MOLECULAR PHARMACOLOGY, 8, 371-373

SHORT COMMUNICATION

On the Conformation of Acetylcholine and Acetylthiocholine

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(Received January 10, 1972)

SUMMARY

A conformational map for acetylthiocholine has been constructed by the method of perturbative configuration interaction using localized orbitals. A global minimum, which is not apparent for acetylcholine, appears at τ_1 = 60–80 degrees and τ_2 = 180 degrees. This corresponds to a *trans* conformation and is in agreement with the preferred solution and crystal conformation.

We have recently studied (1) by the method of perturbative configuration interaction using localized orbitals (PCILO), the conformation of acetylcholine as a function of the torsion angles τ_1 and τ_2 (Fig. 1). The results summarized in Fig. 2 indicate the existence of a global energy minimum at τ_1 = 180 degrees and τ_2 = 60 degrees, corresponding to a *gauche* arrangement of the O_1 and N^+ atoms. A number of other local minima are present, including one, 3 kcal/mole above the global minimum at τ_1 = τ_2 = 180 degrees, corresponding to an all-*trans* conformation.

Figure 2 also depicts the X-ray-determined conformation of 17 acetylcholine derivatives [taken from a recent compilation by Baker *et al.* (2)] and thus extends our previous comparison between theory and experiment carried out with a more restricted number of compounds (1). The majority of the derivatives cluster in the region of the global minimum. In fact, as demonstrated by Baker *et al.* (2) (see also ref. 3), the great majority of structures of the $(CH_3)_3N^+$—C—C—O— type adopt the *gauche* conformation. A few compounds are close to other local minima and thus substantiate the significance of these minima as well.

Three compounds in Fig. 2, however, fall clearly outside the regions of predicted stability. One of them (No. 10) corresponds to a rigid cyclopropyl derivative whose conformational freedom is thus restricted. The other two (Nos. 11 and 12) represent analogues of acetylcholine in which the esteric oxygen is replaced by sulfur and selenium, respectively. It can be seen that these compounds adopt a *trans* conformation (4).

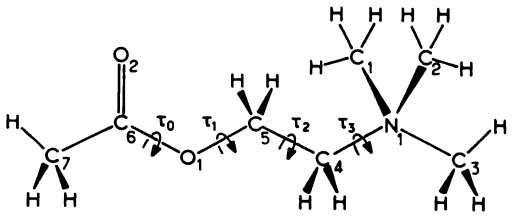

FIG. 1. *Torsion angles τ_1 and τ_2 in acetylcholine (and acetylthiocholine)*

In the computations it is assumed that τ_0 = τ_3 = 180 degrees (see ref. 1).

