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A CALORIMETRIC AND NMR DETERMINATION OF THE MICROSCOPIC PROTONATION CONSTANTS OF SOME *N*-METHYL-SUBSTITUTED α,ω-THIADIAMINES

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ABSTRACT

A method has been developed to calculate the microscopic protonation constants for some asymmetric *N*-methyl-substituted α,ω-thiadiamines, *n*,*m*-(R)(R′)NSN (R = H or CH_3; R′ = CH_3; $n = 2$ or 3 and $m = 2,3$ or 4). The method is based on differences in enthalpies of protonation between the *N*-methyl substituted diamines *n*,*m*-(R)(R′)NSN and their corresponding non-substituted *n*,*m*-NSN analogues. A comparison of the calorimetric microscopic constants with those obtained with the ^{1}H-NMR technique confirms the value of the proposed calorimetric method. The microbasicity of the amino functions follows the sequence: secondary > primary ≫ tertiary.

INTRODUCTION

In previous papers [1] we demonstrated the establishment of a tautomeric protonation equilibrium for asymmetric diamines of the type (R)(R′)–N–$(CH_2)_n$–S–$(CH_2)_m$–NH_2 (R = H or CH_3; R′ = CH_3; $n = 2$ or 3 and $m = 2$, 3 or 4). In some instances the relative concentration of each tautomeric species may be determined from calorimetric [2] or NMR techniques [3].

In this investigation we propose another calorimetric method which is based upon the drastic changes in protonation enthalpy or entropy of the *N*-methyl-substituted diamines in comparison with their non-substituted analogues. The value of the method may be evaluated by comparison with the results obtained from the ^{1}H-NMR method. The latter is based upon the resonance signal from the methyl groups which shows one sharp peak over the whole pH range, indicating a fast equilibrium between the different species. Moreover, the resonance signal is influenced only by changes in the protonation of the nitrogen adjacent to the methyl group. From a chemical shift of the methyl group as a function of pH the relative concentrations of

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TABLE 1

The investigated diamines

Formula	Abbreviation [a]
$CH_3NH(CH_2)_2S(CH_2)_2NH_2$	2,2-(Me)NSN
$CH_3NH(CH_2)_2S(CH_2)_3NH_2$	2,3-(Me)NSN
$CH_3NH(CH_2)_2S(CH_2)_4NH_2$	2,4-(Me)NSN
$(CH_3)_2N(CH_2)_2S(CH_2)_2NH_2$	2,2-(Me_2)NSN
$(CH_3)_2N(CH_2)_2S(CH_2)_3NH_2$	2,3-(Me_2)NSN
$NH_2(CH_2)_2S(CH_2)_3N(CH_3)_2$	2,3-NSN(Me_2)
$(CH_3)_2N(CH_2)_3S(CH_2)_3NH_2$	3,3-(Me_2)NSN

[a] See ref. 1(a).

each tautomeric species or the microconstants may be calculated [4]. Table 1 lists the diamines investigated.

EXPERIMENTAL

Reagents

The syntheses of the *N*-methyl-substituted diamines have been described in a previous paper [1a]. Solutions of the amines, potassium hydroxide and nitric acid were prepared and standardized following the normal procedure [1]. All solutions were made up to an ionic strength of 0.5 with KNO_3.

NMR study

NMR spectra were recorded on a 90 MHz HFX-5 Bruker spectrometer. TMS was used as an external standard. Sample tubes were rotated at a speed of about 4500 rpm. The sample temperature was $25 \pm 1°C$. Shifts were recorded in Hz units. The reproducibility was estimated to be better than 0.2

TABLE 2

Resonance frequency shift [a] of fully deprotonated (Δ_b) and protonated (Δ_a) diamines

Diamine	Δ_b	Δ_a
2,2-(Me_2)NSN	237.1	300.1
2,3-(Me_2)NSN	239.6	303.5
2,3-NSN(Me_2)	236.5	298.7
3,3-(Me_2)NSN	237.0	301.0

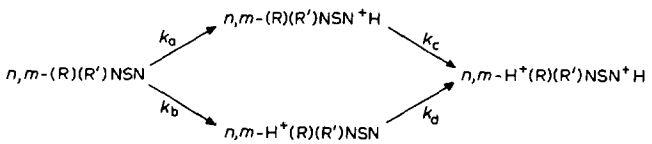
[a] In Hz vs. TMS.

