The Acid–Base Behaviour of Hexamine and its N-Acetyl Derivatives

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The protonation equilibria and decomposition reactions in aqueous hydrochloric acid of hexamine and its acylated derivatives (2), (3), and (4) have been examined by u.v. and ^{1}H n.m.r. spectroscopy. pK_a Values at 25 °C are: hexamine 4.89, 3,7-diacetyl-1,3,5,7-tetra-azabicyclo[3.3.3.1]nonane (DAPT) 0.7, 1,3,5,7-tetra-acetyl-1,3,5,7-tetra-azacyclo-octane (TAT) −2.5, and 1,3,5-triacelyl-1,3,5-triaza cyclohexane (TRAT) −2.3. Rates of decomposition of the protonated substrates decrease in the order DAPT > TAT > hexamine.

Reaction of hexamine with picryl acetate may involve nucleophilic catalysis *via* the N-acetylhexaminium cation (6).

Hexamine (hexamethylenetetramine) (1) has wide synthetic applications and is the starting point for preparations of the explosives HMX (1,3,5,7-tetranitro-1,3,5,7-tetra-azacyclo-octane) and RDX (1,3,5-trinitro-1,3,5-triazacyclohexane).[1] Recently preparations of HMX have been reported which are based on the initial acetolysis of hexamine followed by nitrolysis.[2] It is known[3,4] that, under appropriate conditions, acetolysis may yield DAPT (3,7-diacetyl-1,3,5,7-tetra-aza-bicyclo[3.3.1]nonane) (2), TAT (1,3,5,7-tetra-acetyl-1,3,5,7-tetra-azacyclo-octane) (3), or TRAT (1,3,5-triacetyl-1,3,5-triazacyclohexane) (4). Yields in the acetolysis and nitrolysis reactions are affected by the acidity of the medium.

Tada, in an early study,[5] followed the decomposition of hexamine in aqueous acid by titration of the unreacted acid. In this paper we examine the acid–base behaviour of hexamine and its N-acetyl derivatives. We have included u.v. and n.m.r. methods in the examination of the initial reversible protonation of the substrates and the kinetics of the subsequent decomposition reactions. Some results are also reported for reactions of substrates (1) and (2) with picryl acetate.

Experimental

Hexamine was a commercial specimen. DAPT was prepared by the method of reference 4; recrystallisation from acetone yielded a white crystalline solid, m.p. 195—198 °C (lit.,[4] 195—198 °C). TAT was prepared from DAPT by the method of reference 2; trituration with ethanol gave crystals, m.p. 153—158 °C (lit.,[2] 157—158 °C). 1,3,5-Triacetyl-1,3,5-triazacyclohexane was prepared by the method of reference 3 to give the hydrated form (m.p. 71.5—73.5 °C); recrystallisation from anhydrous ethanol gave anhydrous crystals, m.p. 93—95 °C (lit.,[3] 93—96 °C). Picryl acetate was prepared[6] from picric acid and acetic anhydride in the presence of perchloric acid; recrystallisation from light petroleum gave crystals, m.p. 96 °C (lit.,[6] 96 °C). Heating paraformaldehyde and acetamide in a 1:1 molar ratio at 120 °C in an autoclave for 10 h gave[7] a clear liquid containing N-acetylaminomethanol (MeCONHCH$_2$OH).

U.v.-visible measurements were made with a Pye Unicam SP8-100 instrument. Kinetic and equilibrium measurements were made at 25 °C using freshly prepared solutions of reagents; kinetics were in all cases run under first-order conditions and rate coefficients were determined by standard methods. ^{1}H N.m.r. spectra were recorded with a Varian EM360L instrument using TMS or DSS as internal reference.

*U.v. Data.*—We find that in water DAPT has λ_{max} 192 nm, ε 2.1 × 10^4, and TAT has λ_{max} 196 nm, ε 4 × 10^4. Values of

Table 1. Values of extinction coefficients (l mol^{-1} cm^{-1}) in water at 25 C

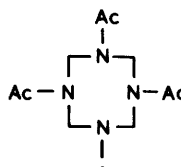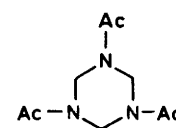|	Wavelength (nm)			
	200	210	220	230
Hexamine	1 000	350	45	4
Hexamine hydrochloride		100	40	
DAPT	16 000	8 000	4 000	1 200
TAT	30 000	13 000	3 000	800
TRAT		10 000	2 000	450
Acetamide	800	150	50	10
Acetic acid		50	30	6
Hydrochloric acid	25	1	0.3	
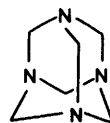
(1) Hexamine
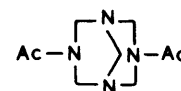
(2) DAPT

(3) TAT

(4) TRAT

extinction coefficients at wavelengths 200—230 nm for starting materials and other species which may be present in reacting solutions are shown in Table 1.

