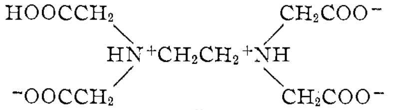
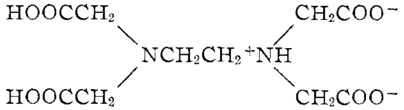
Structure of Sodium Ethylenediaminetetraacetic Acid in Aqueous Solution

Sir:

In a recent correspondence Langer[1] suggests that the data of Sawyer and Tackett[2] are inconsistent with the structure (I) proposed for D_3Y^- in aqueous solution. He proposes a structure (II) which he feels fits the data better and also fits in with his structure of H_4Y in the solid phase. His criticism is that Sawyer and Tackett state "at conditions where D_3Y^- is the major species, a small peak at 1700 cm.$^{-1}$ plus a peak three times as large at 1620 cm.$^{-1}$ would be expected if one COOH group plus three COO^- groups attached to the protonated nitrogen atoms is the proper structure," when Nakamoto, Morimoto, and Martell[3] have shown the extinction coefficients of the COOH peak to be about one-third that of the COO^- peak. Actually, our statement was meant to indicate a qualitative rather than a quantitative relationship, since the nature of the "bulge" at 1700 cm.$^{-1}$ does not allow a meaningful area measurement to be made. The evidence in support of structure I for D_3Y^- is the data shown in Table I of our publication.[2] These data indicate that under solution conditions where D_3Y^- is the major EDTA species, the area of the 1620 cm.$^{-1}$ peak is equal to three-fourths the maximum area of that peak when D_2Y^{-2} is the major species in solution. If D_3Y^- had two carboxylic acid groups, the area of the 1620 cm.$^{-1}$ peak would be equal to one-half its maximum area. As would be expected, the pD at which this area is one-half is lower than the pD for D_3Y^- but still near the solution conditions where D_3Y^- is the major species if the correction of the dissociation constants for D_2O solutions is valid. Thus, as Langer concludes, it is difficult to determine between the above structures on the basis of infrared data of their aqueous solutions.



I



II

It has been shown,[2-4] however, that H_2Y^{-2} exists as a double "zwitterion" in aqueous solution. Thus it can be assumed that protonation takes place on one of the available carboxylate groups when D_3Y^- is formed. Langer's[1] structure for D_3Y^- assumes that the proton shifts from one of the protonated nitrogen atoms to the carboxylate group which is adjacent to the carboxylic acid group, while our structure assumes that no such migration takes place.

It is of interest to consider the inductive and field effects of the various groups, as well as dissociation constants of related compounds, to determine if such a shift is expected. Fruton and Simmonds[5] consider the dissociation constants for the diaminocarboxylic acid, lysine. From titration data the following apparent dissociation constants are found: $pK_1 = 2.2$ (COOH); $pK_2 = 8.95$ $(\alpha - NH_3^+)$; $pK_3 = 10.5$ $(\epsilon - NH_3^+)$. This indicates that the amino group furthest from the carboxylate group is the strongest base, or that the inductive effect of the carboxylate group decreases the basicity of the amino group nearest it. Because D_2Y^{-2} has two carboxylate groups near each of its protonated nitrogen atoms and D_3Y^-, initially, must have only one carboxylate adjacent to one of the protonated nitrogen atoms, it appears that that protonated nitrogen atom would become a stronger base as D_3Y^- is formed from D_2Y^{-2} and have less tendency to lose its proton to a carboxylate group. In his monograph, Gould[6] has considered the relationship between inductive and field effects and the reactivity of molecules. He states that both ammonium ions and carboxylic acid groups have negative inductive effects (*i.e.*, they tend to strengthen a carboxylic acid when substituted in place of a methyl group in the α position). From his discussion, it appears that on going from D_2Y^{-2}, which has two adjacent groups, to D_3Y^-, which initially has a carboxylic acid group adjacent to a carboxylate group, the basic nature of the carboxylate group would decrease. A consideration of the effects of hydrogen bonding on the carboxylate group of hydrogen maleate results in the same conclusion. Thus it does not appear that the proton would migrate from a more basic nitrogen atom to a less basic carboxylate group.

The n.m.r. results of Kula, Sawyer, Chan, and Finley[4] for methyliminodiacetic acid show that the nitrogen atom is protonated first, as the solution acidity is increased, and then one carboxylate group is protonated. They observed no chemical shifts which would indicate that after the one carboxylate group was protonated, the proton on the nitrogen migrated to the other carboxylate group. More recent n.m.r. data[7] on the protonation of the anion of diethylenetriaminepentaacetic acid (DTPA) have shown definitely that the nitrogen atoms are protonated first. As additional protons are added there is no evidence that protons migrate from the nitrogen atoms to the carboxylate groups. The anion of ethylenediaminetetraacetic acid would be expected to behave as DTPA.

On the basis of the above discussion, it appears reasonable that structure I proposed by Sawyer and Tackett[2] is more plausible for D_3Y^- in solution than that proposed by Langer,[1] structure II.

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[1] H. G. Langer, *Inorg. Chem.*, **2**, 1080 (1963).

[2] D. T. Sawyer and J. E. Tackett, *J. Am. Chem. Soc.*, **85**, 314 (1963).

[3] K. Nakamoto, Y. Morimoti, and A. E. Martell, *ibid.*, **85**, 308 (1963).

[4] R. J. Kula, D. T. Sawyer, S. I. Chan, and C. M. Finley, *J. Am. Chem. Soc.*, **85**, 2930 (1963).

[5] J. S. Fruton and S. Simmonds, "General Biochemistry," John Wiley and Sons, 2nd Ed., New York, N. Y., 1953.

[6] E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959.

[7] R. J. Kula and D. T. Sawyer, *Inorg. Chem.*, in press.