Theoret. chim. Acta (Berl.) 32, 77—79 (1973)

An *ab initio* SCF Molecular Orbital Study of Acetylcholine

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Received June 22, 1973

A standard *ab initio* (STO 3G) study indicates, in distinction to the *ab initio* molecular fragment results, that the preferred conformation of acetylcholine is gauche.

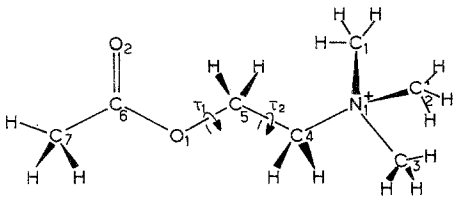
Key words: Acetylcholine – Conformational energy map.

The conformational properties of acetylcholine have been the subject of a greater number of theoretical investigations than have been those of any other molecule of pharmacological interest. Indeed, most of the approximate quantum-mechanical molecular orbital methods in current use (EHT, CNDO, INDO, PCILO) have been applied to this problem, as have also been the "empirical" procedures using partitioned potential functions. These studies have been reviewed and discussed recently [1, 2] in relation to the available experimental evidence: the most plausible results appeared to favor a *gauche* conformation of the cationic nitrogen with respect to the ester oxygen and indicate a moderate energy difference and a moderate energy barrier (3 - 4 kcal/mole) between this form and the fully extended one.

However, a recent computation with the "*ab initio* molecular fragments" procedure [3] somewhat reopened the problem by predicting the fully extended form as the most stable one, with relatively high values of the energy difference (10 to 19 kcal/mole) between this and the gauche forms. In view of this situation and also of other unsettled questions we deemed it interesting to construct a complete conformational energy map of acetylcholine using a *standard ab initio* SCF method. We chose the STO 3G procedure [4] which has proven satisfactorily reliable both in conformational [5, 6] and structure studies [7]. Computations were done using the programme Gaussian 70 [8].

For the geometrical input data we have used those of the acetylcholine chloride crystal [9]. The conformational energy map was built as a function of the two essential torsion angles τ_1 and τ_2 (see Fig. 1) at 30° intervals (we recall that the torsion angle τ of the bonded atoms A–B–C–D is the angle between the planes ABC and BCD viewed from the side of A; τ is positive for clockwise rotation of the far end with respect to the near one, with $\tau = 0°$ corresponding to the *cis*-planar arrangement of the bonds AB and CD).

The results are indicated in Fig. 2, where the isoenergy lines (in kcal/mole) are traced with respect to the global energy minimum taken as energy zero. This minimum corresponds to $\tau_1 = 150°$, $\tau_2 = 60°$ and represents a *gauche* arrangement about the C_4–C_5 bond. It is a broad minimum and the only really significant



I. ACETYLCHOLINE

$\tau_1 = \tau(C_6 - O_1 - C_5 - C_4)$

$\tau_2 = \tau(O_1 - C_5 - C_4 - N_1^+)$

Fig. 1. Atom numbering and torsion angles of interest in acetylcholine

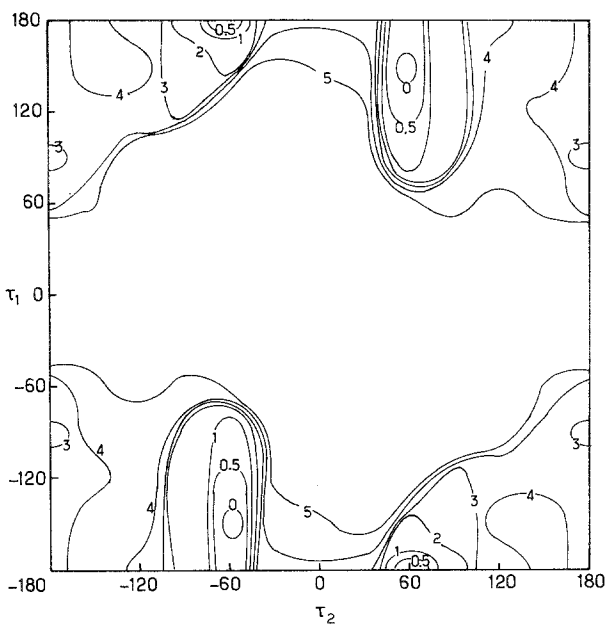


Fig. 2. Conformational energy map of acetylcholine. Energy contours in kcal/mole above global minimum ($\tau_1 = 150°$, $\tau_2 = 60°$) calculated *ab initio* (STO 3 G)

one. The fully extended *trans* form ($\tau_1 = \tau_2 = 180°$) is in a plateau region about 4 kcal/mole above the global minimum. The central region of the map is high in energy due to unfavorable steric interactions in the highly folded conformations where τ_1 and τ_2 approach zero. The map accounts satisfactorily for the observed *gauche* conformation of acetylcholine in its crystal [9] and in solution [10]. In its general features it is strikingly similar to the map constructed by the PCILO method [11] and contradicts the results of the molecular fragments method. As a second significant result of our *ab initio* treatment, we present in Fig. 3 the atomic charges obtained in the classical Mulliken population analysis for the

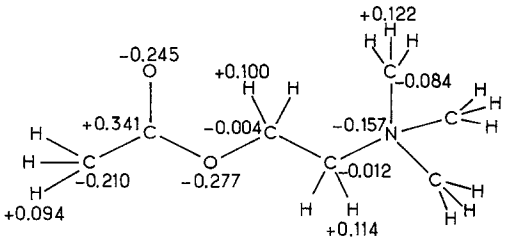


Fig. 3. *Ab initio* STO 3 G charges (electron units) in the global minimum form of acetylcholine (positive sign means deficiency of electrons). Hydrogen atom charges are the average of equivalent atoms

most stable *gauche* conformation of the molecule. Of particular interest is the distribution in the cationic alkyl ammonium head concerning which there have been disagreements among the previous computations. Thus the PCILO calculations [11] show the positive charge essentially distributed among the hydrogen atoms of the three methyl groups and of the α methylene group with the nitrogen and the adjacent carbon atoms nearly neutral. In contrast, computations by the INDO method [12] predict that the positive charge should be essentially localized on the nitrogen and the adjacent carbon atoms.

The distribution of charges in this part of the molecule is of obvious relevance to its interaction with a nucleophile such as water or a "cationic" receptor site. It is seen in Fig. 3 that the *ab initio* charges confirm the picture of the positive charge as being spread-out on the exterior of the cationic head on the methyl hydrogen atoms.

We thank the Royal Society for a fellowship (to G. N. J. Port) awarded under its European Programme.

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