A NEW EXAMPLE OF CONFORMATIONAL FLEXIBILITY OF CHOLINE DERIVATIVES

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Summary: Phenyl-4-carbamylcholine is a new example of different conformation in solution and in the solid state for C_α-C_β unsubstituted choline derivatives.

It has been recently reported that carbamylcholine (Carbachol) (I) shows different conformations about the C_α-C_β bond of the cholinic fragment N^+-CH_2-CH_2-O in the solid state[1] and in solution[2], a result that, being not in favour of a strong electrostatic stabilization[3] of the synclinal (G) conformation about this bond, supports the idea that the frequency with which this conformation has been observed in the crystal state and in solution for many choline derivatives should be related not only to intra- but also to inter-molecular effects.

This view, firstly suggested on the basis of theoretical results derived with the classical empirical method of partition of the energy in physically relevant contributions (PEM) for the acetylcholine (ACh) molecule[4,5], and later supported also on the basis of a number of semi-empirical quantum mechanical computations[6,7], is further enhanced by the experimental data on a simple derivative of choline, the phenyl-4-carbamylcholine (Phe-carbachol) (II).

It has been reported[8] that Phe-carbachol shows in the solid state an extended antiplanar (T) conformation about the C_α-C_β bond, but a folded (AG) conformation, intermediate between an anticlinal (A) and a synclinal one, about the C_β-O bond ($\Psi_3 = 162°$ and $\Psi_2 = -106°$)(+). After Carbachol this

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(+) Internal rotation angles are numbered in agreement with Shefter (9).

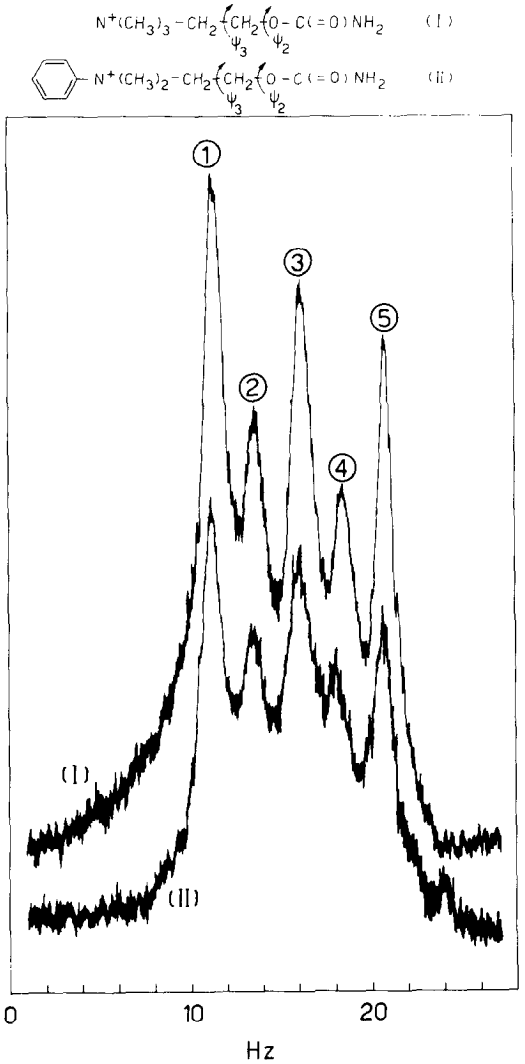

Fig. 1 : Part of NMR spectrum of Carbachol (I) and Phe-carbachol (II) in D_2O, showing N-CH_2 protons. The spectra are shifted to bring peaks number 1 into coincidence.

is therefore the second case of a cholinic derivative with unsubstituted atoms in the N^+-CH_2-CH_2-O segment to show an extended conformation about the C_α-C_β bond.

The interest for this molecule is furthermore enhanced by the consideration that crystal packing effects can be clearly appreciated in that Phe-carbachol differs from Carbachol in conformation about the C_β-O bond, in spite of the presence in both crystals of a Br--H-N-H--Br hydrogen bond net.

The behaviour in solution of this molecule offers another interesting opportunity for checking the degree of stability of a known conformation about the $-CH_2-CH_2-$ bond in cholinergic substrates; we have carried out therefore the NMR analysis of Phe-carbachol in D_2O solution.

The signals for the N-methylene protons (Fig. 1) turn out to be quite similar to those already reported for ACh[10] and Carbachol, it is possible therefore to derive for Phe-carbachol important conformational conclusions without carrying on a complete analysis of the spectrum.