Because the replacement of O by S (or Se) represents an important structural

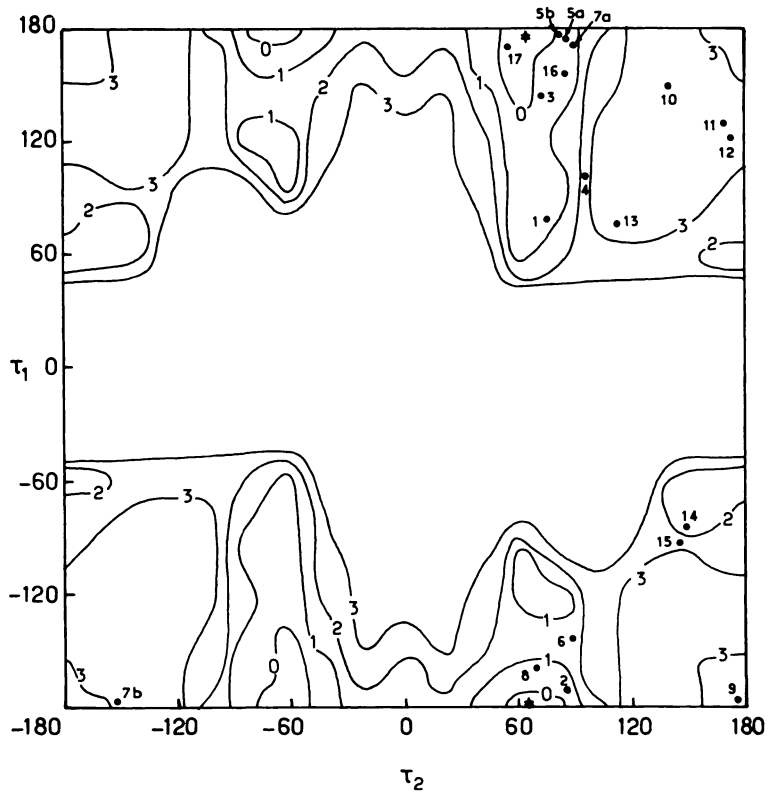

FIG. 2. *Conformational energy map of acetylcholine (PCILO method)*

Isoenergy curves in kilocalories per mole with respect to the global minimum, ±, taken as zero energy. Shown are experimental conformations (●) in crystals of: *1*, acetylcholine bromide; *2*, acetylcholine chloride; *3*, L(+)-muscarine iodide; *4*, L(+)-*cis*-2(S)-methyl-4(R)-trimethylammonium methyl-1,3-dioxolane iodide; *5*, 5-methylfurmethide iodide (*a* and *b*); *6*, L(+)-S-acetyl-β-methylcholine iodide; *7*, D(+)-R-acetyl-α-methylcholine iodide (*a* and *b*); *8*, *erythro*-acetyl-α(R),β(S)-dimethylcholine iodide; *9*, carbamoylcholine; *10*, (+)-*trans*-2(S)-acetoxycyclopropyl-1(S)-trimethylammonium iodide; *11*, acetylthiocholine bromide; *12*, acetylselenocholine iodide; *13*, (−)-R-3-acetoxyquinuclidine methiodide; *14*, 2(S)-trimethylammonium-3(S)-acetoxy-*trans*-decahydronaphthalene iodide; *15*, *threo*-acetyl-α(S),β(S)-dimethylcholine iodide; *16*, lactoylcholine iodide; *17*, dimethylphenylpiperazine.

change, the inclusion of acetylthiocholine in Fig. 2 may be questioned. We have therefore constructed a separate conformational energy map for this molecule. The results (Fig. 3) are striking. First, the allowed conformational space (within the same limit of 3 kcal/mole above the global minimum) has decreased considerably. Second, the region of the energy minimum corresponding to a *gauche* conformation has disappeared completely. Finally, a new global minimum has appeared at τ_1 = 60–80 degrees and τ_2 = 180 degrees, corresponding to a *trans* conformation, close to the observed one. The agreement between theory and experiment is thus satisfactory.

Both acetylcholine and acetylthiocholine conserve their preferred conformations, *gauche* or *trans*, in solution (5–7). While it is obvious from Fig. 3 that the conformation of acetylthiocholine is expected to be relatively frozen and should not depart from the *trans* one, a larger degree of conformational freedom is conceivable for acetylcholine in principle, on the basis of Fig. 2. Our calculations indicate, however, that the

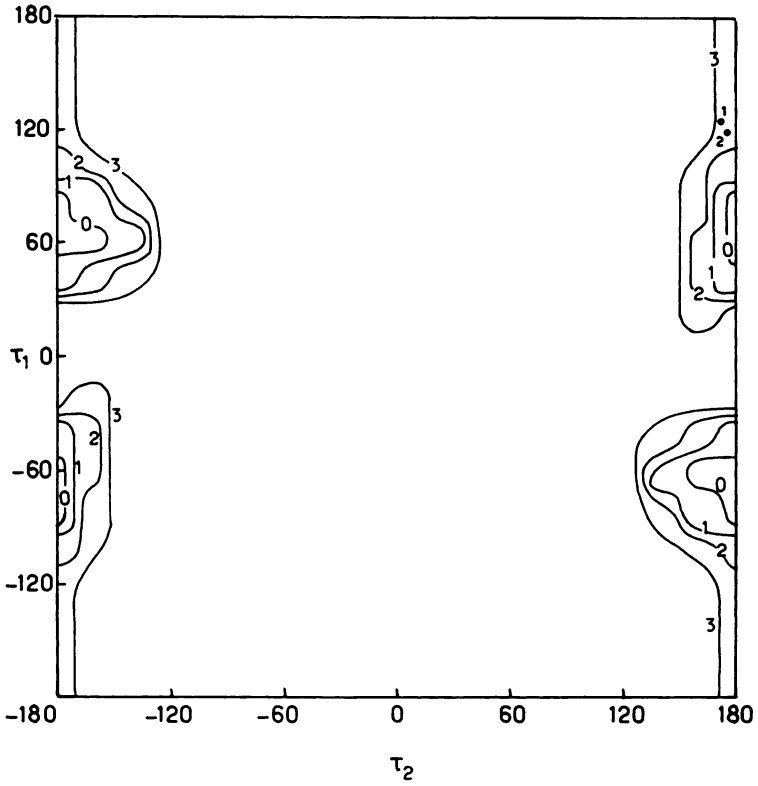

FIG. 3. *Conformational energy curve of acetylthiocholine (PCILO method)*
Isoenergy curves in kilocalories per mole with respect to the global minimum, ∔, taken as zero energy. Shown are experimental conformations (●) in crystals of: *1*, acetylthiocholine; *2*, acetylselenocholine (4).

transitions from the *gauche* to the *trans* conformation would involve a barrier height of about 4 kcal/mole. Apparently this barrier is sufficient to prevent the transition. [A similar barrier would be involved in the transition to the form postulated to be involved in hydrolysis by cholinesterase (τ_1 = 180 degrees, τ_2 = 150 degrees) (8). The environment of the enzyme may be more effective in this respect than the solvent, H_2O.]

Although calculations carried out for isolated molecules cannot a priori be considered representative of their conformations in crystals or in solution, the results presented here for acetylcholine derivatives and its analogues indicate a close relationship between the two situations.

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