

Nitrogen-15 Studies of the Mechanisms of Acetolyses of Hexamethylenetetramine and 3,7-Diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane (DAPT)

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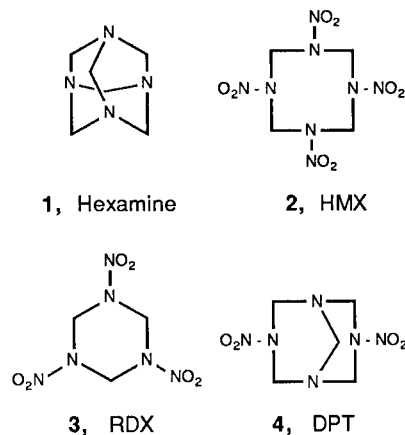
Received September 26, 1986

[$^{15}\text{N}_4$]-Hexamethylenetetramine (Hexamine), and [$^{15}\text{N}_4$]-3,7-diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane (DAPT) have been prepared starting from $^{15}\text{NH}_3$. Synthetic acetolysis reactions were performed using mixtures of pure [$^{15}\text{N}_4$]- and [$^{14}\text{N}_4$]-compounds and the destination of the nitrogen isotopes in the products was determined mass spectrometrically. The results show that relatively little isotopic mixing occurs in the acetolysis of hexamine to DAPT though the formation of some products with isotopic composition [$^{14}\text{N}_3^{15}\text{N}_1$] and [$^{14}\text{N}_1^{15}\text{N}_3$] indicates limited ring cleavage. However the more severe conditions used in the formation of 1,3,5-triacetyl-1,3,5-triazacyclohexane (TRAT) give rise to considerable isotopic scrambling. The acetolysis of DAPT to give 1,3,5,7-tetraacetyl-1,3,5,7-tetraazacyclooctane occurs by selective cleavage of the methylene bridge.

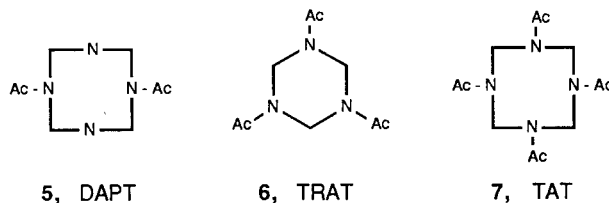
J. Heterocyclic Chem., **24**, 1163 (1987).

Bachmann and co-workers [1-3] showed that the nitrolysis of hexamethylenetetramine (hexamine) (1) with ammonium nitrate, nitric acid and acetic anhydride produced mixtures of the powerful explosives 1,3,5,7-tetra-nitro-1,3,5,7-tetraazacyclooctane (HMX) (2), and 1,3,5-tri-nitro-1,3,5-triazacyclohexane (RDX) (3). Mechanisms postulated [1-5] for these reactions include the selective cleavage of hexamine, or the total cleavage to simple molecules followed by nitration and recombination. Evidence for the latter pathway has been adduced from studies using ^{14}C and ^{15}N isotopes as tracers [6,7]. The ^{14}C work showed that nitration to give 2 and 3 involved complete non-selective degradation of hexamine to fragments containing chemically equivalent methylene groups, and that methylene groups derived from paraformaldehyde could enter into a common pool with those from hexamine for the formation of the final products. However it was found that isotopic carbon exchange between unreacted hexamine and paraformaldehyde did not occur during nitration [6]. The use of $^{15}\text{NH}_4\text{NO}_3$ established the possibility of exchange of the amino nitrogens with hexamine during nitration [2,7]. The tracer studies also showed that the formation of 2 from 3,7-dinitro-1,3,5,7-tetraazabicyclo[3.3.1]nonane (DPT) (4) involved extensive decomposition rather than the simple cleavage of the methylene bridge.

