2,2′-Diethoxy-*N*-formylbenzhydrylamine (**30**) was obtained in 93% yield (10.2 g), mp 170–171°. *Anal.* ($C_{18}H_{21}NO_3$) C, H, N.

2,2′-Dialkoxybenzhydrylamines.—A suspension of 10 g of the appropriate *N*-formyl derivative in 50 ml of HCl 5% was refluxed until a clear soln was obtd. After cooling the amine·HCl crystd.

2,2′-Dimethoxybenzhydrylamine·HCl (**31**) was obtained in 76% yield (7.8 g), mp 246–247°. *Anal.* ($C_{15}H_{18}ClNO_2$) C, H, Cl, N.

2,2′-Diethoxybenzhydrylamine·HCl (**32**) was obtained in 85% yield (9.8 g), mp 239–240°. *Anal.* ($C_{17}H_{22}ClNO_2$) C, H, Cl, N.

2,2′-Dialkoxybenzhydrylamides.—A soln of 0.01 mole of $ClCOCH_2Cl$ or $BrCOCHBrCH_3$ in 10 ml of C_6H_6 was added over a period of 0.5 hr to a cold, stirred soln of 0.02 mole of the appropriate free benzhydrylamine in 10 ml of C_6H_6. The mixture was kept at 20–25° for 12 hr and then filtered. The filtrate was treated with an excess of the appropriate amine and the mixture was refluxed for 15 hr. After cooling, C_6H_6 extract was filtered, washed twice with H_2O, and dried ($MgSO_4$), the solvent was evaporated, and the hydrochloride was prepared (EtOH–ether).

2,2′-Dialkylbenzhydryl Esters.—A soln of 0.01 mole of $ClCOCH_2Cl$ or $BrCOCHBrCH_3$ in 10 ml of C_6H_6 was added over a period of 0.5 hr to a cold, stirred soln of 2.12 g (0.01 mole) of di-*o*-tolylcarbinol[10] and 0.89 ml (0.011 mole) of pyridine in 30 ml of C_6H_6. The mixture was stirred an addn 0.5 hr. It was filtered, the filtrate treated with an excess of the appropriate amine, and the mixture kept at 40–45° for 3 days. After cooling, it was treated as described in the above procedure.

Acknowledgment.—We thank the Instituto Nacional de Farmacologìa y Bromatologìa for providing the necessary facilities for biological assays. This work was supported by a grant from the Consejo Nacional de Investigaciones Cientìficas y Técnicas.

(10) H. H. Hatt, *J. Chem. Soc.*, 1631 (1929).

Molecular Orbital Conformation of Phenyl Choline Ether

LEMONT B. KIER*

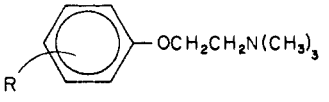
Columbus Laboratories, Battelle Memorial Institute, Columbus, Ohio

AND JACK M. GEORGE

College of Medicine, The Ohio State University, Columbus, Ohio

Received July 1, 1970

Over the past decade a considerable amount of theoretical interest has been shown in the structural considerations of the nicotinic activity of a variety of molecules. Fukui studied a series of phenyl choline ethers, (I), using simple Hückel MO calculations.[1]



I

The study revealed that the substituent groups influence frontier electron density at the O and the superdelocalizability at the ortho positions, and that these indices correlated with nicotinic activity. The suggestion was made that the O atom and the ortho position on the ring might be spatially related to the onium group in the phenyl choline ethers in the same manner as the ether and CO oxygen atoms in the potent nicotinic agent, ACh (Figure 1). Thus an ortho ring position would play a role at the receptor comparable to the carbonyl O atom.

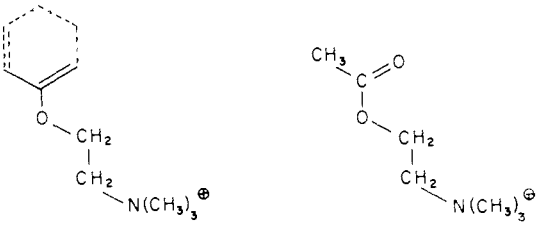


Figure 1.—Spatial relationship between phenyl choline ether and acetylcholine postulated by Fukui[1] and predicted from this study.

We have reported extended Hückel MO calculations on both ACh[2] and nicotine[3] in which we concluded that both nicotine and ACh can assume preferred conformations in which the pyridine N and carbonyl O atoms, respectively, are of similar distance from the onium groups in each molecule (Figure 2). The role

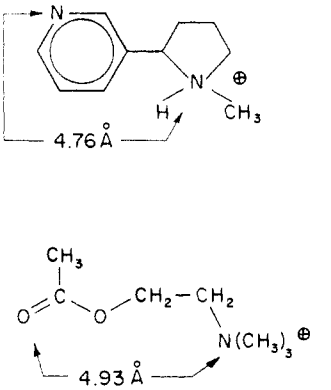


Figure 2.—Spatial relationship between nicotine and acetylcholine in their predicted preferred conformations.[3]

of the ether O in the nicotinic activity of ACh is not evident from this comparison, since there is no atom in nicotine that appears equivalent to the ether O at a receptor. The receptor equivalence of the pyridine N and the carbonyl O is certainly suggested from these studies.

