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NONEQUIVALENCE BETWEEN THE GEMINAL DIHYDROXYPHOSPHINYL GROUPS IN SOME 2-SUBSTITUTED 1-AMINOETHYLIDENEDIPHOSPHONIC ACIDS

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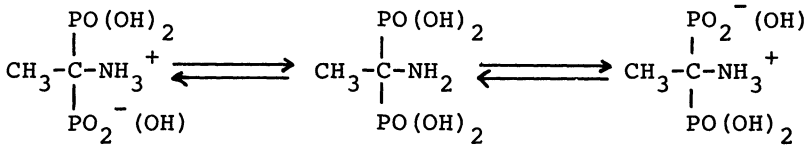
Spectroscopic nonequivalence between the geminal $PO(OH)_2$ groups of some aminodiphosphonic acids with a highly electronegative substituent at 2-position of 1-aminoethylidenediphosphonic acid was found by ^1H NMR measurement in D_2O. This may result from the formation of an inner salt between amino group and one of the $PO(OH)_2$ groups.

A solution of 1-aminoethylidenediphosphonic acid(1) in water contains many species in so rapid equilibrium, as is the case for amino acids,[1] that the geminal $PO(OH)_2$ groups must be equivalent to each other.



(I)

(1)

In fact, the methyl protons of 1 were shown in ^1H NMR spectrum[2] to couple with the adjacent two phosphorus atoms equivalently and their signals were split into a 1:2:1 triplet at δ 1.65(J= 14 Hz). Similarly, the methylene protons of 2-7 were represented by a triplet as summarized in Table 1. Of course, further coupling was observed arising from the adjacent other nuclei, if any. The spectroscopic equivalence of the geminal $PO(OH)_2$ groups of 1-7 is accounted for by our observations. However, ^1H NMR spectra of the methylene protons of 8-12 exhibited a pair of doublet unexpectedly. One of the geminal $PO(OH)_2$ groups

Table 1. ^1H NMR Spectral Data of $XCH_2C(NH_2)[PO(OH)_2]_2$ in D_2O

Compound[3]	X	ppm	Multiplicity	J_{PCCH} (Hz)
1	H	1.65	3	14
2	Me	2.24	12	13 J_{HCCH} 6
3	ClC_6H_4	3.23	3	12
4	C_6H_5	3.22	3	12
5	EtOCO	3.09	3	12
6	NH_2CO	2.98	3	12
7	$(HO)_2OP'$	2.57	6	13 $J_{P'CH}$ 18
8	F	4.65	8	12, 8 J_{FCH} 67
9	Cl	4.20	4	12, 8
10	Br	4.07	4	12, 8
11	MeO	3.90	4	12, 9
12	OH	4.19	4	12, 9

seems to be in a different spectroscopic environment from another(J= 8-9, 12 Hz).

If there exists the rotational isomers in 8-12, the rotaional isomers should exist in 3-7 with a bulky substituent[ClC_6H_4, C_6H_5, CO_2Et, $CONH_2$, $PO(OH)_2$] at 2-position. However, the splitting pattern of the methylene protons of 3-7 appeared as a 1:2:1 triplet. And the fact is also known that the methylene protons of 2-chloro-1-hydroxyethylidenediphosphonic acid,[4] analogous to 9 in structure, couple with the adjacent two phosphorus atoms and are split into a 1:2:1 triplet (J= 11.5 Hz). Therefore, it seems unreasonable to explain our observations on 8-12 in terms of the rotational isomers.

The introduction of the highly electronegative atom such as halogen or oxygen at 2-position of 1 weakens the basicity of the amino group and/or strengthens the acidity of the geminal $PO(OH)_2$ groups due to its large electron-withdrawing inductive effect. It is assumed, therefore, that such an inner salt formed between the weaker basic and the stronger acidic function hardly dissociates even in aqueous solution, and that the proton exchange between $PO_2^-(OH)$ and $PO(OH)_2$ in equilibrium is slow within the ^1H NMR time scale.

Although most obvious way of altering the rate of the proton exchange is to change the temperature,[5] the methylene signals of 8-12 were superposed upon a large

and broad H_2O signal as the temperature was increased, and we could not discriminate the change in the split pattern of them. Another way of finding out the origin of nonequivalence between the geminal $PO(OH)_2$ groups of 8-12 must be done by measuring ^1H NMR spectrum in a strongly acidic or basic solution. That is, the inner undissociated salt is presumed to be destroyed by protonation on amino group with the stronger acid or deprotonation from four acidic functions with the stronger base.