Recently methods for the preparation of HMX from hexamine have been reported [8] involving acetylation followed by nitrolysis. Hence there is current interest in acetolysis reactions. Following initial reports [4,9] that reaction of hexamine with acetic anhydride produced



3,7-diacetyl-1,3,5,7-tetraazabicyclo[3.3.1]nonane (DAPT) (5), efficient methods for the synthesis of DAPT and of 1,3,5-triacetyl-1,3,5-triazacyclohexane (TRAT) (6) have been found. Thus DAPT is formed [10] in high yield when the reaction is carried out at 10° in the presence of water and with the addition of either sodium hydroxide or of ammonium acetate. The production of TRAT is favoured [11] by high temperature and anhydrous conditions. Acetylation [8] of DAPT produces 1,3,5,7-tetraacetyl-1,3,5,7-tetraazacyclooctane (TAT) (7).



We have previously [12] examined the acid-base behaviour and decomposition reactions of hexamine and its acetylated derivatives in aqueous acid. We report here studies of the mechanisms of acetylation using ^{15}N compounds. The experiments were designed to assess the extent of ring-cleavage occurring during acetylation reactions. Our general strategy was to prepare starting materials containing *ca* 100% ^{15}N and to carry out synthetic reactions on mixtures of pure ^{15}N and ^{14}N compounds. The destination of the isotopes in the isolated products was determined mass-spectrometrically. The results discussed below show, in contrast to the tracer studies of nitrolysis [6,7], that only limited ring-cleavage occurs during acetolysis.

EXPERIMENTAL

Gaseous $^{15}\text{NH}_3$ was obtained from Amersham International (isotopic abundance 98%). Reaction with aqueous formaldehyde solution produced ^{15}N -Hexamine which was concentrated under reduced pressure [13]. Excess formaldehyde was converted to paraformaldehyde and removed by filtration, leaving a solution of hexamine which was evaporated under reduced pressure. The 2% abundance of $^{14}\text{NH}_3$ will lead to the formation of a product with isotopic composition of *ca* 92% [$^{15}\text{N}_4$]-Hexamine and 8% [$^{15}\text{N}_3$][$^{14}\text{N}_1$]-Hexamine. DAPT was prepared from this product by reaction with acetic anhydride in the presence of aqueous sodium hydroxide at 10° using the same conditions precisely as used by Siele, Warman and Gilbert [10].

Mass spectrometric measurements were made with a 7070E instrument from V. G. Analytical Ltd. Measurements were made using two methods of ionisation, Electron Impact and Chemical Ionisation. In Electron Impact the molecular ion was monitored (mass *M*); measurements here were made with sufficiently low pressures of sample to avoid self-protonation. Chemical ionisation using *iso*-butane as reagent gas gave rise to the protonated species, (*M* + 1) $^+$. When this technique was used we quote results in terms of the parent species whose mass, *M*, is one unit smaller than that observed.

In Table 1 we give results for compounds prepared with nitrogen in natural abundance (^{14}N 99.63%, ^{15}N 0.37%). The peaks with masses *M* + 1 and *M* + 2 are due to naturally occurring ^{13}C and ^{15}N . Data are also given for hexamine and DAPT prepared from $^{15}\text{NH}_3$. In all cases the intensities of the *M* + 1 and *M* + 2 peaks, relative to *M* = 100, are in satisfactory agreement with those calculated theoretically using known natural abundances. This agreement provides good evidence that our analytical technique is sound.

Table 1

Mass Spectrometric Data for Starting Materials

Compound	Observed Intensities			Theoretical		
	<i>M</i>	<i>M</i> + 1	<i>M</i> + 2	<i>M</i>	<i>M</i> + 1	<i>M</i> + 2
^{14}N -Hexamine	100	11	0.5	100	8	0.3
^{14}N -DAPT	100	13	1.5	100	12	1.0
^{14}N -TRAT	100	13	1.8	100	11	1.2
^{14}N -TAT	100	16	2.3	100	16	1.7
^{15}N -Hexamine	100	6.5	0.2	100	6.7	0.2
^{15}N -DAPT [a]	100	10.3	1.0	100	10.1	1.0

[a] An *M*-1 peak, relative intensity 8, is observed corresponding to DAPT with isotopic composition [$^{15}\text{N}_3$][$^{14}\text{N}_1$].