Formaldehyde and ammonium acetate do not show significant absorption above 200 nm. For all measurements involving hydrochloric acid the reference cell contained acid of the appropriate concentration.

Determination of Formaldehyde.—This was done by precipitation as the dimedone derivative.[8] In a control experiment it was found that reaction of 2.9 mmol of formaldehyde with an excess of dimedone in water gave, after drying, 3.0 mmol of the adduct. The formaldehyde released by reaction of DAPT and TAT in aqueous acid was determined in this way. In a typical experiment, a known concentration of DAPT was made up in

1M hydrochloric acid at 25 °C and left standing for a given time, after which it was neutralised to pH 5—7 with aqueous sodium hydroxide solution and added to an excess of dimedone in water. The mixture was left for 15 min. The resulting precipitate was filtered, dried under vacuum, and weighed.

pK_a *Value for Hexamine.*—The pH values were determined after the addition of known volumes of 0.1M hydrochloric acid solution to 50 cm^3 of 0.01M hexamine in water at 25 °C. Treatment of the data according to the method of Albert and Serjeant[9] gave a value of pK_a 4.89 ± 0.03. In a second experiment, an excess of acid was added to attempt diprotonation. However, pH measurements indicated that no depletion of acid concentration, beyond that required for mono-protonation, occurred in solutions containing ≤0.1M acid. We can estimate that for diprotonation, $pK_{a,2} < 2$.

Results and Discussion

Literature values for the pK_a of hexamine are 6.30 at 25 °C (ref. 10), 5.18 at 45 °C (ref. 5), and 4.86 at 25 °C (ref. 11). Our value of 4.89 ± 0.03, obtained by potentiometric titration, is in good agreement with the latter value. Although a considerably weaker base than 1-aza-,1,3-diaza-or 1,3,5-triaza-adamantane,[11] hexamine will be nearly completely protonated in dilute acid solution. [1]H N.m.r. measurements, taken in deuterium oxide to minimize the effects of solvent absorption, show a band at δ 4.70 for hexamine which shifts progressively to lower field as the concentration of deuterium chloride is increased and reaches a value of δ 5.0, corresponding to the deuteronated species, in a solution of molar ratio of 1:1 hexamine:DCl. Similarly, a solution, in deuterium oxide, of the salt hexamine hydrochloride gives a band at δ 5.0 for the methylene protons of the proto-nated form. In agreement with Tada,[5] who found a value of 6.05 × 10^{-6} s^{-1} for the decomposition of the protonated form in water at 30 °C, n.m.r. spectra show that little decomposition of the salt occurs over several days.

In more concentrated acid, the band due to methylene protons shifts further downfield, reaching a position of δ 5.45 corresponding to the dideuteronated species. A single band is observed, indicating rapid equilibration of deuterons between the four nitrogen atoms. Use of the D_o''' acidity function, assumed equal to the H_o''' function,[12–14] yields in Table 2 a value of $pK_{a,2}$ −1.25 ± 0.25 for the dideuteronated acid. The dissociation constant of the diprotonated acid is expected[14] to be ca. 2—3 times larger than that of the dideuteronated acid, leading to a value of $pK_{a,2}$ −1.7 ± 0.3 for diprotonated hexamine in water.

N.m.r. measurements of the decomposition reaction in 6.6M deuterium chloride in deuterium oxide show the formation of a series of four bands between δ 4.7—5.0. These are likely to result from the formation of formaldehyde and NCH_2O and/or NCH_2N species[15] which may be protonated in strongly acidic media.