In a recent study by Crow, *et al.*, a series of ring-substituted phenyl choline ethers was considered using simple Hückel theory.[4] The relationships between calculated reactivity indices and nicotinic activity revealed correlations only with the energy of the highest occupied MO and the superdelocalizability at the ring ortho positions. These findings agree with those of Fukui[1] except for the lack of a correlation between an oxygen reactivy index and activity. The suggestion arising from these results was that the aromatic ring interacts with the receptor, probably at one of the ortho positions, to form a charge-transfer complex.

A basic problem still remains with the phenyl choline ethers if the ortho ring position is to be seriously considered as mimicking the carbonyl O of ACh at the

* To whom correspondence should be addressed.

(1) F. Fukui, C. Nagata, and A. Imamura, *Science*, **132**, 87 (1960).

(2) L. B. Kier, *Mol. Pharmacol.*, **3**, 487 (1967).

(3) L. B. Kier, *ibid.*, **4**, 70 (1968).

(4) J. Crow, O. Wassermann, and W. Holland, *J. Med. Chem.*, **12**, 764 (1969).

nicotinic receptor. That problem is whether a phenyl choline ether molecule has a conformational preference, as suggested by Fukui[1] (Figure 1), relating the features of both molecules. The subject of this study is therefore the prediction of the phenyl choline ether conformation.

Experimental Section

The calcns were made using the extended Hückel theory first described by Hoffmann.[5] The parameters employed were those suggested by Hoffmann[6] and employed by us.[2] We have used this approach extensively to study the conformations of a wide variety of drug molecules with significant success in reproducing experimental values.[6,7] In spite of its limitations, Hoyland has shown that extended Hückel theory is superior to currently available semiempirical MO methods for the prediction of conformation.[8] In this study we have calcd the conformation of unsubstituted phenyl choline ether, assuming that the ring substituents considered by Fukui[1] and Crow[4] were sufficiently removed from the aliphatic bonds studied that their influence on the conformational preference would be negligible. We have previously justified this assumption with a quantum mechanical argument.[9] The $^{+}NMe_3$ group was assumed to be staggered to the atoms bonded to the adjacent C and was held in this conformation throughout the study.

Results

The series of calculations on phenyl choline ether have led to a minimum total energy corresponding to the conformation shown in Figure 3. As can be seen in Figure 3a, the O, N relationship is predicted to be gauche, while the phenyl ring plane is perpendicular to the O–CH_2 bond, as shown in Figure 3b.

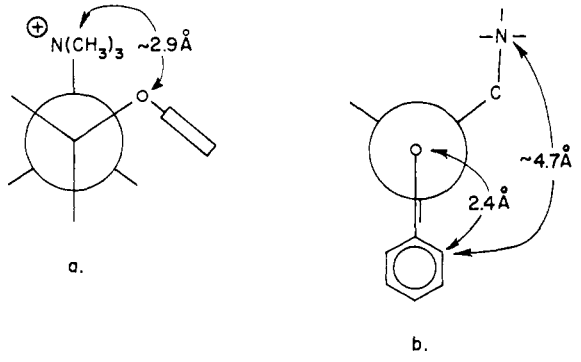


Figure 3.—Calculated preferred conformation of phenyl choline ether (a) viewed down the CH_2–CH_2 bond and (b) viewed down the O–CH_2 bond.

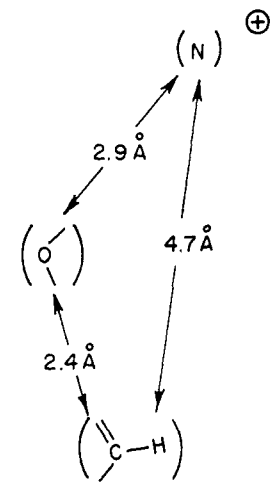


Figure 4.—Calculated pattern of atoms in phenyl choline ether.

The distances separating the center of the onium group, the O, and the nearest ortho ring position are shown in Figure 4. The N to ring ortho C atom distance is predicted to be 4.62 Å, while the distance presumed to be comparable in nicotine was 4.76 Å[3] and in the "nicotinic conformation" of ACh, 4.93 Å.[6]

Discussion

The calculations show that an ortho position of the Ph ring can assume a distance from the onium group close to the range predicted for comparably charged atoms in nicotine and ACh. This finding supports the suggestion made by Fukui[1] and extends the conclusions reached by Crow, *et al.*[4] From our study on nicotine[3] and the failure to demonstrate an ether O index correlating with activity,[4] we are lead to restate our previous conclusions that two features in a nicotinic molecule are primarily responsible for activity. The calculations in this study, however, show that the ether O in phenyl choline occupies a position relative to the onium group and a ring ortho position in the same molecule, roughly similar to the pattern predicted for the 3 comparable atoms in ACh in its "nicotinic" conformation. This ether O may not, however, be functional at the nicotinic receptor.

We conclude from this study that the predicted conformation of phenyl choline ether leads to structural features similar to those previously hypothesized to be the nicotinic pharmacophore.

Acknowledgment.—This study was supported by National Institutes of Health Grant GM-16321.

(5) R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963).
(6) L. B. Kier in "Fundamental Concepts in Drug–Receptor Interactions," J. Danielli, J. Moran, and D. Triggle, Ed., Academic, New York, N. Y., 1970.
(7) L B. Kier in "Molecular Orbital Theory in Drug Research," Academic, New York, N. Y., 1971.
(8) J. R. Hoyland in "Molecular Orbital Studies in Chemical Pharmacology," L. B. Kier, Ed., Springer-Verlag, New York, N. Y., 1970.
(9) L. B. Kier, *J. Med. Chem.*, **11**, 441 (1968).