^{13}C Nuclear Magnetic Resonance Study of the Protonation Sequence of Some Linear Aliphatic Polyamines

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The ^{13}C n.m.r. spectra are reported as a function of pH for 1,2-diaminoethane [en], *N*-(2-aminoethyl)propane-1,3-diamine [2,3-tri], 1,4,7,10-tetra-azadecane [trien], and 1,4,8,11-tetra-azaundecane [2,3,2-tet]. The previously reported amine shift parameters π and π^+ are used to determine the protonation sites in the charged forms of the polyamines and the associated microscopic pK_a values.

Various physical techniques have been used to investigate the protonation sequence of polybasic acids in solution but the presence of more than one form (*e.g.* un-, mono-, and poly-protonated) at a given pH leads to problems over assignment[1] unless the individual forms can be unambiguously characterised (as, for example, with the aminopolycarboxylates studied[2] by i.r. spectroscopy). The linear aliphatic polyamines $H_2N[CH_2]_k$-$NH[CH_2]_l(NH[CH_2]_m)_nNH_2$ (where k—m = 2—4 and n = 0—3), which are of considerable interest in co-ordination chemistry, are particularly difficult to analyse because the basicities of the nitrogen atoms in the component fragments $NH_x[CH_2]_zNH_y$ (where x, y = 1 or 2 and z = 2—4) are so similar. ^1H N.m.r. spectroscopy has been used[3,4] in a few cases but problems of interpretation arise because of the comparatively poor resolution of the spectra and the averaging effects due to rapid proton transfer. Spectral resolution is less of a problem with ^{13}C n.m.r. spectroscopy but here the long-range effects[5] are often sufficient to cause the chemical shift to be influenced by the state of protonation of more than one site.[6] Consequently, it has often been difficult to assign all the observed peaks unequivocally, even for the unprotonated or fully protonated forms of the polyamines.[7-10]

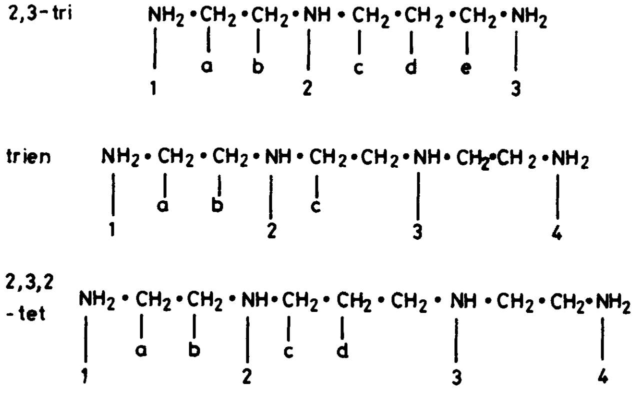
We have recently analysed[11] the ^{13}C chemical shifts of several aliphatic polyamines by means of a two-term empirical relationship, employing amine shift parameters, π and π^+. This enabled us to group the resonances to provide an unambiguous assignment in each case. In the present paper we report pH-titrations of the ^{13}C n.m.r. spectra of 1,2-diaminoethane [en], *N*-(2-aminoethyl)propane-1,3-diamine [2,3-tri], 1,4,7,10-tetra-azadecane [trien], and 1,4,8,11-tetra-azaundecane [2,3,2-tet], and the use of the π and π^+ parameters to determine the protonation sites in the principal intermediates.

Experimental

The solutions were made up and the ^{13}C n.m.r. spectra were determined as described previously.[11] Although it is customary[12] to add an empirical term 0.4 to convert pH into pD, it is also necessary,[13] in comparing our data with the published acid dissociation constants, to allow for the deuterium isotope effect on pK_a. We shall consider this matter in more detail in a future paper, but for the degree of accuracy required now we have chosen to make no correction to the measured pH values.

Analysis

The atoms and non-equivalent C atoms in the polyamines are identified as in the Scheme. The measured chemical shifts δ of the C atoms in 2,3-tri, trien, 2,3,2-tet, and en at different pH are represented by the points in Figure 1. The titration curves in Figures 1a—c and 2 are constructed from these data by the following method.



Scheme.

At a given pH, each nitrogen atom N_i (i = 1—4 for trien, 2,3,2-tet; 1—3 for 2,3-tri) carries an effective fractional positive charge f_i determined by the degree of protonation and this influences the chemical shift of each carbon atom in the $N_iH_x[CH_2]_zN_jH_y$ fragment (or fragments) of which it is a member (x,y = 1,2; z = 2,3). Thus, the chemical shift of each C atom is determined by the degree of protonation f_i, f_j of each of its two nearest nitrogen atoms N_i, N_j, as well as its type (primary of secondary amine) and proximity to the carbon in question (α, β, or γ). The absence of cross-terms (*i.e.* terms involving both N_i and N_j) is assumed,[11] as is any influence on the chemical shift from non-neighbouring fragments.

