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An NMR study of sequential intermediates and collateral products in the conversion of 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) to 1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecane (TATU)

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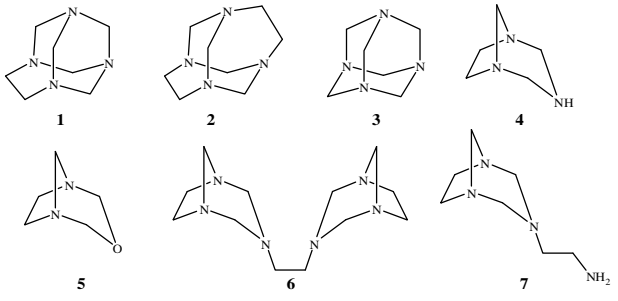
Abstract

In situ ^{1}H nuclear magnetic resonance spectroscopy was used to investigate the processes that occur during the synthesis of 1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecane (TATU). NMR analysis showed a reaction mixture containing more than one compound. The production of these intermediates and collateral products was rationally supported by a careful ^{1}H NMR monitoring study. We characterized 1,3,5-triazabicyclo[3.2.1]octane (TABO, **4**) and 3-(2-aminoethyl)-1,3,5-triazabicyclo[3.2.1]octane (AETABO, **7**) by ^{1}H and ^{13}C NMR in D_2O solution inside the NMR sample tube, as an intermediate and collateral product of the reaction, respectively. Further, a reaction of 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) with ^{15}N-labeled ammonium chloride was carried out. The ^{15}N NMR and GC–MS experiments indicated that ^{15}N was incorporated into TATU, TABO, and urotropine.

Keywords: 1,3,6,8-Tetraazatricyclo[4.3.1.1^{3,8}]undecane; TATU; 1,3,6,8-Tetraazatricyclo[4.4.1.1^{3,8}]dodecane; TATD; Kinetic; In situ NMR; Aminal cage

Recently we reported on the one-pot, but multistep, preparation of the new cyclic aminal 1,3,6,8-tetraazatricyclo[4.3.1.1^{3,8}]undecane (TATU, **1**) by an unusual ring contraction-rearrangement of 1,3,6,8-tetraazatricyclo-[4.4.1.1^{3,8}]dodecane (TATD, **2**) when reacted with ammonium fluoride in water.[1] The present study was aimed at establishing the structures of compounds produced in the reaction of aminal (**2**) with ammonium fluoride in water and elucidating the possible pathways of their formation.

The reaction can follow several pathways. In particular, it can be assumed that TATD undergoes recyclization under the action of NH_4F as a result of the ring-chain transformation through an unstable open-chain way. This reaction falls under the most general definition of molecular rearrangements as chemical reactions associated with a change in the bond sequence (molecular skeleton) and breaking the principle of minimum structural changes.[2] NMR experiments have been extensively used by several authors to probe reactions without disturbing the system and providing useful structural and kinetic information about reactions in equilibrium.[3] Thus, in our experimental study of aminal cage reactivity, we decided to revise the reaction between **2** and ammonium fluoride in D_2O to obtain **1**, two aminals amenable to NMR analysis. The goals of this study were (1) to obtain information about product composition; (2) to identify the intermediates



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involved in the reaction pathway; (3) to gain a better understanding of the overall reaction mechanism; (4) to determine some preliminary evidence of the kinetic reaction.