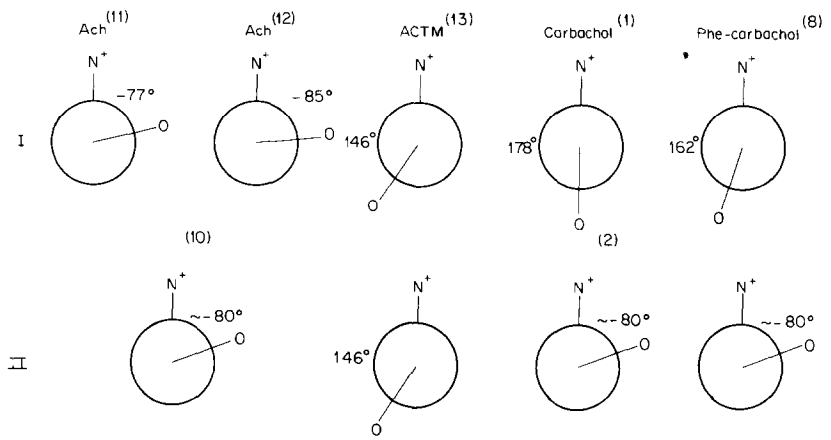

Fig. 2 : Newman projections of the N^+-C-C-O conformation for Phe-carbachol and some other significant molecules:
(I) Conformation in the solid state
(II) Conformation in solution
Conformation of ACTM in solution, due to ring rigidity, is assumed to be the same as in the solid state.
References are indicated in parentheses.

As shown from the detailed computations of Culvenor and Ham on ACh[10] and Conti et al.[2] on Carbachol the appearence of the 5-line multiplet of the N^+-CH_2 methylene signals allows the derivation of approximate values for the $N(J_{AX} + J_{AX}')$ and $L(J_{AX} - J_{AX}')$ parameters of the AA'XX' spin system directly from lines 1-5 and 2-4 of the multiplet.

For ACh, Carbachol and Phe-carbachol the 1-5

separation is 9.8, 9.4 and 9.5 Hz respectively whereas for the 2-4 separation the values are 4.2, 4.8 and 4.6 Hz.

In agreement with the analysis of Culvenor and Ham we can therefore conclude that Phe-carbachol, by preferring in solution, like ACh and Carbachol (Fig. 2), a folded synclinal conformation about the C_α-C_β bond, suggests the existence of low energy barriers among the allowed conformations and in the meanwhile indicates that the crystal packing forces are of sufficient strenght to make accessible to choline derivatives all the theoretically predicted conformations.

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References

1) Barrans, Y., and Clastre, J., C.r. hebd. Séanc. Acad. Sci., Paris, 270, 994 (1970)
2) Conti, F., Damiani, A., Pietronero, C., and Russo, N., Nature New Biology, 233, 232 (1971)
3) Sundaralingam, M., Nature, 217, 35 (1968)
4) Liquori, A. M., Damiani, A., and De Coen, J. L., J. Mol. Biol., 33, 445 (1968)
5) Ajò, D., Bossa, M., Damiani, A., Fidenzi, R., Gigli, S., Lanzi, L., and Lapiccirella, A., J. theoret. Biol., 34, 15 (1972)
6) Pullman, B., Courriere, Ph., and Coubeils, J. L., Mol. Pharmac., 7, 397 (1971)
7) Ajò, D., Bossa, M., Damiani, A., Fidenzi, R., Gigli, S., and Ramunni, G., 5° Jerusalem Symposium on "The Conformation of Biological Molecules and Polymers" (Jerusalem, 1972), in press
8) Barrans, Y., and Dangoumau, J., C. r. hebd. Séanc. Acad. Sci., Paris, 270, 480 (1970)
9) Shefter, E., in "Cholinergic Ligand Interactions" (edit. by Triggle, D. J., Moran, J. F., and Barnard, E. A.), 86 (Academic Press, London and New York, 1971)
10) Culvenor, C. C. J., and Ham, N. S., Chem. Comm. 15, 537 (1965)
11) Canepa, F. G., Pauling, P. J., and Sörum, H., Nature, 210, 907 (1966)
12) Herdklotz, J. K., and Sass, R. L., Biochem. Biophys. Res. Comm., 40, 583 (1970)
13) Chotia, C., and Pauling, P., Nature, 226, 541 (1970)