DAPT.—The diacetyl derivative (2) is a considerably weaker base than hexamine and potentiometric measurements indi-cated negligible protonation in 0.01M aqueous acid. However, u.v. measurements were effective in determining the protonation equilibrium and following the decomposition reaction. Meas-urements at 230 nm in 0—1M aqueous hydrochloric acid showed that the initial absorption decreased with increasing acid concentration, and that the remaining absorption slowly faded. The first of these effects is attributed to protonation [equation (1)]. The acidity of the medium is best described by an acidity function.[12] In these fairly dilute solutions the various acidity functions for hydrochloric acid do not deviate markedly. However, since, as will be discussed later, protonation occurs on a tertiary nitrogen atom of DAPT, the H_o''' function is most appropriate.[12,13] Hence we define the equilibrium constant, K, for protonation by equation (2). The data in Table 3 give a value

$$DAPT + H^+ \rightleftharpoons DAPT \cdot H^+ \qquad (1)$$

$$K = \frac{[DAPT \cdot H^+]}{[DAPT]h_o'''} \qquad (2)$$

for K of 5.5 ± 1 l mol^{-1}. Rate coefficients for the slow fading reaction increase with increasing acidity but reach a limiting value at around 1M acid. This behaviour is best interpreted in terms of rate-determining decomposition of the protonated substrate, equation (3), which leads to equation (4). The slow step will probably involve some measure of solvent assistance. The data in Table 3 give a good fit with equation (4) with values

$$DAPT + H^+ \xrightarrow{K} DAPTH^+ \xrightarrow{k} products \qquad (3)$$

$$k_{obs.} = \frac{kKh_o'''}{1 + Kh_o'''} \qquad (4)$$

of k (9 ± 1) × 10^{-4} s^{-1}, and K 5 l mol^{-1}. The values of K obtained from the equilibrium and kinetic measurements are in

Table 2. [1]H N.m.r. shifts corresponding to the conversion of mono-deuteronated hexamine[a] into the dideuteronated form in deuterium oxide

[DCl]/M	[DCl]$_{Free}$/M	D_o'''[c]	δ[d]	$pK_{a,2}$[e]
0.3	0.1		5.00	
1.0	0.78		5.05	
1.5	1.26	−0.55	5.10	−1.1
2.0	1.73	−0.87	5.15	−1.2
3.0	2.70	−1.41	5.23	−1.4
4.0	3.64	−1.89	5.35	−1.3
6.6	6.21	−3.06	5.43	
11.4[b]	11.0[b]		5.45	

[a] Stoicheiometric concentration of hexamine is 0.20M. [b] This measure-was made in hydrochloric acid in water. [c] From ref. 13 the assumption is made that in these solutions values for D_o''' are equal to values for H_o''', see ref. 14. [d] [1]H N.m.r. shifts of methylene protons. [e] Calculated as $D_o''' + \log_{10}(\delta - 5.00)/(5.45 - \delta)$.

Table 3. Equilibrium and rate data for reaction of DAPT (6 × 10^{-4}M) with hydrochloric acid in water at 25 °C

[HCl]/M	h_o'''[a]	Absorbance[b] (230 nm)	K^c/l mol^{-1}	$10^4 k_{obs.}$/s^{-1}	$10^4 k_{calc.}^d$/ s^{-1}
0		0.75			
0.050	0.050	0.65	5.6		
0.075	0.077	0.60	6.3		
0.10	0.105	0.57	6.1	3.2	3.1
0.15	0.17	0.55	4.5		
0.20	0.23	0.50	5.2	4.8	4.8
0.25	0.29	0.45	6.5		
0.30	0.34			5.6	5.7
0.40	0.49			6.4	6.4
0.50	0.69			6.7	7.0
0.70	1.12			8.1	7.6
0.80	1.41			8.5	7.9
0.90	1.78	0.33		8.2	8.1
∞		0.29			

[a] $h_o''' \equiv$ antilog $(-H_o''')$ from ref. 13. [b] Initial value, before fading reaction. [c] K calculated as $(A_o − A)/h_o'''(A − A_x)$. [d] Calculated from equation (4) with k 9 × 10^{-4} s^{-1}, and K 5 l mol^{-1}.

Table 4. Rate coefficients for the decomposition of DAPT in deuterium oxide containing deuterium chloride at 25 °C

[DCl]/M	d_o'''	$10^4 k_{obs.}/s^{-1}$	$10^4 k_{calc.}^a/s^{-1}$
0.030	0.030	2.5	2.9
0.060	0.061	4.7	4.6
0.10	0.105	6.0	6.0
0.30	0.34	8.2	8.3
0.50	0.69	8.9	9.0
0.60	0.90	9.2	9.2
0.90	1.78	9.5	9.6

[a] Calculated from equation (4) with k 1×10^{-3} s^{-1} and K 14 l mol^{-1}.