The ^{1}H NMR spectra of the crude reaction mixtures (Fig. 1a–c) showed that both the starting aminal TATD (**2**) and TATU (**1**) were present. In addition, a close inspection also revealed the presence of species with low intensity signals, which can be attributed to intermediates or collateral products. The downfield signal appearing as a singlet at δ 4.45 was assigned at the aminalic protons of urotropine (**3**) by comparison with the spectrum of a mixture of purified samples of **1**, **2**, and **3** (Fig. 1d), which showed well-separated signals between 2.25 and 4.50 ppm. This spectrum had five singlets, two of which were attributable to ethylenic protons of **1** and **2** (δ 3.01 and 3.03, respectively), while others were attributable to aminalic protons at 3.75 for **2**, 4.04 for **1**, and 4.45 for **3**. The one-proton doublet at δ 3.62 and 4.31 with geminal coupling of 13.5 Hz was attributed to aminalic protons of **1**. The splitting pattern, coupling constants, and NMR ratios of the signal protons at δ: 4.15 ($J = 10.2$ Hz), 3.84 ($J = 13.1$ Hz), 3.36 ($J = 12.7$), and 3.18 ($J = 10.4$ Hz) (Fig. 2a), with an intensity ratio of 1:2:2:1, can indeed be attributed to one of the secondary products (intermediate or collateral products). These resonances were clearly differentiated as two AB-systems with a typical coupling constant of geminal protons.

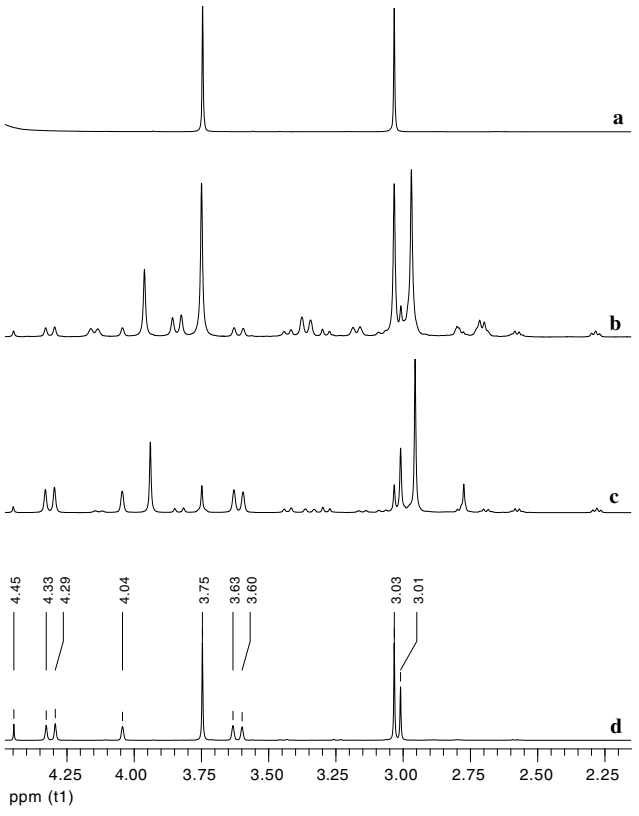


Fig. 1. ^{1}H NMR spectra of a reaction mixture of **2** (1.41 M) and NH_4F (4.50 M) in a D_2O at (a) $t = 0$ s, (b) $t = 20$ min 17 s, and (c) $t = 440$ min. (d) ^{1}H NMR spectrum of a mixture of **1** (0.09 M), **2** (0.09 M), and **3** (0.01 M) in D_2O.

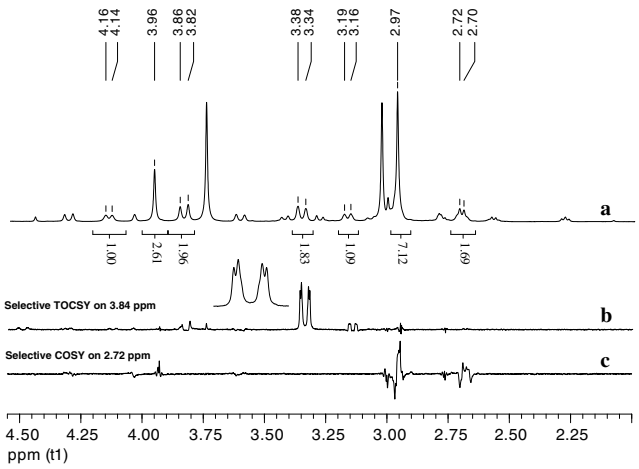


Fig. 2. TOCSY-selective experiments for **4**.