Preparative Experiments Using Mixtures of 'Pure' ^{14}N and ^{15}N Starting Materials.

Seven separate experiments were performed using mixtures of starting materials containing nitrogen isotopes in natural abundance (designated ^{14}N material) with materials derived from 98% $^{15}\text{NH}_3$ (designated ^{15}N material). The products, which had in all cases physical properties in good agreement with published data, were monitored by mass spectrometry. The raw data were corrected for *M* + 1 and *M* + 2 peaks due to ^{13}C in natural abundance. The data reported give the relative absolute abundances of ^{14}N and ^{15}N in the products. Values given are accurate to ± 5 units.

a) DAPT from ^{14}N -Hexamine and ^{15}N -Hexamine in Acetic Anhydride and Water.

To a mixture of ^{14}N -hexamine (0.5 g) and ^{15}N -hexamine (0.42 g) [overall atomic ratio $^{14}\text{N}:^{15}\text{N} = 100:78$] with water (0.5 g) was slowly added acetic anhydride (2 g) with stirring and cooling to 10° . The mixture was stirred at 10° for 30 minutes and then evaporated. The crude DAPT which separated was recrystallised twice from acetone. Mass spectroscopic data are in Table 2.

b) DAPT from ^{14}N -Hexamine and ^{15}N -Hexamine with Acetic Anhydride and Aqueous Sodium Hydroxide.

The method given in reference [10] was applied to a mixture of ^{14}N -hexamine (0.5 g) and ^{15}N -hexamine (0.42 g) [overall atomic ratio $^{14}\text{N}:^{15}\text{N} = 100:78$]. Mass spectroscopic data for the separated DAPT are in Table 2.

c) DAPT from ^{14}N -Hexamine and ^{15}N -Hexamine using Acetic Anhydride and Ammonium Acetate [10].

To a mixture of ^{14}N -hexamine (0.5 g, 3.6 mmoles), ^{15}N -hexamine (0.42 g, 2.9 mmoles) and ^{14}N -ammonium acetate (0.22 g, 2.9 mmoles) with water (0.5 g) was slowly added acetic anhydride (2 g) with stirring at 10° . The mixture was stirred at 10° for 30 minutes and evaporated to yield DAPT which was recrystallised twice from acetone. [Overall atomic ratio $^{14}\text{N}:^{15}\text{N} = 100:65$]. Mass spectroscopic data are in Table 2.

d) DAPT from ^{15}N -Hexamine and ^{14}N -Ammonium Acetate using Acetic Anhydride.

The method used in c) was applied to a mixture of ^{15}N -hexamine (0.42 g, 2.9 mmoles) and ^{14}N -ammonium acetate (0.28 g, 3.6 mmoles); overall atomic ratio $^{14}\text{N}:^{15}\text{N} = 34:100$.

Table 2

Relative Isotopic Composition of DAPT Prepared in Experiments (a)-(d)

Experiment	[$^{14}\text{N}_4$]	[$^{14}\text{N}_3, ^{15}\text{N}_1$]	[$^{14}\text{N}_2, ^{15}\text{N}_2$]	[$^{14}\text{N}_1, ^{15}\text{N}_3$]	[$^{15}\text{N}_4$]
a)	100	47	15	41	68
b)	100	45	<5	43	78
Random [a]	100	320	380	194	37
c)	100	46	12	42	58
d)	11	9	4	26	100

[a] This is the relative distribution of isotopes expected for a random distribution with the starting composition used in a) and in b).

e) Hexamine Recovered from Reaction of ^{14}N -Hexamine and ^{15}N -Hexamine with Acetic Anhydride and Water.