Experiments with 8-10 failed because, on treatment with a NaOH solution, these were readily dehydrohaloganated and tetrasodium 1-oxoethane-1,2-diphosphonate[6] was isolated, wherein one of the geminal $PO(OH)_2$ groups underwent a 1,2-shift. In the case of 11, the signal for the methylene protons unfortunately has the same chemical shift value as that for methoxy group in the pH range over 10.

1-Amino-2-hydroxyethylidenediphosphonic acid(12), which is highly soluble in water over a wide pH range and stable in alkaline solution, is most suitable for our purpose. When a probe solution of 12 was made strongly basic with NaOD(pH 10), the spectrum of the methylene protons dramatically changed from a pair of doublet (J= 9, 12 Hz) to a 1:2:1 triplet(J= 12 Hz). Again neutralized with D_3PO_4, the spectrum of 12 returned to the original one. On the other hand, when it was acidified with D_3PO_4(pH 1), the spectrum was again represented by a triplet(J= 9 Hz), although it was a little broad because of the viscosity of the probe solution (Fig. 1).

It is of interest that, with the introduction of a strongly electron-withdrawing atom into 2-position of 1, the geminal $PO(OH)_2$ groups of 1 became nonequivalent.

Further investigation of the detailed structure of 8-12 is now in progress.

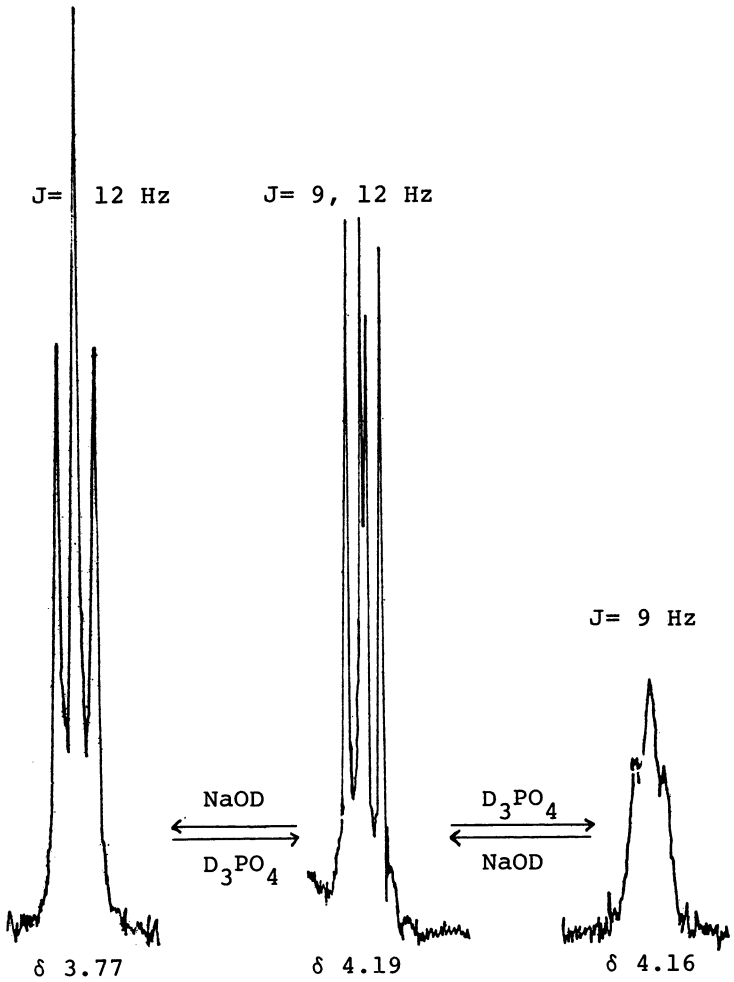


Fig. 1 ^{1}H NMR spectrum of 12

References and Footnotes

1) J.D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York(1965), p. 707.

2) ^{1}H NMR Spectra were obtained at 100 MHz on a JNM-TS-100 spectrometer, with DSS as an internal reference in D_2O.

3) These(1-12) wereprepared by the method of Plöger[W. Plöger, N. Schindler, K. Wollmann, and K. H. Worms, Z. Anorg. Allg. Chem., 389, 119(1972).

4) O. T. Quimby, W. A. Cilley, J. B. Prentice, andD. A. Nicholson, J. Org. Chem., 38, 1867(1973).

5) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed., Pargamon, London(1969), Part 5.

6) This was assigned by comparing analytical and spectral data with those of the literature(4).

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