Table 5. Production of formaldehyde from DAPT in aqueous hydrochloric acid, 1M, at 25 °C

Time/s	Mols of formaldehyde[a] produced per mol of DAPT	$10^4 k_{obs.}^b/s^{-1}$
300	0.8 ± 0.2	11
600	1.2	9
1 200	1.7	8
7 200	2.8	8

[a] Determined by precipitation as the dimedone adduct. [b] Using an 'infinity value' of 2.8 mol of formaldehyde.

reasonable agreement and lead to a pK_a value for DAPT of 0.7 ± 0.1.

We also measured the rate of the fading reaction in deuterium oxide containing deuterium chloride. It is known [12,14] that in dilute solutions the acidity functions for hydrochloric acid in water and deuterium chloride in deuterium oxide are identical. The values in Table 4 yield a value for k of $(1 ± 0.1) \times 10^{-3}$ s^{-1} which is identical, within experimental error, with the value obtained in water. The value for K of 14 ± 1 l mol^{-1}, yielding a pK_a value in D$_2$O of 1.15 ± 0.05, is ca. 3 times higher than the value in water. This result showing the higher basicity for DAPT in deuterium oxide than in water is in accord with literature values [14,16] for other nitrogen bases, and provides further evidence for the mechanism shown in equation (3).

We expected that the decomposition reaction of DAPT in aqueous acid would produce formaldehyde, and in an experiment with 1M hydrochloric acid precipitated the liberated formaldehyde as the dimedone adduct.[8] This method of analysis is less accurate than the spectrophotometric measurements, but the data in Table 5 indicate that, after 2 h, 3 mol of formaldehyde had been produced per mol of DAPT at a rate compatible with the result in Table 2.

Further information regarding the decomposition products was obtained from ^{1}H n.m.r. measurements in D$_2$O. The spectrum of DAPT shows bands at δ 2.1 (s, acetyl), and 4.4 (s, CH$_2$ bridge), with two AB quartets (J 13 Hz) due to CH$_2$ protons with shifts of 4.3 and 5.6, and 4.9 and 5.1 respectively. The spectrum has been analysed previously[17] on the basis of restricted rotation about the N–C bonds of the acetyl functions. To test the reversibility of the initial protonation reaction a solution of DAPT in deuterium oxide containing 1M deuterium chloride was allowed to stand for 45 s and was then neutralised with sodium deuterioxide solution; the spectrum of the neutralised solution was that of DAPT. The decomposition of DAPT in 1M deuterium chloride produces three main bands at δ 2.1, 4.5, and 4.8. The latter band (δ 4.8) is at the position expected for formaldehyde hydrate in 1M acid. The band at δ 2.1 is due to an acetyl group and that at 4.5 is at the position expected[15] for NCH$_2$O hydrogens. We find that the spectrum of N-acetyl-aminomethanol (MeCONHCH$_2$OH) in 1M deuterium chloride

Table 6. Protonation of TAT in aqueous hydrochloric acid at 25 C

HCl/mol l^{-1}	$-H_A^a$	Absorbance (220 nm)	$-pK_a^b$
0		0.65	
3.4	1.19	0.65	
5.7	1.92	0.60	2.43
8.0	2.60	0.57	2.80
8.2	2.65	0.55	2.69
8.4	2.70	0.50	2.30
8.6	2.75	0.49	2.25
10.2	3.25	0.47	

[a] From reference 19. [b] $pK_a = H_A + \log_{10}(A_o - A)/(A - A_x)$, with $A_x = 0.44$.

Table 7. Protonation of TRAT in aqueous hydrochloric acid at 25 °C

HCl/mol l^{-1}	$-H_A^a$	Absorbance (230 nm)	$-pK_a^b$
0		0.53	
3.4	1.19	0.53	
5.7	1.92	0.49	2.43
6.8	2.24	0.455	2.34
8.0	2.60	0.405	2.16
9.1	2.91	0.395	2.33

[a] From reference 19. [b] $pK_a = H_A + \log_{10}(A_o - A)/(A - A_x)$ with $A_x = 0.36$.

gives bands at δ 2.1 and 4.5; that is at precisely the positions observed in the decomposition products of DAPT. Hence our data indicate that in 1M acid the stoicheiometry of the decomposition reaction is given by equation (5). The kinetic

$$DAPT \longrightarrow 3CH_2O + 2CH_3CONHCH_2OH \quad (5)$$

data, taken with the failure to observe intermediates other than protonated DAPT, indicate that the initial C–N bond breaking in the protonated substrate is rate determining.

