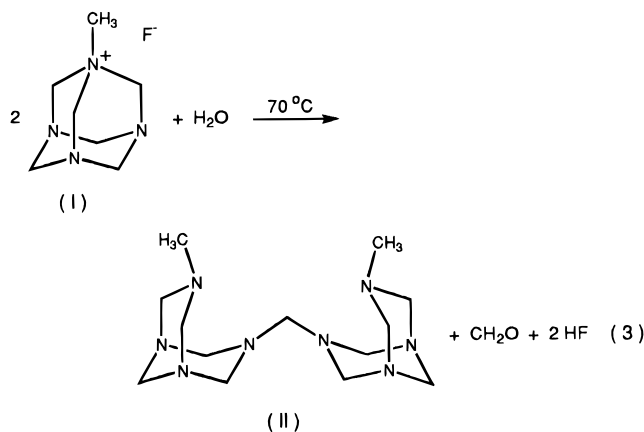
(15) Harmon, K. M.; Keefer, P. K. *J. Mol. Struct.* **1992**, *270*, 19.

(16) Morgan, K. R.; Curtis, N. F. *Aust. J. Chem.* **1980**, *33*, 1157.

(13) Scholz, E. *Karl Fischer Titration, Methoden zur Wasserbestimmung*; Springer Verlag: Berlin, 1984.

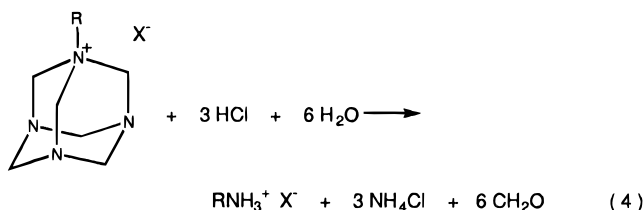
chloroform. Azeotroping off the water with 2-propanol gives highly pure and anhydrous 1-methylhexamethylenetetramine fluoride. This simple, high-yield, one-step synthesis eliminates the need for expensive starting materials, such as CH_3I and AgF , used in the previously reported¹⁰ multistep synthesis. The high yield of I in eq 2 is amazing in view of the complexity of the adamantane-type, tricyclic structure of I and is an excellent example for a self-assembling reaction.

Ring Opening and Coupling Reaction. The condensation of two 1-methylhexamethylenetetramine fluoride molecules in the presence of some water results (see eq 3) in the formation of a neutral, methylene-bridged structure containing two symmetric groups of bicyclic N,N-bridged triazine rings (II).

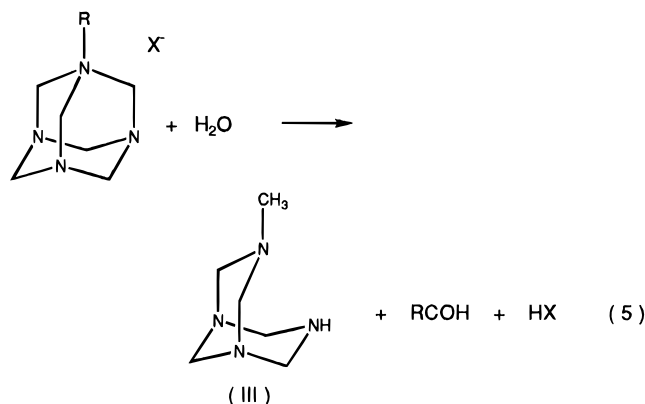


This substance sublimes out of hydrated 1-methylhexamethylenetetramine fluoride at 70 °C under a dynamic vacuum and forms colorless, clear crystals. These crystals were characterized by ^{13}C and ^1H NMR spectroscopy, Raman spectroscopy, and a single-crystal X-ray structure analysis. The substance is very hygroscopic and melts at 80 °C. It is reasonably soluble and stable in solutions of benzene, DMSO, and acetone. Starting with hydrated 1-methylhexamethylenetetramine, the maximum yield of the coupled product, obtained under our reaction conditions, was about 6%. The use of anhydrous 1-methylhexamethylenetetramine as a starting material, under otherwise identical reaction conditions, produced only traces of II and establishes the requirement of water for reaction 3.