Hz. The NMR study has been restricted to the asymmetric disubstituted diamines n,m-(Me_2)NSN. For each of these diamines 10–15 solutions were prepared with an amine concentration of about 0.06 M. To these solutions a varying amount of standardized 0.5 M HNO_3 was added to yield the amine in different degrees of protonation. In order to obtain respectively the fully protonated and the fully deprotonated diamine, the first solution contained a slight excess of HNO_3 whereas the last solution contained an excess of KOH. The resonance frequently shifts of the fully protonated and deprotonated diamines are summarized in Table 2.

CALCULATIONS

Calorimetric method

The protonation constants at each protonation stage (K_1, K_2) and their corresponding thermodynamic functions, reported in some previous papers [1], are summarized in Table 3. Because of the existence of two tautomeric forms (see scheme 1), these constants are mixed constants.



Scheme 1

The microconstants (k_a, k_b, k_c and k_d) are related to the mixed macroconstants by the expressions

$$K_1 = \frac{\{n,m\text{-}^{+}\mathrm{H(R)(R')NSN}\} + \{n,m\text{-(R)(R')NSN}^{+}\mathrm{H}\}}{\{\mathrm{H}^{+}\}\{n,m\text{-(R)(R')NSN}\}} = k_a + k_b \qquad (1)$$

$$\frac{1}{K_2} = \frac{\{\mathrm{H}^{+}\}\{n,m\text{-}^{+}\mathrm{H(R)(R')NSN}\} + \{n,m\text{-(R)(R')NSN}^{+}\mathrm{H}\}}{\{n,m\text{-}^{+}\mathrm{H(R)(R')NSN}^{+}\mathrm{H}\}} = \frac{1}{k_c} + \frac{1}{k_d} \qquad (2)$$

The fraction of the tautomeric form with the proton on the primary amino group can be expressed as

$$\alpha = \frac{\{n,m\text{-(R)(R')NSN}^{+}\mathrm{H}\}}{\{n,m\text{-(R)(R')NSNH}^{+}\} + \{n,m\text{-}^{+}\mathrm{H(R)(R')NSN}\}} \qquad (3)$$

$$= k_a/K_1 = K_2/k_c \qquad (4)$$

NMR method

The method for determining the microconstants from the methyl proton resonance frequency shifts is based on two assumptions:

TABLE 3

Protonation constants and corresponding thermodynamic functions [a,b,c]

	$\log K_1$	$\log K_2$	$-\Delta G_1$	$-\Delta G_2$	$-\Delta H_1$	$-\Delta H_2$	$T\Delta S_1$	$T\Delta S_2$
2,2-NSN	9.682(2)	8.821(2)	55.25(2)	50.34(2)	54.1(3)	53.3(6)	1.1(3)	−2.9(6)
2,3-NSN	10.139(2)	9.161(2)	57.89(1)	52.30(3)	56.0(2)	54.8(5)	1.9(2)	−2.5(5)
2,4-NSN	10.441(2)	9.249(3)	59.59(2)	52.78(2)	56.9(3)	55.1(6)	2.7(3)	−2.3(6)
3,3-NSN	10.365(2)	9.628(2)	59.16(1)	54.95(2)	56.5(2)	55.9(4)	2.7(2)	−0.4(5)
3,4-NSN	10.509(5)	9.809(4)	59.97(3)	55.98(3)	57.3(2)	56.3(5)	2.7(2)	−1.0(4)
4,4-NSN	10.730(5)	10.047(4)	61.24(3)	57.34(2)	57.6(3)	56.9(6)	3.6(3)	0.5(6)
2,2-(Me)NSN	9.855(5)	8.892(4)	56.24(3)	50.75(2)	49.2(3)	51.9(5)	7.0(3)	−1.2(5)
2,3-(Me)NSN	10.255(5)	9.437(5)	58.53(3)	53.86(3)	54.3(4)	50.9(7)	4.2(4)	3.0(7)
2,4-(Me)NSN	10.510(6)	9.551(5)	59.98(3)	54.51(3)	55.6(3)	50.7(5)	4.4(3)	3.8(5)
2,2-(Me_2)NSN	9.430(9)	8.384(9)	53.82(5)	47.85(5)	48.0(3)	40.5(6)	5.8(4)	7.4(7)
2,3-(Me_2)NSN	10.052(6)	8.721(5)	57.37(3)	49.77(3)	52.3(3)	38.4(5)	5.1(3)	11.4(5)
2,3-NSN(Me_2)	9.753(5)	9.005(5)	55.66(3)	51.39(3)	44.9(3)	47.1(5)	10.8(3)	4.3(2)
3,3-(Me_2)NSN	10.16(2)	9.32(1)	58.0(1)	53.19(6)	52.6(4)	43.0(6)	5.4(5)	10.2(2)

[a] 25°C; 0.5 mole dm^{-3}(K)NO_3; ΔG, ΔH and $T\Delta S$ in kJ $mole^{-1}$.

