Correspondence

Protonation Studies of the Anion of Diethylenetriaminepentaacetic Acid by Nuclear Magnetic Resonance[1]

Sir:

Recently there has been considerable controversy regarding the positions of protonation for the tetraanion of ethylenediaminetetraacetic acid (EDTA).[2] Using proton n.m.r. the first two protonations of the tetraanion have been shown to occur at the nitrogen atoms of EDTA.[3] Because H_4EDTA precipitates when further protonation occurs, it is not possible to determine the protonation sites for the third and fourth protons. However, these protons are assumed to add to the carboxylate groups with no migration of the protons on the nitrogen atoms. Because diethylenetriaminepentaacetic acid (DTPA) is similar to EDTA and does not precipitate at low pH values the n.m.r. spectra of this ligand have been studied as a function of solution pH to ascertain its protonation characteristics and, by analogy, those of EDTA.

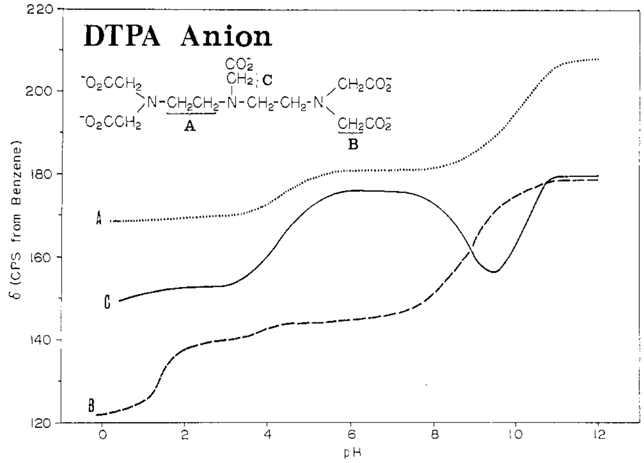

Fig. 1.—Chemical shifts as a function of pH for the protons of DTPA, 56.4 Mc.

A 0.5 *M* aqueous solution of DTPA was adjusted to pH 12 with KOH. Samples were then taken as the pH was lowered with HNO_3. The n.m.r. spectra were recorded with a Varian HR-60 spectrometer equipped with a 56.4 Mc. probe. A plot of the chemical shift (in c.p.s. *vs.* an external reference of benzene) of the various $-CH_2$ groups as a function of pH is shown in Fig. 1. Because the A and C resonances are shifted to lower field at about pH 9.3, the first protonation of the pentaanion ($pK \approx 10.5$) must occur at the central nitrogen atom. However, when the second protonation ($pK \approx 8.6$) takes place the B and A resonances are shifted downfield and the C resonance is shifted back upfield. This has been interpreted as the addition of a proton to one of the end nitrogen atoms plus a migration of the proton on the central nitrogen atom to the other end nitrogen leaving the C protons more shielded. Thus after two protonations the two end nitrogen atoms are protonated and the central nitrogen is unprotonated. The third protonation ($pK \approx 4.3$) occurs at the middle nitrogen atom. This conclusion is based on the observation that the A and C protons are shifted downfield whereas the B resonance remains constant. At this point all three nitrogen atoms of DTPA are protonated. Two more hydrogen ions add to the end carboxylate groups of DTPA at approximately pH 1.5, which is indicated by the B resonance being shifted downfield while the A and C resonances remain essentially constant.

The assignment of the A, B, and C resonances (Fig. 1) has been made by integration of the signal intensities as well as by analogy with n.m.r. data for other polyaminocarboxylic acids.[3,4] Both the B and C resonances are sharp single lines, whereas the A resonance varies from a sharp single line at high pH to a broad complex multiplet below pH 11. The latter phenomenon is brought about by the protonation of the various nitrogen atoms, which causes the two CH_2 groups of the ethylenic group to become nonequivalent. However, the difference in chemical shifts for these two CH_2 groups is relatively small (probably of the order of magnitude of the coupling between the groups), and consequently the A resonances exhibit a second-order splitting which essentially prohibits detailed assignments to be made for the individual CH_2 groups. As a result of this consideration only the center of this multiplet has been plotted *vs.* pH. Any change in δ of one of the CH_2 groups should be reflected by a corresponding (although smaller) change in the δ of the center of the multiplet. This choice permits the general shape of the A curve to be obtained and shows that after the three nitrogen atoms are protonated, further protonation leads only to simple addition of H^+ to the carboxylate groups without migration of nitrogen protons. In any case the sequence and place of protonation for DTPA can be established without considering the A resonances. Additional n.m.r. studies are currently in progress on the metal chelates of DTPA and of cyclohexanediaminetetraacetic acid and will be reported in the future.

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Received November 8, 1963

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(1) This work was supported by the United States Atomic Energy Commission under Contract No. AT(11-1)-34, Project No. 45, and by a National Science Foundation Predoctoral Fellowship to R. J. K.

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