TAT and *TRAT*—In each of these compounds all the nitrogen atoms carry acetyl groups and, in accord with the very weakly basic nature of amides,[18] protonation occurs only in concentrated acid solutions. Measurements, shown in Table 6, of absorbances at 220 nm and use of the H_A acidity scale,[18,19] defined by the protonation of amides, give a value for the pK_a of TAT of −2.5 ± 0.3. In 10.2M acid, where the substrate is largely protonated, the slow decrease in absorbance at 220 nm was used to obtain a value of 2×10^{-5} s^{-1} for the decomposition reaction. The ^{1}H n.m.r. spectrum of TAT in deuterium oxide shows bands at δ 2.25 (acetyl) and 5.1 (methylene). In 6.6M deuterium chloride solution, where TAT will be partially deuteronated, the initial spectrum shows bands at δ 2.35 and 5.2. These bands very slowly decay with time and major bands in the spectrum of the decomposition products are at δ 2.15 and 4.8, attributed to acetic acid and formaldehyde respectively. Treatment with dimedone of a reaction mixture which had been left for ten days and then neutralised indicated the formation of 3.8 ± 0.4 mol of formaldehyde per mol of TAT.

U.v. data for the protonation of (TRAT) are in Table 7 and lead to a pK_a value of −2.3 ± 0.2. The n.m.r. spectrum of (TRAT) in deuterium oxide gives bands at δ 2.25 (acetyl) and 5.3 (methylene) and is similar to that previously reported in deuteriochloroform.[3] The initial spectrum in 6.6M deuterium chloride shows bands at δ 2.35 and 5.4. With time these bands are replaced by a strong band at δ 2.15 attributed to acetic acid

Table 8. Comparison of pK_a values, and rate coefficients for decomposition, of monoprotonated bases in water at 25 °C

|	pK_a	k/s^{-1}
Hexamine	4.89 ± 0.03^a	6×10^{-6} (30 C)^c
	-1.7 ± 0.3^b	
DAPT	0.7 ± 0.1	9×10^{-4}
TAT	-2.5	2×10^{-5}
TRAT	-2.3	not measured

^{a} Monoprotonation. ^{b} Diprotonation. ^{c} From ref. 5.

and bands in the range 4.8—5.0, in which a major absorption at δ 4.8 is attributed to formaldehyde.

Comparison of Hexamine, DAPT, TAT, and TRAT.—The data collected in Table 8 show that DAPT is a considerably weaker base than is hexamine. However the basicity is greater than expected [18] for protonation of an amide function so that structure (5) is indicated. Protonation of TAT and of TRAT must involve the amide group. However, even for amides,[18] these are extremely feeble bases due to the cumulative electron-withdrawing effects of the acetyl groups.

$$Ac-N \underset{L-N-J}{\overset{\underset{\Gamma-N^+}{\overset{H}{\underset{\downarrow}{}}}}{\diagdown}} N-Ac$$

(5)
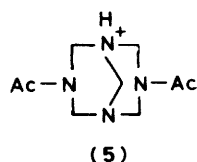
The first-order rate coefficients shown in Table 8 relate to the spontaneous decomposition of the protonated substrates in water. Although protonated hexamine decomposes very slowly in water it should be noted that Tada[6] quotes a value at 30 °C of 6.3×10^{-4} 1 mol^{-1} s^{-1} for acid-catalysed decomposition of protonated hexamine [equation (6)]. Thus in 1M hydrochloric

$$\text{hexamine H}^+ + \text{H}^+ \longrightarrow \text{products} \qquad (6)$$
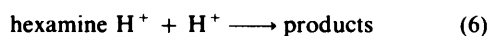
acid the observed rate coefficient for decomposition of hexamine (6.3×10^{-4} s^{-1}) will approach the value observed for DAPT in the same medium. The greater spontaneous reactivity observed for (5) than for the hexaminium cation can be attributed to the electron-withdrawing effect of the N-acetyl groups which encourage solvent-assisted C–N bond fission. Our results show that for DAPT in 1M hydrochloric acid the initial bond-breaking is rate determining in the overall decomposition and leads to the formation after 2 h of formaldehyde and N-acetylaminomethanol [equation (5)]. The latter product is unlikely to be stable indefinitely at this acid concentration.