To a mixture of ^{14}N -hexamine (0.5 g) and ^{15}N -hexamine (0.42 g) [overall atomic ratio $^{14}\text{N}:^{15}\text{N} = 100:78$] with water (0.5 g) was slowly added acetic anhydride (0.7 g) with stirring at 10° . The solution was stirred at 10° for 30 minutes and then evaporated. In this case insufficient acetic anhydride was present for complete reaction and hexamine was separated from the residue and purified by crystallisation from acetone, in which it is less soluble than is DAPT. Mass spectrometry gave the

following relative isotopic abundances for the separated hexamine, [$^{14}\text{N}_4$] 100; [$^{14}\text{N}_3, ^{15}\text{N}_1$] 6; [$^{14}\text{N}_2, ^{15}\text{N}_2$] 11; [$^{14}\text{N}_1, ^{15}\text{N}_3$] 7; [$^{15}\text{N}_4$] 72.

f) TAT from ^{14}N -DAPT and ^{15}N -DAPT.

A mixture of ^{14}N -DAPT (0.5 g) containing nitrogen isotopes in natural abundance and ^{15}N -DAPT (0.5 g) [overall atomic ratio $^{14}\text{N}:^{15}\text{N} = 100:93$] was heated with acetic anhydride for 3 hours at 110° to yield TAT as described previously [8]. The relative isotopic abundances in the separated TAT were, [$^{14}\text{N}_4$] 100; [$^{14}\text{N}_3, ^{15}\text{N}_1$] 11; [$^{14}\text{N}_2, ^{15}\text{N}_2$] 5; [$^{14}\text{N}_1, ^{15}\text{N}_3$] 5; [$^{15}\text{N}_4$] 93.

g) TRAT from ^{14}N -Hexamine and ^{15}N -Hexamine using Acetic Anhydride.

^{14}N -Hexamine (0.5 g) and ^{15}N -hexamine (0.42 g) [overall atomic ratio $^{14}\text{N}:^{15}\text{N} = 100:78$] were reacted with excess acetic anhydride at 98° as described in the literature [11]. The TRAT produced had the isotopic composition given in Table 3.

Table 3

Relative Isotopic Composition of TRAT Prepared from ^{14}N -Hexamine and ^{15}N -Hexamine

	[$^{14}\text{N}_3$]	[$^{14}\text{N}_2, ^{15}\text{N}_1$]	[$^{14}\text{N}_1, ^{15}\text{N}_2$]	[$^{15}\text{N}_3$]
Experimental	100	125	84	63
Calculated for Random distribution	100	237	185	47

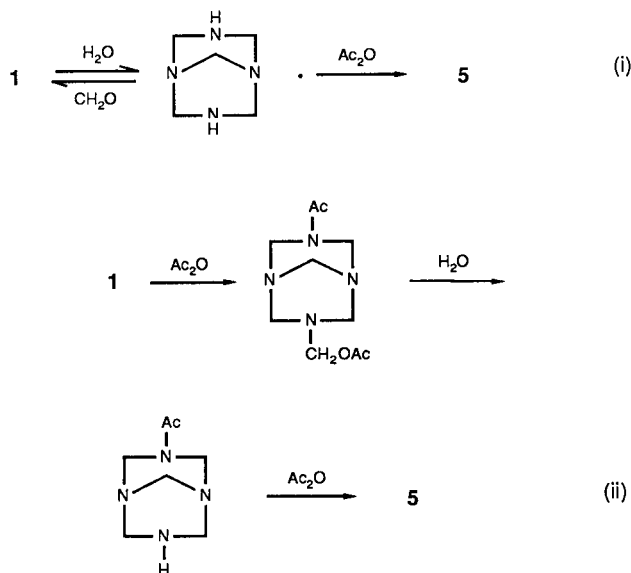
Discussion.