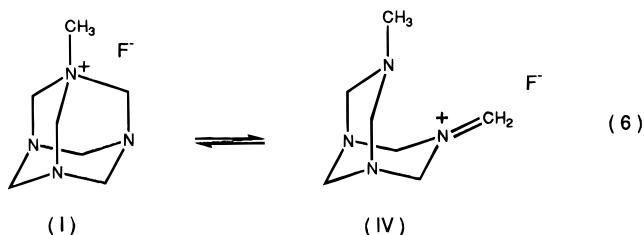
Ring-opening reactions of quaternary alkylhexamethylenetetramine salts in aqueous solutions are well known.¹² Under strongly acidic conditions, a complete destruction of the ring system occurs in a reaction generally referred to as the Delepine reaction (eq 4).¹⁷



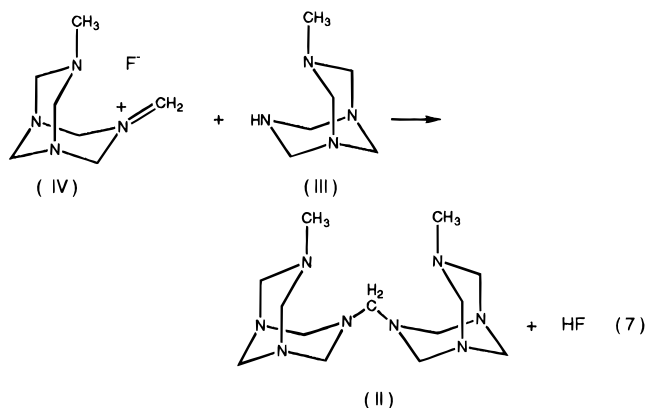
Under neutral conditions, only a partial ring opening with formation of a 1-methyl-1,3,5,7-tetraazabicyclo-3.3.1-nonane (III) and an aldehyde occurs. This reaction is known as the Sommelet reaction^{18,19} and constitutes a general synthesis for aldehydes (eq 5).



Schnekenburger and Kaufmann have shown¹² that reaction 5 also occurs even if only a small excess or stoichiometric amounts of water are present. However, to our knowledge, the coupling reaction 3, observed in this study, has not previously been reported and might be characteristic of the fluoride. The following mechanism is proposed for this reaction: The first step is the Sommelet reaction (eq 5), resulting in the formation of the bicyclic amine III. This step is accompanied by reaction 6, which is the ring opening of one of the triazine rings by the



strong base, F^- , followed by the coupling reaction (eq 7) between the free amine III and the ring-opening product IV.



Our proposed mechanism is in accord with the following experimental observations: (i) the coupling reaction requires the presence of water and does not proceed under anhydrous conditions; (ii) the yields are quite low, which supports the postulated need for the simultaneous production of the two starting materials III and IV; (iii) the residue from the sublimation experiments was anhydrous 1-methylhexamethylenetetramine fluoride (I), which did not produce any additional coupled product II, once all the water had been removed from the system.

An alternate mechanism, starting out with reaction 6, followed by a coupling reaction with a second molecule of 1-methylhexamethylenetetramine fluoride to give an intermediate dication that then would undergo a Sommelet-type reaction with the elimination of 1 mol of formaldehyde and 2 mol of HF is also possible but, in our opinion, less likely.

(17) Delepine, M. C. R. **1895**, 120, 501; **1897**, 124, 292; *Bull. Soc. Chim.* **1895**, 13, 358.

(18) Sommelet, M. C. R. **1913**, 157, 852; *Bull. Soc. Chim.* **1915**, 17, 82; **1917**, 23, 96.

(19) Angyal, S. J.; Penman, D. R.; Warwick, G. P. *J. Chem. Soc.* **1953**, 1742.

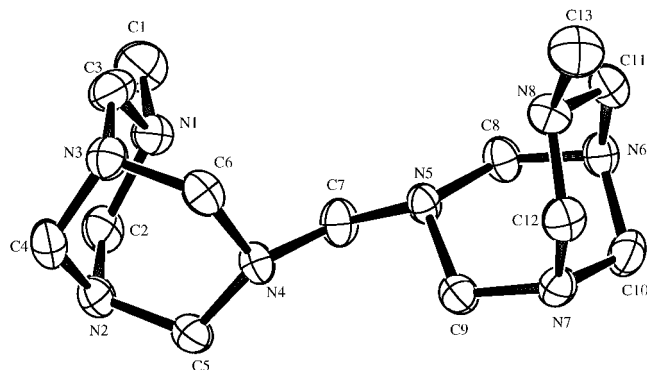


Figure 1. ORTEP plot of the structure and atom labeling scheme for II. Thermal ellipsoids are drawn at the 50% probability level, and hydrogen atoms are omitted for clarity. Average bond distances (Å) and angles (deg): N–C, 1.460 ± 0.015 ; N–C–N, 114.0 ± 3.2 ; C–N–C, 112.3 ± 5.5 ; N4–C7–N5, $111.3(2)$.