[b] Numbers in parentheses are the standard deviations on the last significant figure.

[c] Results obtained in a previous investigation: see ref. 1.

TABLE 4

Microconstants and α-values for asymmetric thiadiamines [a]

	$\log k_a$		$\log k_b$		$\log k_c$		$\log k_d$		α	
	Cal.	NMR	Cal.	NMR	Cal.	NMR	Cal.	NMR	Cal.	NMR
2,2-(Me)NSN	9.2 (6)		9.8 (6)		9.5 (6)		9.0(6)		0.22($\pm$0.16)	
2,3-(Me)NSN	10.09(7)		9.75(8)		9.60(7)		9.94(8)		0.69($\pm$0.10)	
2,4-(Me)NSN	10.39(5)		9.89(6)		9.67(5)		10.17(6)		0.76($\pm$0.09)	
2,2-(Me_2)NSN	9.26(3)	9.25(5)	8.94(4)	8.97(5)	8.55(3)	8.57(5)	8.88(4)	8.84(5)	0.68($\pm$0.05)	0.66($\pm$0.08)
2,3-(Me_2)NSN	9.96(2)	10.00(6)	9.32(3)	9.13(6)	8.81(2)	8.78(6)	9.45(3)	9.64(6)	0.81($\pm$0.03)	0.9 ($\pm$0.1)
2,3-NSN(Me_2)	9.36(6)	9.32(3)	9.52(7)	9.55(3)	9.39(6)	9.43(3)	9.23(7)	9.21(3)	0.40($\pm$0.06)	0.37($\pm$0.03)
3,3-(Me_2)NSN	10.04(3)	10.04(6)	9.52(5)	9.51(6)	9.44(3)	9.43(6)	9.96(4)	9.98(6)	0.77($\pm$0.04)	0.8 ($\pm$1)

[a] Values in parentheses are the deviations on the last significant figure.

(i) the shielding of the basic site adjacent to the methyl group is linearly related to the fraction of time it is protonated. The validity of this assumption has been proven by Grunwald et al. [5];

(ii) the other basic site (primary nitrogen) has no influence on the shielding. This has been confirmed by a PMR study on the protonation of 2-(Me)NN(Me) [4]. Since in the investigated thiadiamines both basic sites are still further removed from each other, the assumption made above certainly remains valid.

The resonance frequently shift Δ(vs. TMS) of the methyl protons may then be expressed as

$$\Delta = \frac{\{n,m\text{-}^{+}\mathrm{H}(\mathrm{Me_2})\mathrm{NSN}\} + \{n,m\text{-}^{+}\mathrm{H}(\mathrm{Me_2})\mathrm{NSN}^{+}\mathrm{H}\}}{C_L}\Delta\Delta_t + \Delta_b \qquad (5)$$

where $\Delta\Delta_t$ equals the difference in resonance frequency shift between the fully protonated and deprotonated diamine; Δ_b = the resonance frequency shift of the fully deprotonated diamine; and C_L = the analytical concentration of the diamine.

From eqn. (5) and considering the dissociation scheme it can be derived that

$$k_b = \frac{\Delta\Delta \cdot C_L - \{n,m\text{-}\mathrm{H}^{+}(\mathrm{Me_2})\mathrm{NSN}^{+}\mathrm{H}\} \cdot \Delta\Delta_t}{\Delta\Delta_t \cdot \{\mathrm{H}^{+}\} \cdot \{n,m\text{-}(\mathrm{Me_2})\mathrm{NSN}\}} \qquad (6)$$

and

$$k_d = \frac{\{n,m\text{-}^{+}\mathrm{H}(\mathrm{Me_2})\mathrm{NSN}^{+}\mathrm{H}\} \cdot \Delta\Delta_t}{\{\mathrm{H}^{+}\}[\Delta\Delta \cdot C_L - \{n,m\text{-}\mathrm{H}^{+}(\mathrm{Me_2})\mathrm{NSNH}^{+}\} \cdot \Delta\Delta_t]} \qquad (7)$$

where $\Delta\Delta = \Delta - \Delta_b$.