For a particular C atom, therefore, the chemical shift δ is given by equation (1) where π_i, π_j are the π-parameters for the two nearest amino-groups (in the unprotonated state, corresponding to $f_i = f_j = 0$) and π_i^+, π_j^+ are their π^+-parameters (for the protonated state, corresponding to $f_i = f_j = 1.0$). Equation (1) was written for each C atom in the molecule using the measured shift δ at a given pH and the known[11] π- and π^+-parameters. From this series of simultaneous equations, the degree of protonation f_i of each N atom in the amine was determined by an iterative least-squares procedure.

$$\delta = f_i\pi_i^+ + (1 - f_i)\pi_i + f_j\pi_j^+ + (1 - f_j)\pi_j \qquad (1)$$

The 'best' values of f_i, together with the overall degree of protonation Σf_i, are shown in Figure 2 as a function of pH. The titration curves in Figures 1a—c were constructed by using these values in equation (1). For reasons of symmetry, it was not possible to separate f_1 from f_4 and f_2 from f_3 in the tetramines.

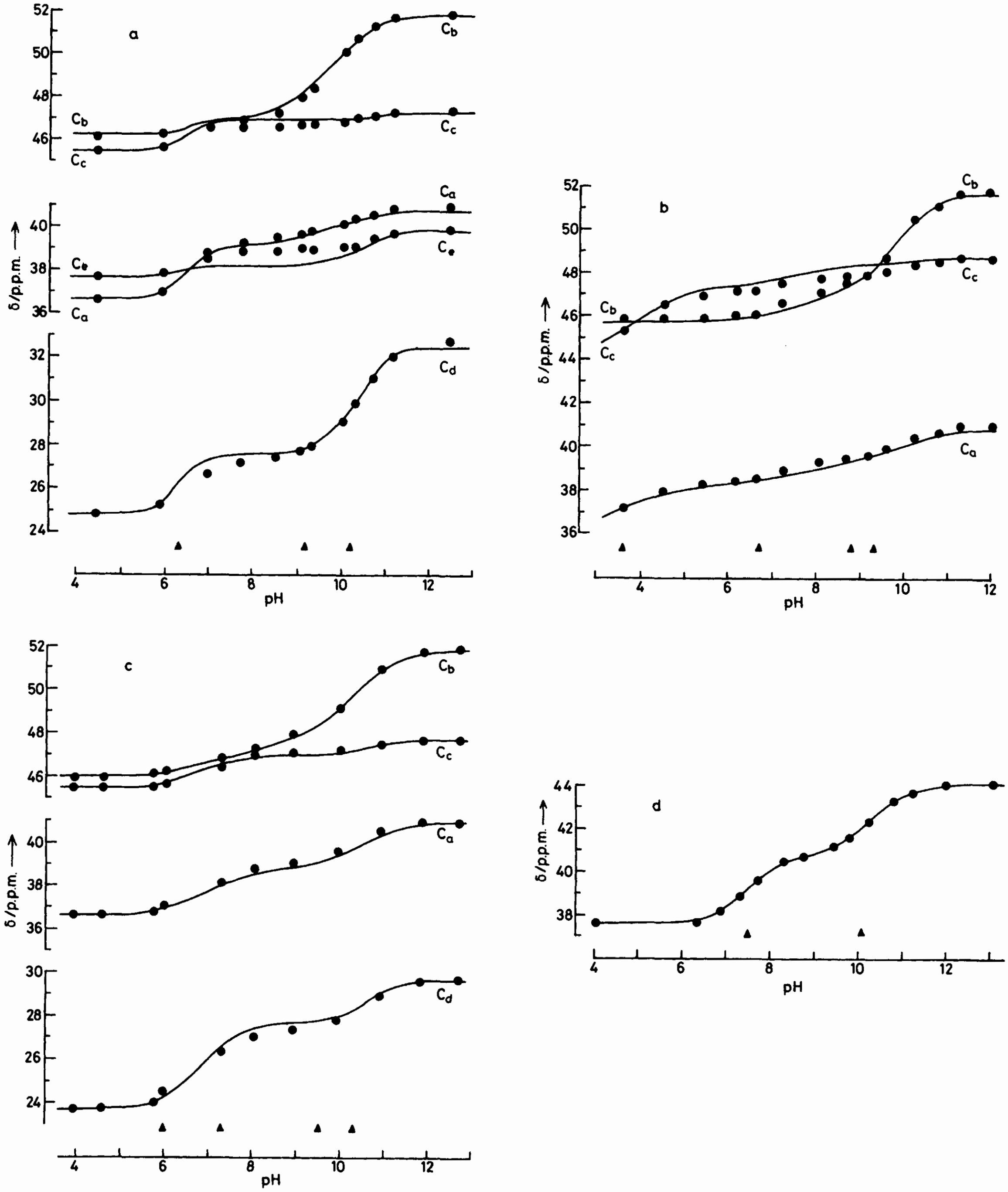


Figure 1. ^{13}C N.m.r. chemical shifts as a function of pH. Assignments and references for pK_a values are indicated: a, 2,3-tri; b, trien; c, 2,3,2-tet; d, en

Discussion

Our titration curves for 2,3-tri (Figure 1a) are consistent with those reported[7] by Delfini *et al.* if it is assumed that trimethylsilyl propionate, which they used as an internal standard, has a chemical shift of δ *ca.