Table 1. Crystal Data and Structure Refinement for $C_{13}H_{28}N_8$

emp form.	$C_{13}H_{28}N_8$
form. wt	296.4
cryst syst	monoclinic
space grp	$C2/c$
unit cell dimens	$a = 22.600(2)$ Å, $\alpha = 90^\circ$ $b = 7.579(2)$ Å, $\beta = 105.83(2)^\circ$ $c = 19.222(2)$ Å, $\gamma = 90^\circ$
volume (Å ³)	3167.6(9)
Z	8
density (calcd) (g/cm ³)	1.243
absorpn coeff (mm ⁻¹)	0.649
$F(000)$	1296
cryst size (mm)	$0.2 \times 0.2 \times 0.2$
reflns collected	2198
ind reflns	1672 [$R(\text{int}) = 0.021$]
data/restraints/params	1339/0/190
goodness-of-fit on F^2	1.53
final R indices [$F > 4\sigma(F)$]	$R1 = 0.0361$, $wR = 0.0391$
R indices (all data)	$R1 = 0.0470$, $wR2 = 0.0704$

The crystal structure of the coupled product (II) is shown in Figure 1, and the crystallographic data are collected in Tables 1 and 2. As can be seen from Figure 1, the bond distances and angles within the two ring systems are quite normal and as expected. However, the two bicyclic systems are not coplanar and form a dihedral angle of about 78° . Since the rotational barrier about the N–CH₂–N bridge bond is expected to be quite low, the dihedral angle may be a solid state, i.e., packing, effect, and rotation to a coplanar configuration, as shown in the drawings for compound II, may be a low activation energy process. One could envision that compound II in its coplanar configuration might act as a clamshell and exhibit, due to its eight ternary nitrogen atoms with the free valence electron pairs of four of them pointing towards the cavities, interesting properties as a potential cryptand.

Table 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($\text{Å}^2 \times 10^3$) for II

	x	y	z	$U(\text{eq})^a$
N(1)	933(1)	6762(3)	–254(1)	42(1)
N(2)	1880(1)	5926(3)	–560(1)	43(1)
N(3)	992(1)	4054(3)	–920(1)	45(1)
N(4)	1724(1)	3605(3)	294(1)	38(1)
N(5)	1437(1)	2569(3)	1339(1)	34(1)
N(6)	1231(1)	1929(3)	2509(1)	39(1)
N(7)	1983(1)	211(3)	2141(1)	40(1)
N(8)	896(1)	–627(3)	1736(1)	41(1)
C(1)	539(2)	8276(4)	–232(2)	64(1)
C(2)	1501(1)	7350(4)	–416(2)	48(1)
C(3)	608(1)	5476(4)	–788(2)	52(1)
C(4)	1503(1)	4834(4)	–1133(2)	51(1)
C(5)	2145(1)	4775(4)	57(2)	46(1)
C(6)	1242(1)	2887(4)	–304(2)	44(1)
C(7)	1537(1)	4114(4)	930(2)	44(1)
C(8)	1228(1)	3227(4)	1954(2)	42(1)
C(9)	1997(1)	1499(4)	1582(2)	42(1)
C(10)	1839(1)	1144(4)	2737(2)	49(1)
C(11)	783(1)	532(4)	2293(2)	45(1)
C(12)	1540(1)	–1196(4)	1911(2)	46(1)
C(13)	491(1)	–2152(4)	1641(2)	65(1)

^a Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Conclusions

Although the low solubility of 1-methylhexamethylenetetramine fluoride in most common solvents and its propensity toward ring opening under aqueous and, particularly, acidic conditions do not make it a naked fluoride ion source with broad applications, the partially ring-opened coupling product II might be of interest as a potential cryptand in view of the presence of eight ternary nitrogen atoms. If the rotational barrier about the CH₂-bridge is as low as expected, the free molecule could readily be rotated into a clamshell-type configuration.

Acknowledgment. The work at the Phillips Laboratory was financially supported by the Propulsion Directorate of the U.S. Air Force, and one of us (R.Z.G.) acknowledges the Deutsche Forschungsgemeinschaft for a scholarship. The authors thank Prof. Surya Prakash for stimulating and fruitful discussions.

Supporting Information Available: A structure determination summary (Table S1), tables of anisotropic thermal parameters and hydrogen atomic coordinates (Tables S2 and S3), a tabulation of bond lengths and bond angles (Table S5), and a packing diagram for II (Figure S1) (8 pages). See any current masthead page for ordering and Internet access information.

JA963168M