Using the known macroscopic protonation constants (K_1 and K_2) and the analytical concentration (C_L) of the diamine, the concentrations of the species in eqns. (6) and (7) may be calculated from a Fortran IV program EQUIL [6]. From those and the experimentally determined resonance frequency shifts the microconstants k_b and k_d may then be calculated as well as k_a and k_c from eqns. (1) and (2). The results obtained from this method are compared to those of the calorimetric method in Table 4.

RESULTS AND DISCUSSION

Because the enthalpies of protonation for the di- and tetramethyl-substituted diamines n,m-(Me)NSN(Me) and n,m-(Me_2)NSN(Me_2) are unknown, a calculation of the α-values and microsconstants for our asymmetric diamines, following the method proposed by Paoletti et al. [2c], is impossible. However, as was pointed out earlier [1b], the difference in both the enthalpy $\delta(-\Delta H)$ and the entropy of protonation $\delta(T\Delta S)$ between a

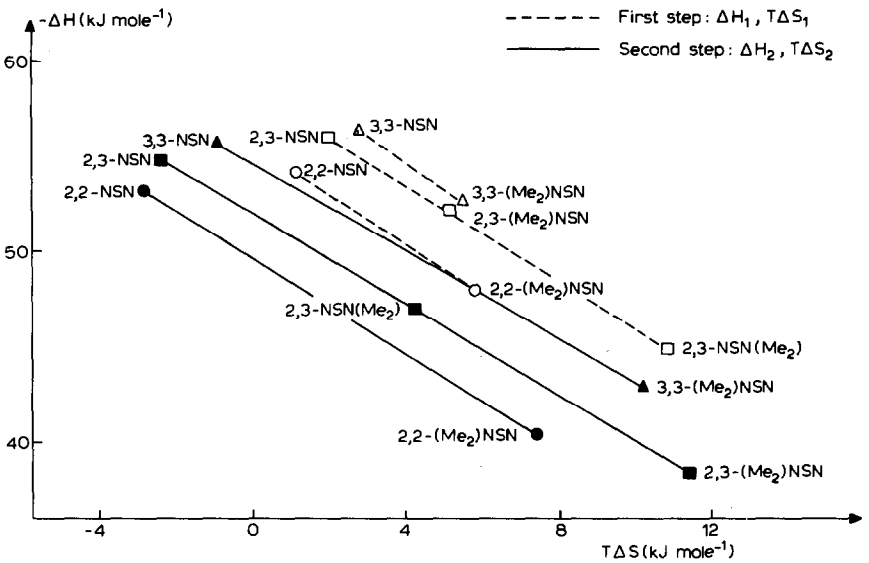


Fig. 1. $-\Delta H$ vs. $T\Delta S$ for the protonation of α, ω-thiadiamines and their methyl-substituted analogues.

primary amine, e.g. n,m-NSN, and its corresponding N-methyl-substituted analogue, n,m-(Me)NSN or n,m-(Me_2)NSN, is dominated by the difference in solvation between their corresponding ammonium ions. Hence it is not surprising (see Figs. 1 and 2) that for each such analogous pair of amines and at each protonation stage the ratio $k = \delta(-\Delta H)/\delta(T\Delta S)$ is almost constant (k is about -0.8 between primary → secondary and about -1.3

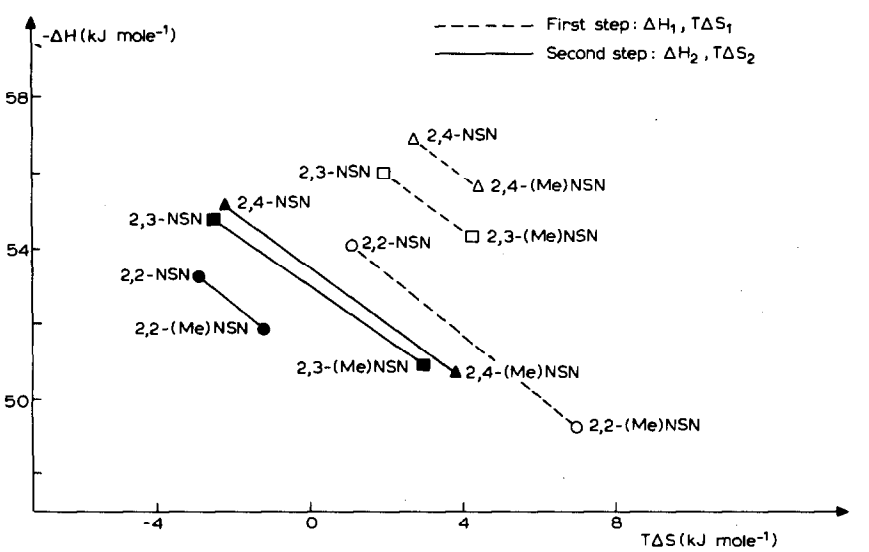


Fig. 2. $-\Delta H$ vs. $T\Delta S$ for the protonation of α, ω-thiadiamines and their dimethyl-substituted analogues.

