MOLECULAR PHARMACOLOGY, 11, 663–666

The Use of the Counter-Ion in Molecular Orbital Calculations of Histamine Conformations

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(Received January 27, 1975)

SUMMARY

ABRAHAM, RAYMOND J. & BIRCH, DENIS (1975) The use of the counter-ion in molecular orbital calculations of histamine conformations. *Mol. Pharmacol.*, 11, 663–666.

The introduction of the counter-ion into complete neglect of differential overlap (CNDO) calculations of the conformations of histamine dication and the two monocations produces results in good agreement with the observed conformations in aqueous solution. The significance of these results and their relationship to the "supermolecule" approach is discussed.

INTRODUCTION

The use of molecular orbital calculations to predict the conformations of biologically active molecules in solution is of increasing importance (1), providing in principle a powerful and often unique method of obtaining such information.

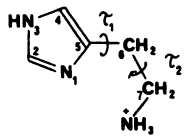
However, the proper evaluation of solvent effects still raises many problems. For specific solvation one of the most promising lines of approach is to include explicitly the solvating species, as in the supermolecule approach of Pullman and coworkers (2, 3). We wish to outline here an alternative, complementary approach which to date has not been considered, the use of the counter-ion, and to show that this is also capable of promising results for the case of histamine.

Because of the importance of histamine in pharmacology, numerous molecular orbital calculations have been performed on histamine and its charged species (2, 4–6) (Fig. 1). (We follow the nomenclature and conventions of refs. 2 and 5.)

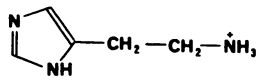
Originally Kier (4) and later, more extensively, Ganellin *et al.* (5, 6) showed that extended Hüuckel theory calculations predicted two populated rotamers for both the dication and predominant monocation (Fig. 1a), a *trans* (τ_2 = 180°) and a *gauche* (τ_2 = 60°) rotamer, with the *trans* more stable by approximately 1 kcal/mole in both cuses. These conclusions were shown to agree with the experimental results for aqueous solutions, but also, somewhat surprisingly, CNDO calculations gave the very different predictions that the dication would be predominantly *trans* and the monocation predominantly *gauche* (5). Pullman and Port (2), using the PCILO[1] method, obtained results similar to the CNDO calculations and also confirmed these by STO-3G calculations *ab initio* on the isolated molecule. The discrepancy between these calculations for the isolated molecule and the aqueous solution data was then resolved by these workers using

[1] The abbreviations used are: PCILO, perturbative configuration interaction using localized orbitals; CNDO, complete neglect of differential overlap.

(a)



(b)



(c)

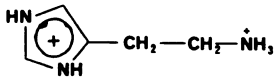


FIG. 1. *N_3—H monocation (a), N_1—H monocation (b), and dication (c) of histamine*
The form shown corresponds to $\tau_1 = \tau_2 = 0°$.

the "supermolecule" approach, in which all the hydration sites are bound by water of solvation.

METHODS

Our calculations use instead the $\bar{F}$ counter-ion, together with the CNDO approximation (7», as follows: Calculations on simpler molecules are required originally in order to fix the minimum energy position of the $\bar{F}$, which is found along the N—H bond of the $^+NH_3$ group with an HF distance of 1.15 A. This is kept constant in all subsequent calculations. Furthermore, to preserve the symmetry of the $CH_2 \cdot CH_2 \cdot {}^+NH_3$ side chain, the fluorine atom is positioned in a *trans* orientation to C_6 (Fig. 1).

With this addition, which is the *only* extra modification for both the dication and the monocation calculations, the energies for the *gauche* and *trans* rotamers have been calculated as a function of the τ_1 dihedral for the two cases and compared with the calculations for the isolated molecules in Figs. 2–4. For the purposes of this comparison it is not necessary to obtain a complete conformational energy map, and these results can be directly compared in this form with the CNDO and extended Hüuckel theory results of ref. 5 and the calculations *ab initio* of ref. 2.

RESULTS AND DISCUSSION

The results are of some interest. The considerable extra stability of the *trans* rotamer of the dication in the isolated molecule is almost completely removed to give an energy difference of about 1 kcal/mole in favor of the *trans* form (Fig. 2). Similarly, the large stabilization of the *gauche*

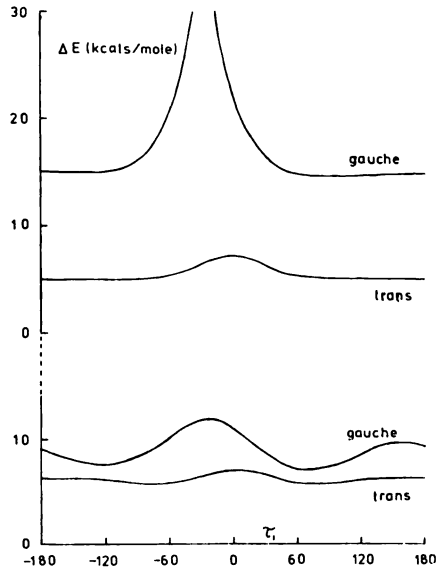


FIG. 2. *Calculated energies (CNDO) for histamine dication (above) and histamine dication monofluoride (below)*