Based on the chemical shifts, we suggested the presence of CH_2-aminalic groups in its structure (**4**). To isolate the spin systems from the spectrum of reaction mixture, 1D TOCSY experiments were performed.[4] Irradiation of the signal at 3.84 ppm produced enhancements at 3.36 and 3.18 ppm (Fig. 2b). The appearance of signal at 3.36 ppm as a doublet of doublets ($J = 12.7$ and 2.1 Hz) indicated the presence of long-range NMR coupling constants. The homonuclear small coupling constant value, which is attributed to a $^4J_{HH}$ coupling constant between W-positioned hydrogen atoms in bicyclic compounds,[5] suggested that compound **4** had a bicyclic structure. Aside from these resonances, the NMR ratio of the signal proton at 2.71 ppm (Fig. 2a) and its typical signal patterns of particular $-CH_2CH_2-$ ring moieties indicated that this resonance can be assigned to an ethylene bridge in a bicyclic system. In fact, a COSY irradiation[6] of this signal resulted in a signal enhancement at ≈2.92 ppm (Fig. 2c) that overlapped with another major resonance at 2.97 ppm, all of which vindicated the presence of an ethane-bridge. Again, comparison of the ^{1}H NMR spectra of **4** with those of the known compounds 3-oxa-1,5-diazabicyclo[3.2.1]-octane (**5**)[5a] and 3,3′-ethane-1,2-diylbis-1,3,5-triazabicyclo[3.2.1]-octane (**6**)[5b] (Table 1) showed very similar δ and J values suggesting that compound **4** had the bicyclo[3.2.1]octane nucleus. Based on these data, compound **4** was identified as 1,3,5-triazabicyclo[3.2.1]-octane (TABO, **4**). Besides urotropine, TATU, and TATD, the GC–MS analysis of this solution confirms the formation of **4**. TABO (**4**) had in its EIMS the molecular ion peak at m/z 113 correct for the formula $C_5H_{11}N_3$, and the fragmentation pattern was consistent with the speculative fragmentation course. To the best of our knowledge, although its structure was claimed in a patent,[7] its NMR data are unprecedented.

We also focused on the strong peaks at 3.96 and 2.97 ppm, with approximate intensities, 2.61; 7.12 (Fig. 2a). In principle, these signal protons did not show

Table 1
Comparison of select δ and J values, for **4**, **7**, **5**, and **6**

Entry	(AB)2	AB	AA′BB′
4[a]	3.84 (d, $J = 12.9$); 3.36 (dd, $J = 12.9, 2.1$)	4.15 (d, $J = 10.4$); 3.18 (d, $J = 10.4$)	2.97; 2.71
7[a]	3.65 (d); 3.51 (d)	3.97 (d); 3.30 (d)	3.21 (dd); 2.80 (dd)
5[b]	4.75 (d, $J = 9.6$); 4.26 (d, $J = 9.6$)	4.20; 3.30	3.30; 2.38
6[c]	3.62 (dd, $J = 10.7, 1.5$); 3.40 (dd, $J = 10.7$)	3.89 (dd, $J = 10.5, 1.9$); 3.30 (dd, $J = 10.5, 1.5$)	2.79 (dd, $J = 10.6, 4.4$); 3.17 (ddd, $J = 10.6, 4.4, 1.9$)

[a] This work.
[b] Ref. 5a.
[c] Ref. 5b.

