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# The preferred conformation of noradrenaline and a consideration of the α-adrenergic receptor

LEMONT B. KIER

*Division of Biochemistry, Columbus Laboratories, Battelle Memorial Institute, Columbus, Ohio, U.S.A.*

The preferred conformation of noradrenaline has been calculated using extended Hückel molecular orbital theory. The conformation was found to be identical to the previously calculated conformation of (–)-ephedrine in respect to the relation of the quaternary and hydroxyl groups and the phenyl ring. These findings reinforce the previous hypothesis of the nature of the α-adrenergic receptor and also support the view that these molecules function at the receptor in their preferred conformations.

In a previous study, the preferred conformation of ephedrine and pseudoephedrine was calculated using molecular orbital theory (Kier, 1968d). The results indicated that ephedrine and pseudoephedrine had preferred conformations represented by Fig. 1a and b, respectively. The presentations of the four isomers to an assumed relatively planar receptor led to a hypothesis of a receptor pattern that was consistent with the ranking of α-adrenergic potency of the four compounds (see Fig. 2).

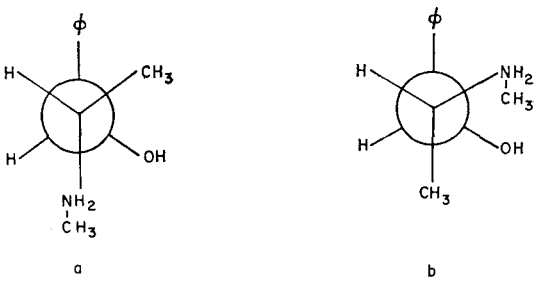



FIG. 1. Calculated preferred conformations of ephedrine (a) and ψ-ephedrine (b).

In view of the results of this work on ephedrine isomers, it now seems appropriate to pursue the same kind of approach with noradrenaline, the most potent of the α-adrenergic agonists, to determine whether the calculated preferred conformation of this molecule is consistent with the postulated hypothetical α-adrenergic receptor model.

A few comments on the molecular orbital theory and the use of the preferred conformation to describe the receptor are in order. Molecular orbital calculations are made on conservative molecules, that is, molecules that do not interact with an environment. The relation between the calculated geometry and the geometry in a crystal or in solution is unknown. However, demonstration of consistency among calculated, crystal, and solution data in our laboratory (Kier, 1967a, b; 1968a, b, c, d)

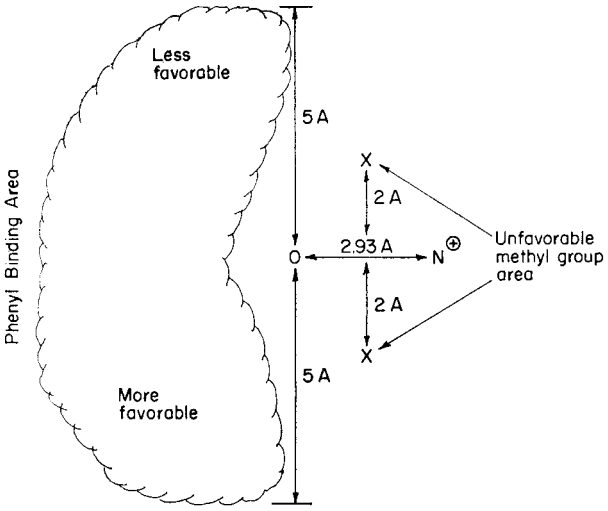



FIG. 2. Postulated α-adrenergic receptor features based on ephedrine isomer studies (Kier, 1968d), and noradrenaline studies (present work).

as well as by others (Giordano, Hamann & others, 1967; Jordan & Pullman, 1968) is an encouraging sign that a relation perhaps exists.

My calculations have revealed energy minima for a particular conformation, from which I have derived hypotheses concerning the corresponding biological receptors. Although it could be argued that a drug molecule may not interact to form a drug-receptor complex in its preferred conformation, it is assumed that interaction occurs in the preferred form. A further premise that has been made is that a calculated rotational barrier of sufficient magnitude will not be overcome by interaction with solvent or another molecule, provided the approach of the drug to the receptor does not permit covalent bond formation. This is certainly so in the highly reversible agonists I have examined to date. Even if the drug in its preferred conformation is not complexed with the receptor, some specific conformation related to the preferred one must engage the receptor or the high degree of structural specificity found for many agonists would not be experienced. The potent muscarinic agents acetylcholine, muscarine and muscarone were found (Kier, 1967b) to present three comparable heteroatoms in a similar relation in their calculated preferred conformations. This consistency suggested that, in this instance, the molecules function at their common muscarinic receptor in their preferred conformations. In a study of histamine (Kier, 1968b), it was found that histamine in its $H_1$ preferred conformation presented two nitrogen atoms separated by a distance comparable to the internitrogen distance in a potent antagonist molecule. In a third study, on 5-hydroxytryptamine, the internitrogen distance in the calculated preferred conformation corresponded to the internitrogen distance in the potent antagonist lysergic acid diethylamide (Kier, 1968c).