Formation of DAPT from Hexamine.

We prepared DAPT from hexamine by reaction with acetic anhydride in the presence of water at 10° using known methods [10]. The results in Table 2 for experiments a-d) indicate that relatively little isotopic mixing has occurred. The most abundant species are those containing the isotopically pure [$^{15}\text{N}_4$] and [$^{14}\text{N}_4$] compositions. For complete isotopic scrambling the species containing mixtures of isotopes would be most abundant. The behaviour during acetolysis thus contrasts markedly with that found during nitrolysis [6,7] when complete randomisation of isotopes was observed.

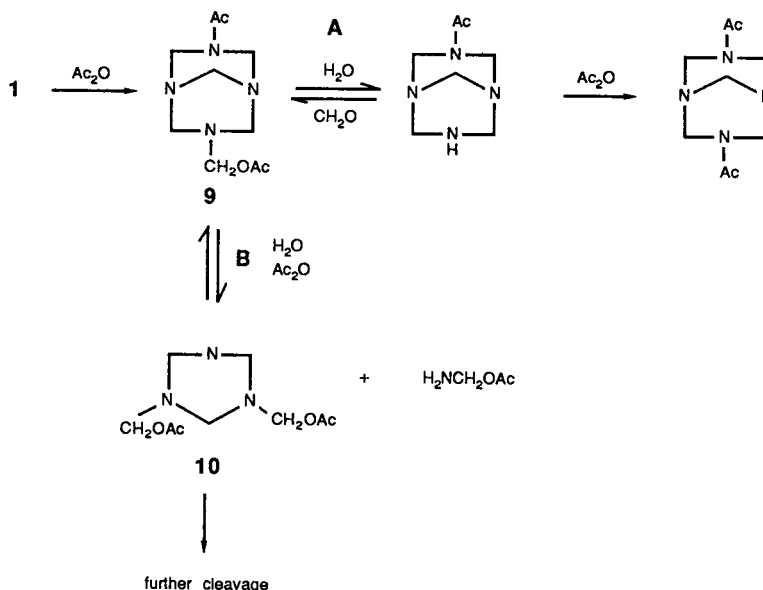
Mechanisms proposed for the formation of DAPT from hexamine include [10] elimination of formaldehyde to give **8** which is acetylated, equation (i), and [14] initial acetylation followed by expulsion of formaldehyde and further acetylation equation (ii). Our isotopic measurements do not distinguish between these mechanisms. However we favour (ii) since it is known [12] that hexamine reacts very readily with acetylation agents and also that the decomposition of hexamine occurs very slowly in the presence of aqueous hydrochloric acid where **8** would be protonated and reversal to **1** unlikely. The latter suggests that concentrations of **8** are likely to be too low to account for the observed reaction.

Nevertheless our results indicate the formation of significant quantities of DAPT containing a 3:1 isotopic ratio. The slightly higher ratio of [$^{14}\text{N}_1, ^{15}\text{N}_3$]/[$^{15}\text{N}_4$] than of [$^{14}\text{N}_3, ^{15}\text{N}_1$]/[$^{14}\text{N}_4$] can be attributed to the presence in the starting material of a little [$^{14}\text{N}_1, ^{15}\text{N}_3$]-hexamine (8%