The initial step in the decomposition of TAT and of TRAT involves cleavage of an N-acetyl bond to produce acetic acid. The slow decomposition observed for TAT is in accord with the low reactivity expected for amides in acidic conditions.[20] In 6.6M acid complete breakdown occurs to yield formaldehyde and acetic acid.

Reaction with Picryl Acetate.—In relation to the formation of DAPT from hexamine we investigated the reaction of hexamine with picryl acetate. This is a very reactive acylating agent and will readily transfer the acyl group with the liberation of picrate ion.[21] Measurements in water at 25 °C in the pH range 2—7 indicated a spontaneous reaction with k_w 4.0 × 10^{-3} s^{-1}. First-order rate coefficients for the formation of picrate in solutions containing hexamine and/or hexaminium chloride are shown in Table 9. They indicate that formation of picrate is accelerated by

Table 9. Rate data for the reaction of hexamine with picryl acetate (4×10^{-5}M) in water at 25 C

[Hexamine]$^a_{stoich}$/ mol l^{-1}	[HCl]$_{stoich}$ mol l^{-1}	$10^3 k^c_{obs.}$/s^{-1}	$10^3 k^d_{calc.}$/s^{-1}
0.025	0.013	7.9	8.0
0.050	0.025	12	12
0.10	0.050	21	21
0.20	0.10	35	38
0.025	0.050	4.1	4.0
0.10	0.20	3.8	4.0
0.20	0.40	4.0	4.0
0.005	0	6.3	5.7
0.010	0	7.6	7.4
0.050	0	24	21
0.10	0	40	38
0.050^b	0	24	
0.10^b	0	43	

^{a} [Hexamine]$_{Free}$ = [Hexamine]$_{stoich}$ − [HCl]$_{stoich}$. ^{b} Solvent is deuterium oxide; $k_{H_2O}/k_{D_2O} = 1.0 \pm 0.1$. ^{c} Measured spectrophotometrically by the formation of picrate at 400 nm. ^{d} Calculated from equation (7) with k_w 4.0 × 10^{-3} s^{-1}, and k_{Hex} 0.34 l mol^{-1} s^{-1}.

Scheme.
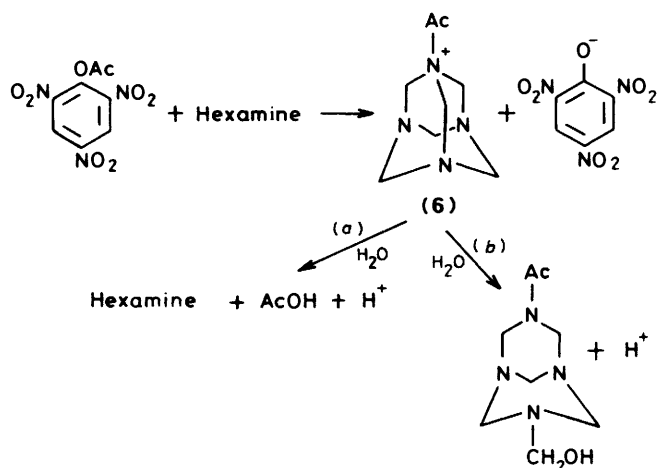
hexamine but that protonated hexamine is unreactive, and accord with equation (7) with k_{Hex} 0.34 l mol^{-1} s^{-1}.

$$k_{obs.} = k_w + k_{Hex}[\text{hexamine}] \qquad (7)$$

In agreement with the very weakly basic nature found for DAPT (Table 7) we find that no acceleration of picrate formation from picryl acetate is observed in solutions containing concentrations up to 0.4 mol l^{-1} DAPT.

Possible modes of action of hexamine in the formation of picrate ions from picryl acetate are: (i) general base catalysis of water attack at the acetyl group, or (ii) direct nucleophilic attack. General base catalysis may be ruled out since the solvent isotope effect (Table 9) of 1.0 ± 0.1 is lower than that required by this mechanism.[22] Hence the reaction is likely to involve formation of the N-acetylhexaminium ion (6), as shown in the Scheme. Our kinetic results do not allow us to determine the fate of the intermediate. Reaction with water might regenerate hexamine [path (a) in the Scheme] to give an example of nucleophilic catalysis.[21] Alternatively, cleavage of an $\overset{+}{N}$–CH$_2$ bond [path (b)] would result in decomposition.

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