These three examples offer a reasonable justification for a working hypothesis that many drug molecules, engaging their receptors in noncovalent complexes, do so in their preferred conformations. As will be seen, the work on the ephedrine isomers and the present study on noradrenaline are a fourth example supporting this hypothesis.

## EXPERIMENTAL

The parameters for the extended Huckel-theory calculations were those previously used (Kier, 1967a). The bond lengths were adopted from X-ray data (Carlstrom & Bergin, 1967) that were known, or were assumed to be, of standard length (Pople & Gordon, 1967). The protonated form of the molecule was considered. The phenolic hydroxyl groups were held stationary, *trans* to each other in relation to the ring plane. The C–C bond of the side-chain was rotated by 60° increments through a full cycle. The phenyl-C bond was considered every 90°.

## RESULTS

The total energy versus angle of rotation of the side-chain C–C bond (Fig. 3) reveals a definite minimum at 180°. At this angle, the amino-group is *trans* to the phenyl ring. The distance separating the oxygen and nitrogen atoms is 2·86Å.

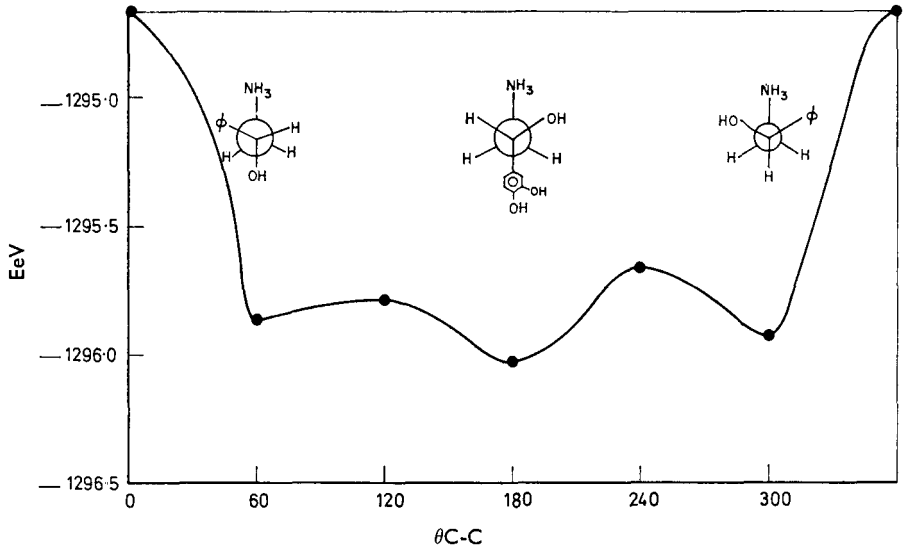
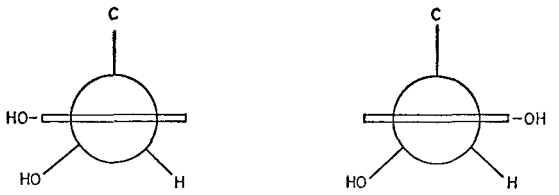



FIG. 3. Energy versus rotation angle of C–C bond in side chain of noradrenaline.




Ia Ib

Rotation of the phenyl group revealed identical energy minima for the 90° and 270° rotamers, depicted by Ia and Ib respectively. Thus, the *meta*-hydroxyl group does not discriminate in either of the two preferred conformations.

The calculated conformation and the conformation derived from X-ray analysis of crystalline (—)-noradrenaline hydrochloride (Carlstrom & Bergin, 1967) are identical.

## DISCUSSION

The calculated preferred conformation of noradrenaline places the nitrogen, oxygen, and phenyl ring of the molecule in the same relation as was found in the calculations of the preferred conformation of ephedrine (Kier, 1968d). The oxygen-to-nitrogen atomic distance in noradrenaline (2·86 Å) is very close to the 2·93 Å interatomic distance calculated for ephedrine. The modest difference is due to the slightly different bond lengths used in calculations.

If a relatively planar receptor surface is assumed, the noradrenaline molecule, in its preferred conformation, could present to this receptor the oxygen, nitrogen, and phenyl ring in an identical manner as does (–)-ephedrine. The *meta* hydroxyl group could be positioned at either Ia or Ib with equal preference, according to these calculations. These findings support my hypothesis of the nature of the α-adrenergic receptor (Fig. 2). The greater potency of noradrenaline over (–)-ephedrine must be due to the presence of at least one phenolic hydroxyl group. That both noradrenaline and (–)-ephedrine are α-adrenergic agonists, and that both present key features in an identical manner in their calculated preferred conformation, and also that both calculations agree with physical data, lends validity to the calculations. It also supports the view that these two molecules engage their receptor in their preferred conformations.

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