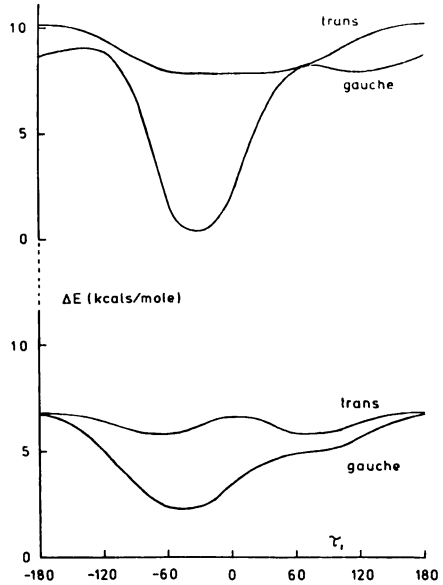


FIG. 3. *Calculated energies (CNDO) for histamine monocation N_3—H tautomer (above) and monofluorides (below)*

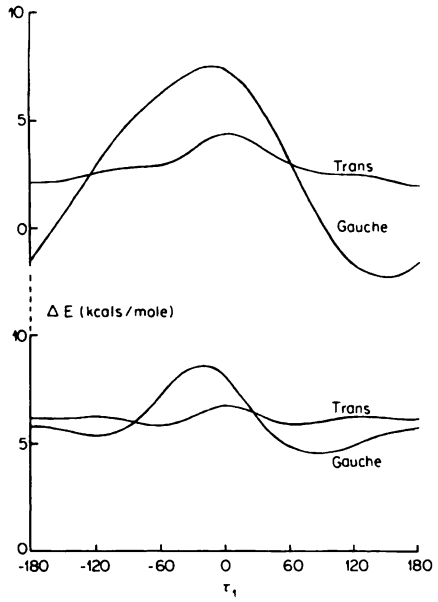


FIG. 4. *Calculated energies (CNDO) for histamine monocation N_1—H tautomer (above) and monofluoride (below)*

isomer of the monocation is now very considerably reduced, although this is still calculated to be the most favored form (Figs. 3 and 4).

The calculated rotamer energies are now in much better agreement with the observed rotamer populations [54% *trans* for the dication and 45% *trans* for the monocation (5)]. Indeed, the calculated rotamer energy difference for the dication is essentially identical with that observed experimentally (approximately 0.5 kcal/mole), a fortuitous but encouraging result. The experimental value for the monocation is around zero kcal/mole, but this of course is an average for the two N—H tautomers. [Ganellin (8) has estimated that 20% of the monocation exists as the N_1—H tautomer.] Thus the calculated *gauche* to *trans* ratio has to be averaged over the two tautomers. This would still favor the *gauche* rotamer, but only by a small amount.

Thus the simple addition of the counter-ion has given CNDO calculated energies in very reasonable agreement with experimental energies for aqueous solution. These results also support the general conclusions of Pullman and Port (2), based on the hydrated molecule approach, that the solution effect is essentially a buffering one, as regards both the repulsion between the two positive charges in the dication and the attraction between the $^+NH_3$ and the N_1 lone pair in the monocation. In the hydrated molecule calculations the N_1 atom was hydrated by a water molecule, which of course alters both the electronic and steric requirements at that atom. However, the same buffering has been obtained in our calculations without adding any further atom other than the $\bar{F}$, which will have zero steric interaction with N_1 in any conformation, and which will also leave essentially unchanged all the other steric interactions in the molecule. This demonstrates both the importance of the electrostatic interactions in these calculations and the extent to which they are reduced by the counter-ion.

It is, however, very important to add a cautionary note. It is clearly evident that neither this method nor the supermolecule approach can realize all the often subtle and complex effects of the aqueous solvent on conformational equilibria, which may be due as much to long-range order in the solvent as to any other cause.

It is more rigorous to regard the counter-ion approach as a relatively simple method of obtaining an approximation to the real situation, and it is pertinent to note that the computational advantages of using 1 extra atom in contrast to 4 water molecules are not insignificant, and may be essential for the calculation of larger molecules.

A more fundamental question is whether the solute molecule is hydrated or exists as an ion pair. Undoubtedly one would expect that at low concentrations in aqueous media a strong base such as histamine monocation should exist largely as the hydrated species. However, at higher concentrations (such as usually occur in NMR measurements) and, more importantly, in nonaqueous media, such as lipids, the existence of ion pair formation is much more likely, and this approach could then mirror the actual conformer situation in such a case.

The two approaches of the hydrated molecule and the ion pair could in principle be

differentiated, as the wave function of the solute, and therefore the net atomic charges, etc., differs for the two cases.

ACKNOWLEDGMENTS

We are most grateful to Dr. C. R. Ganellin for first drawing this problem to our attention and for his interest and encouragement, and to Professor and Mme Pullman for communicating their results prior to publication.

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