proportion of integrals, probably due to that some of the products gave overlapping signals. In fact, 1D COSY experiment (Fig. 2c) clearly demonstrates the superposition of ethylene signals of **4** and 2.97 as discussed below. After correcting the relative integral of signal at 2.97 ppm for the experimental amount of **4** to obtain 5.12, we noted that the magnitude of relative intensities of signals at 3.96 and 2.97 ppm is near 1:2. Thus, based on the chemical shifts observed and NMR ratios, we proposed the structure of imidazolidine (**8**) for this compound. To further support our peak assignments, we carried out various 2D NMR spectroscopic techniques, but most of the information for the confirmation of the peak assignments was obtained by carrying out HMBC and HMQC experiments. Here the assignment of the peaks was confirmed by comparing the rates of consumption of TATD (**2**) and the corresponding formation of peaks assigned to **4** and **8**. Thus, all assigned peaks showed a good consistency along time dependences of their intensities. When all peaks of compounds **1**, **2**, **4**, and **8** were assigned, a number of extremely weak (on the order of 10^{-3} relative to those of **1**) unassigned peaks still remained. Three of these (at 2.28, 2.58, and 2.79 ppm) were ascribed to ethylenic protons while, similarly, two weak peaks were ascribed to aminalic protons (at 3.43 and 3.28 ppm). 1D TOCSY, 1D COSY, and 1D NMR selective irradiation (Fig. 3) allowed us to establish the presence of 3-(2-aminoethyl)-1,3,5-triazabicyclo[3.2.1]octane (AETABO, **7**), whose bicyclic fragment is structurally similar to **4**.

In addition, the NMR spectroscopic data obtained during the investigation provide instantaneous concentrations of detectable species in the reaction mixture. This made it possible to describe a preliminary study of the reaction kinetics between TATD and ammonium fluoride to give TATU. In Figure 4, three different concentration profiles can be clearly identified: one of these from substrate (**2**) which decreases to zero; others of final products (**1, 8**), were increased; and finally, one of an intermediate (**4**), reaching a maximum concentration after about 20 min.

Initially, a decrease in the concentration of TATD, and a corresponding increase in the concentration of **4** and imidazolidine were observed. It is interesting to note that the consumption of **2** during the first hour is directly proportional to the rate of formation of **4** and **8**. Based on these results, we consider that **2** was consumed to preferen-

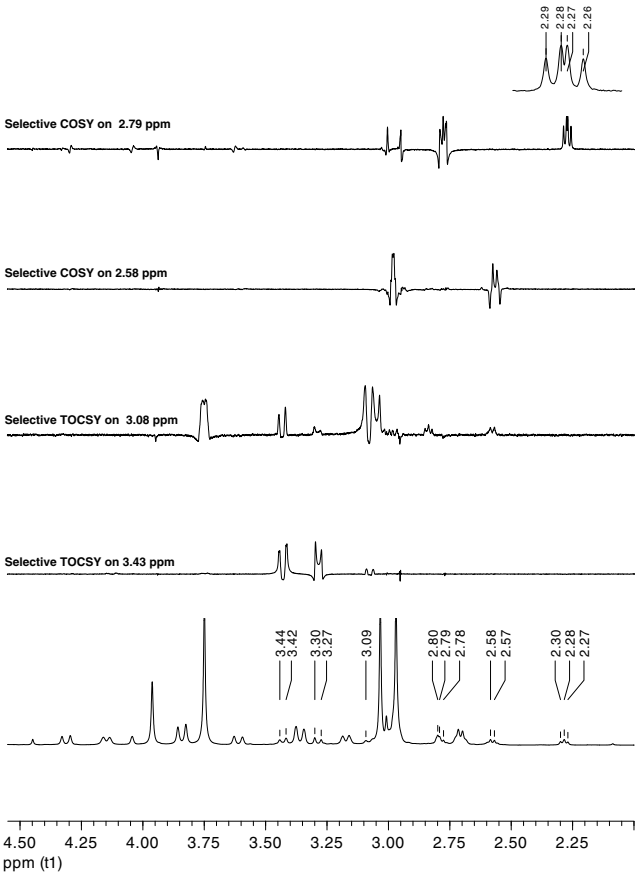


Fig. 3. ^{1}H NMR-selective irradiation experiments for **7**.