* −1.7. Our assignments also coincide with theirs except in the case of C_b and C_c for the high-pH (unprotonated) form of the amine: while they suggest that there is a 'crossover' between the two titration curves at pH *ca.* 7, consideration of the limiting high- and low-pH chemical shifts[11] indicates that the curves approach each other at that pH but do not cross. In fact, the only 'crossover' we find for 2,3-tri is between C_a and C_e at pH *ca.* 6.5. ^{13}C Titration curves have not been reported for trien and 2,3,2-tet but the general form of Figure 1b is reminiscent of the proton n.m.r. titration curves for trien given[3] by Sudmeier and Reilley. In this case (Figure 1b), two 'crossovers' occur between C_b and C_c, at pH *ca.* 4 and at *ca.* 9.5. There is no obvious reason why the limiting values for f_1, f_4 in 2,3,2-tet and f_1 in 2,3-tri should be a little below 1, and we can only assume that the discrepancies are attributable to small errors in one or more of our π^+-parameters[11] or in the low-pH data. An alternative cause might be the omission of cross-terms in our analysis; the need for the latter cannot be ruled out even though the titration of en (Figure 1d) provides no evidence for their importance, the expected shoulder corresponding to the

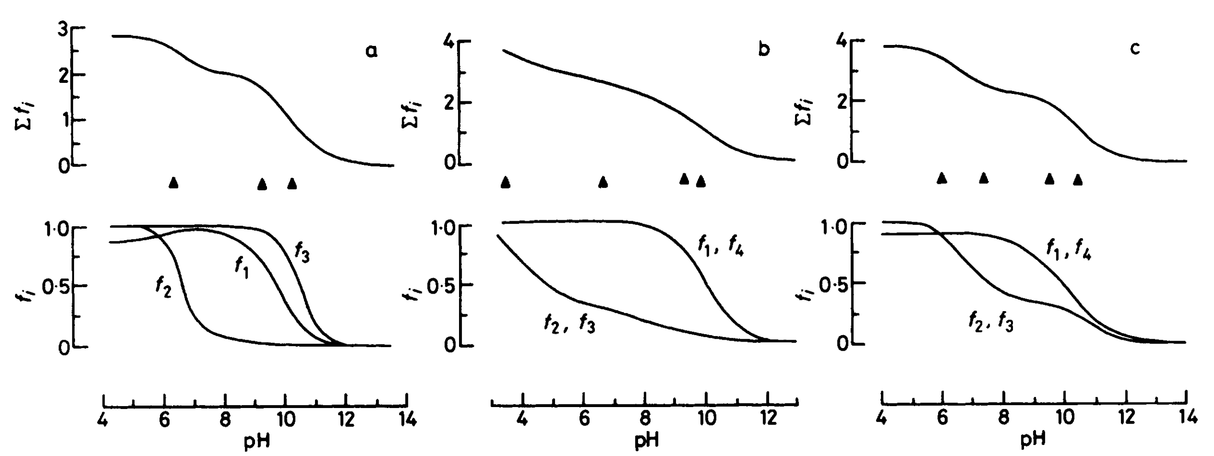


Figure 2. State of protonation of the N atoms as a function of pH (see text). Literature pK_a values are indicated: a, 2,3-tri; b, trien; c, 2,3,2-tet

monoprotonated intermediate enH^+ appearing at the predicted value of δ 40.8 p.p.m.