relative to $^{15}\text{N}_4$). The presence of the mixed products indicates that a certain amount of ring cleavage is occurring. Possibilities are i) exchange of nitrogen between hexamine molecules before acetolysis or ii) exchange during acetolysis, and we consider these in turn. Bachmann and co-workers [2] showed that in acetic acid at 65° slow exchange occurred between ^{14}N -hexamine and ^{15}N -ammonium nitrate (*ca* 15% exchange after 15 minutes). Under nitrolysis conditions exchange is rapid [7]. However our conditions of temperature, 10° , and acidity are far less severe and the observation, experiment e), that little isotopic scrambling has occurred in hexamine recovered during the reaction indicates that it is unlikely that significant exchange is occurring between hexamine molecules. Hence we conclude that it is likely that some exchange is occurring during acetolysis. This might involve the extrusion of ammonia. If this were the case then in experiment c) where the reaction mixture initially contains added ^{14}N -ammonium ions (which would be in rapid equilibrium with extruded ammonia) we would expect to observe a high ratio of [$^{14}\text{N}_1, ^{15}\text{N}_3$]/[$^{14}\text{N}_3, ^{15}\text{N}_1$] products. This follows since the ammonia recombining to form the product would contain almost exclusively ^{14}N . The result in Table 2 negates this hypothesis. A possible mechanism for the partial isotopic scrambling observed might involve extrusion of a solvolysed imine. We have no direct evidence for such a mechanism, but that proposed tentatively in Scheme 1 would allow for the formation of some product containing 3:1 isotopic ratio. Here cleavage of **9** by paths **A** or **B** will involve proton transfer from the solvent to nitrogen followed by, or synchronous with, N-C bond cleavage. Recombination of **10** with solvolysed imine, protected from acetylation by protonation, allows for the observed isotopic exchange. Experimentally it is found

Scheme 1



[10] that addition of ammonium ions results in yields of DAPT greater than 100% based on hexamine, and it has been postulated that the liberated formaldehyde combines with the ammonia to reform hexamine. Our result, experiment d), involving acetylation of ^{15}N -hexamine in the presence of ^{14}N -ammonium acetate is in accord with this hypothesis in that some [$^{14}\text{N}_4$]-DAPT is produced. Further the formation, on a statistical basis, of a relatively large amount of the [$^{14}\text{N}_4$]-DAPT indicates that equilibration of **9** and **10** has reached a fairly advanced stage before extrusion of formaldehyde so that hexamine reformation occurs essentially subsequent to the initial [$^{15}\text{N}_4$]-DAPT formation.

Formation of TAT from DAPT.

The result, experiment f) showing that very little isotopically mixed product is formed during the acetolysis of DAPT to TAT indicates that selective cleavage of the methylene bridge occurs here, in accord with NMR studies [15].

Formation of TRAT from Hexamine.

TRAT was produced [11] by reaction of hexamine with excess acetic anhydride at 98° . The isotopic distribution in the separated product, shown in Table 3, indicates that considerable scrambling has occurred, although there is not complete randomisation. It is possible that due to the much higher temperature used in this experiment exchange of nitrogen occurs in partially cleaved hexamine molecules before acetolysis. However we think that this is probably less likely than exchange during acetolysis. Further cleavage of an intermediate such as **10** followed by

recombination of molecules containing two nitrogen atoms with those containing one nitrogen atom would account for the observed isotopic distribution.

Conclusion.

The conclusion drawn from our experiments and related work [10,11,14] is that formation of DAPT from hexamine is favoured by mild conditions and involves little ring-cleavage. When more extreme conditions are used extensive ring-cleavage occurs promoting formation of TRAT. It is also noteworthy that, in agreement with Scheme 1, the formation of DAPT is favoured by the presence of water. The ^1H nmr measurements [14,16] show that in glacial acetic acid in the absence of water the formation of TRAT is favoured and little DAPT is formed.

Our results indicating that under mild conditions little isotopic mixing occurs in acetolysis reactions contrast with those observed during nitrolysis reactions [6,7]. The conditions used in the reported nitrolyses were, of course, much more severe involving higher acidities and higher temperatures; here the results of ^{14}C and ^{15}N tracer studies [6,7] indicate extensive ring-cleavage to low molecular weight species which then recombine to form products. The intermediacy of $\text{HOCH}_2\text{NHNO}_2$ as a precursor to HMX and RDX was postulated in these systems.

Acknowledgement.

This work has been carried out with the support of the Procurement Executive, Ministry of Defence, U. K.

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