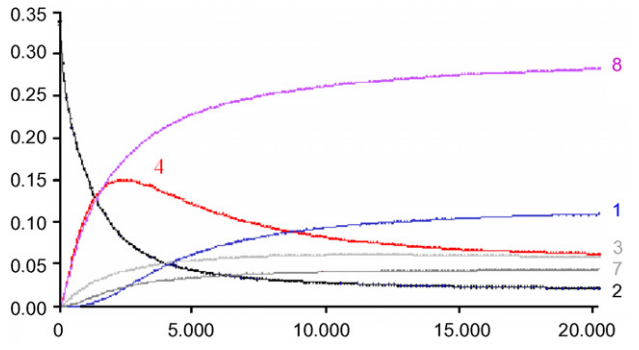
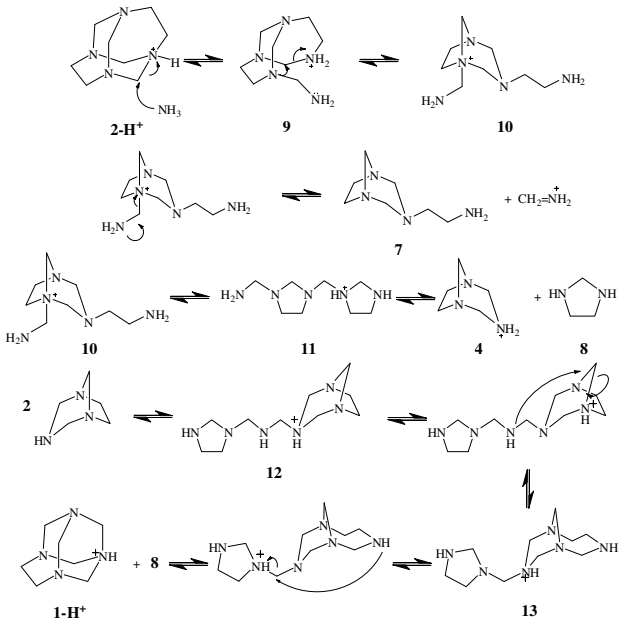


Fig. 4. Concentration (mM) versus time (s) for **1**, **2**, **3**, **4**, **7**, and **8** in the reaction of TATD with NH_4F.

tially produce **4** and **8**. This trend continues until **4** reaches a maximum concentration, as seen in Figure 4. At this point, an increase in the concentration of **1** was observed. Its formation is directly proportional to the rate of consumption of **4**. This observation suggested that not only does the formation of **1** depend on reaching a sufficient concentration of **4**, but more intriguingly that **4** is the precursor of the main product **1**.

Although the pathway for this conversion likely involves the formation of imine or iminium intermediates, the mechanism involving the imine would be less likely because the ring-chain tautomeric equilibrium in aminals is favored toward the formation of open species in the presence of trifluoroacetic acid.[8] A plausible mechanism involving ammonium intermediates is depicted in Scheme 1. The essence of this mechanism is an initial nucleophilic attack by ammonia at the aminal carbon of the protonated aminal producing an open-ring intermediate (**9**). This intermediate could experience a rearrangement process to produce a highly reactive ammonium intermediate 3-(2-aminoethyl)-1-(aminomethyl)-3,5-diaza-1-azoniabicyclo-[3.2.1]octane (**10**). Once intermediate **10** is formed, it could either be converted into AETABO (**7**) (Scheme 1) (by eliminating a aminomethyl moiety) or alternatively, to suffer an intramolecular nucleophilic attack to produce the {[3-(imidazolidin-1-ylmethyl)imidazolidin-1-yl]methyl}amine (**11**). This reaction, as seen in Figure 4, occurs faster than aminomethyl elimination. The decomposition of **11** could afford the detected compounds **4** and **8**, as shown in Scheme 1. Dimerization of **4** followed by rearrangements and subsequent expulsion of imidazolidine would lead to the formation of TATU (Scheme 1).

Although proposed intermediate **4** should be the actual isolated compound derived from the condensation reaction



Scheme 1. Proposed mechanism for forming compound **1**.