^{13}C N.m.r. spectroscopy has been used in several cases (*e.g.* with amino acids[14,15]) to determine the microscopic pK_a of multifunctional species. The general approach is to reconstruct the observed pH dependences of the chemical shifts of the constituent C atoms by means of an empirical parameterization scheme developed with the help of model compounds. In view of the generally good agreement in Figures 1a—c between our measured δ and the titration curves based on the amine shift parameters π and π^+, we feel justified in using the individual f_i plots in Figure 2 for this purpose and have listed the microscopic pK_a for 2,3-tri, trien, and 2,3,2-tet determined this way in the Table, column 4. Further support for this approach is provided by a comparison of the corresponding macroscopic pK_a determined from the plots of total effective charge Σf_i in Figure 2 (Table, column 3) with the pK_a values taken from the literature (Table, column 2).

The tetramines provide an interesting comparison and illustrate the difficulty of predicting *a priori* the protonation sequence in a linear polyamine. A secondary amino group tends to be more basic than a primary (pK_a for isolated amino groups are[16] typically 11.2 and 10.8, respectively) and on this basis it might be expected that N-2 and -3 would be protonated at a higher pH than N-1 and -4. On the other hand, the initial protonation of the end nitrogens would produce the dication with the greatest charge separation, and this would therefore be favoured on entropy grounds.[17] It seems that in the case of trien (Figure 2b) the latter consideration is dominant, with N-1 and -4 being essentially protonated together (average pK_a *ca.* 10), the charge on N-2 then building up rather slowly (pK_a *ca.* 7.5) and finally the fourth proton being added at N-3 (pK_a *ca.* 3.5). With 2,3,2-tet, on the other hand, there appears to be little difference between the basicities of the primary and secondary amine groups (Figure 2c). Here, the primary–primary and primary–secondary forms of the diprotonated species co-exist over a range of pH and although the former is predominant, there is not such a clear-cut preference as in the case of trien. Again, the fourth proton is added at N-3. It is interesting to note that this similarity between the basicities of primary and secondary nitrogen in the 2,3,2-tet dication is reflected in a comparatively large discrepancy between the macroscopic and microscopic values of the third pK_a of this amine (Table). For 2,3-tri the picture resembles that found with trien: the most basic site is N-3 (pK_a *ca.* 10.5), the next is N-1 (*ca.* 9.5), and the least basic is N-2 (*ca.* 6.5). This sequence confirms the conclusions of Delfini *et al.*[7] that for the unsymmetrical triamines the pK_a of the primary nitrogen attached to the larger aliphatic chain is marginally higher than that of the other primary amine, but both are substantially higher than that of the secondary N atom.

Table. Comparison of measured and predicted pK_a values for polyamines (see text)

	Macroscopic pK_a		Microscopic pK_a		
Amine	Lit.[a]	From Figure 2	From Figure 2	Predicted[16]	N atom protonated[16]
2,3-tri	10.2[b]	10.8	10.5	10.3	N-3
	9.2[b]	9.6	9.7	9.9	N-1
	6.3[b]	6.5	6.6	6.8	N-2
trien	9.8[c]	10.7	10.5	10.1	N-1
	9.3[c]	9.4	9.4	9.4	N-4
	6.7[c]	7.3	7.3	6.1	N-2
	3.6[c]	3.7	3.7	3.2	N-3
2,3,2-tet	10.3[d]	11.1	10.7	10.1	N-1 or -2
	9.5[d]	10.0	10.2	9.9[e]	N-4[e]
	7.3[d]	7.4	8.8	7.1[f]	N-1[f]
	6.0[d]	5.8	6.4	5.4	N-3

[a] Under various conditions. [b] See refs. 18, 19. [c] See refs. 20, 21. [d] See ref. 18. [e] Following protonation at N-2 (protonation at N-3, following N-1, is associated with a pK_a of 9.7; and at N-4, following N-1, with a pK_a of 9.5). [f] Following protonation at N-2 and -4 (protonation at N-2, following N-1 and -4, is associated with a pK_a of 6.8).

Although it would be unwise to try to draw any general conclusions about the protonation sequence of linear polyamines from the present study, there does seem to be good agreement between the picture presented here and that predicted by the application of Clark and Perrin's empirical method[16] for calculating the strengths of organic bases. In column 5 of the Table we have listed the 'predicted' microscopic pK_a values corresponding to protonation at the N atom indicated in column 6. Not only does the Clark–Perrin analysis reflect the protonation sequence reported here for 2,3-tri and trien but it also predicts that there will be little to choose between the N atoms in 2,3,2-tet as regards the site of the first (and to a lesser extent the second and third) protonation, as is found to be the case.

The present method of analysis based on amine shift parameters therefore provides a promising route to the microscopic pK_a of aliphatic polyamines. It will be interesting to compare these results with those obtained from proton–carbon two-dimensional n.m.r. spectroscopy, which is also being applied[9] to the problem.

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