between primary → tertiary). Consequently we may deduce that, within each pair of diamines with the same n and m values, each change in $(-\Delta H_1)$ and $(-\Delta H_2)$ (or ΔS_1 and ΔS_2) for n,m-(Me)NSN and n,m-(Me_2)NSN with respect to the corresponding values for the primary amine n,m-NSN may be ascribed mainly to the secondary and tertiary amino group, respectively.

Now, from the protonation scheme 1, it is seen that the relation between the experimentally determined enthalpies at each protonation stage and the microenthalpies is given by the expressions

$$\Delta H_1 = \alpha(\Delta H_a) + (1-\alpha)(\Delta H_b) \tag{8}$$

$$\Delta H_2 = (1-\alpha)(\Delta H_d) + \alpha(\Delta H_c) \tag{9}$$

where ΔH_a, ΔH_d and ΔH_b, ΔH_c are the microenthalpies at the first and the second protonation step of the primary and methyl-substituted nitrogen, respectively.

$$\Delta H_a - \Delta H_1 = (1-\alpha)(\Delta H_a - \Delta H_b) \tag{10}$$

$$\Delta H_d - \Delta H_2 = \alpha(\Delta H_d - \Delta H_c) \tag{11}$$

Moreover, since the enthalpy is a state property it follows that

$$\Delta H_a + \Delta H_c = \Delta H_b + \Delta H_d = \Delta H_1 + \Delta H_2 = \Delta H_\beta$$

and

$$\Delta H_a - \Delta H_b = \Delta H_d - \Delta H_c \tag{12}$$

From eqns. (10), (11) and (12)

$$\frac{\Delta H_a - \Delta H_1}{\Delta H_d - \Delta H_2} = \frac{(1-\alpha)}{\alpha} \tag{13}$$

As the distance between both amino groups is quite large it may be assumed that methyl substitution on a nitrogen has almost no influence on the protonation of the nitrogen at the other side of the molecule. So it is

TABLE 5

The microconstants for some symmetric α,ω-thiadiamines ($\alpha = 0.05$) and some thiamonoamines

	$\log k_a = \log k_b$	$\log k_c = \log k_d$
2,2-NSN	9.38	9.13
3,3-NSN	10.07	9.93
4,4-NSN	10.43	10.35
2,2-(Me_2)NSN(Me_2)	8.81	8.26
2-NS(Me)	9.47	
3-NS(Me)	9.01	
2-(Me_2)NS(Me)	10.09	

TABLE 6

Average group values for the microbasicities in thiadiamines and thiamonoamines

Protonated group	log k_a	log k_b	log k_c	log k_d
$NH_2(CH_2)_2SR$	9.3			9.1
$NH_2(CH_2)_3SR$	10.1			9.9
$NH_2(CH_2)_4SR$	10.4			10.3
$CH_3NH(CH_2)_2SR$		9.8	9.6	
$(CH_3)_2N(CH_2)_2SR$		9.0	8.5	
$(CH_3)_2N(CH_2)_3SR$		9.5	9.4	

reasonable to suppose that the microenthalpies ΔH_a and ΔH_d of the primary amino group in n,m-(R)(R')NSN will approximately equal the enthalpies of the symmetric diamine m,m-NSN at the first (ΔH_1^s) and the second protonation stage (ΔH_2^s) (see Table 3). The α-values obtained from eqn. (13) and the microconstants (as log k) calculated from them with eqns. (3) and (4) are summarized in Table 4. It is seen that the agreement with the NMR results is reasonably good, which confirms that our assumption is acceptable.

Finally, the microconstants obtained (Table 4) for the methyl-substituted amines may be compared to those of some symmetric α,ω-thiadiamines ($\alpha = 0.5$) (Table 5) [1] and the protonation constants of some thiamonoamines [6] (Table 5). It may be seen that

(1) the microbasicity always tends to a typical group value (Table 6); and

(2) the microbasicity, within a series with equal S–N distance, follows the sequence secondary > primary > tertiary, as was already stated for the overall basicities log β_2^H of the diamines [1b].

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