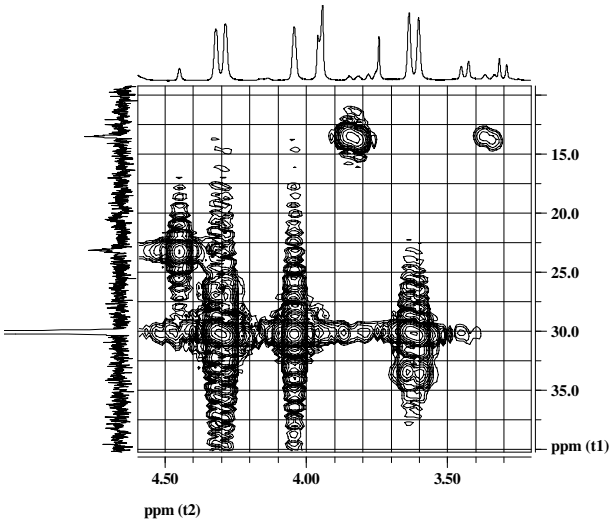


Fig. 5. ^{1}H–^{15}N HMBC contour plot of reaction mixture.

between **2** and NH_4F, we believe that the driving force for its dimerization into **1**, under the studied reaction conditions, is provided by two mechanisms: (i) the additional stability gained in the aminal cage structure of **1** and (ii) imidazolidine acting as an effective H^+ binder. In fact, we cannot exclude the possibility that the free aminal cage is a weak base. For instance, it is possible that it may be even more difficult to insert a proton into the cage, as compared to removing it.

Strong support for this proposal is provided by in situ ^{15}N NMR experiments. TATU labeled with ^{15}N was synthesized from TATD and ^{15}N-enriched ammonium chloride according to the procedure described above for the non-labeled material. Upon the addition of ^{15}N-NH_4Cl to **2**, we observed three signals at 30.2, 23.2, and 13.6 ppm at 296 K relative to NH_4Cl. We assign the low-field line to TATU (**1**). Two-bond ^{1}H–^{15}N HMBC correlation of this signal to aminals protons justified this assignment (Fig. 5). The other resonances at 23.2 and 13.6 ppm were assigned to urotropine (**3**) and TABO (**4**), respectively. The GC–MS analysis of this reaction mixture confirms the formation of TATU-$^{15}N_2$ (M^+ 156, 100%). (We are grateful to a referee and the editor for suggesting these analyses).

In this work, NMR analysis showed a reaction mixture constituted by more than one aminal product: **4**, **7**, urotropine, and imidazolidine, which were characterized by ^{1}H and ^{13}C NMR in a D_2O solution as intermediate or collateral products. Such a conclusion also implies that the above experiments indicated that the actual subproduct of this reaction is imidazolidine but not ethylenediamine, as previously described.[1]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.091.

References and notes

1. Rivera, A.; Núñez, M. E.; Morales-Rios, M. S.; Joseph-Nathan, P. *Tetrahedron Lett.* **2004**, *45*, 7563.
2. Müller, P. *Pure Appl. Chem.* **1994**, *66*, 1077.
3. Yim, C. T.; Zhu, X. X.; Brown, G. R. *J. Phys. Chem. B* **1999**, *103*, 597.
4. (a) Davis, D. G.; Bax, A. *J. Am. Chem. Soc.* **1985**, *107*, 7197; (b) Bax, A.; Davis, D. G. *J. Magn. Reson.* **1985**, *65*, 355; (c) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199.
5. (a) Hocker, J.; Wendisch, D. *J. Chem. Res. (S)* **1977**, 236; (b) Rivera, A.; Ríos-Motta, J. *Tetrahedron Lett.* **2005**, *46*, 5001; (c) Constantino, M. G.; Lacerda, V., Jr.; da Silva, G. V. J.; Tasic, L.; Rittner, R. *J. Mol. Struct.* **2001**, *597*, 129; (d) Ellinger, Y.; Subra, R.; Berthier, G. *J. Am. Chem. Soc.* **1978**, *100*, 4961.
6. (a) Bauer, C. J.; Freeman, R.; Frenkiel, T.; Keeler, J.; Shaka, A. J. *J. Magn. Reson.* **1984**, *58*, 442; (b) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037.
7. Massie, S. N., U.S. Patent 3,914,307, 1975.
8. Eldin, S.; Digits, J. A.; Huang, S.-T.; Jencks, W. P. *J. Am. Chem. Soc.* **1995**, *117*, 6631.