The effects of the anions on uptake of the amines differ from the effects on the release of catecholamines from chromaffin vesicles by these two agents in three important respects.   First, although amphetamine is a more potent releasing agent than tyramine in all the media it is taken up much less, suggesting that amphetamine may be acting on the chromaffin vesicle in a different manner from tyramine.   Second, neither amine releases catecholamines in Na_2SO_4 or in NaCl, although both are taken up to the same extent in these media as they are in the other media.   Third, release of catecholamines by either amine was similar for incubation in $NaHCO_3$ and Na_2CO_3, but uptake was 4-fold less in $NaHCO_3$ than in Na_2CO_3.   It appears that the various anions affect release of catecholamines by mechanisms other than by altering the uptake of the releasing agent.

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The role of solvent interaction in quantum pharmacological studies

Molecular orbital (MO) studies of pharmacological agents are becoming an increasingly important area of research (cf. Kier, 1971, 1972).   However, the physical model from which the quantum mechanical methods are derived probably resembles the molecule most nearly as it exists in the vapour phase.   Consequently, the question arises as to whether the results of MO studies are valid for the molecule in solution, the physical state of greatest interest to the pharmacologist.   The general agreement between calculated configurations and those deduced from crystallographic and/or nmr data, when available, has been used as an argument that the calculated results are applicable to the more interactive states.   In this note, however, the results of a different approach to this question are reported.   The basic Hartree-Fock (H-F) self-consistent field (SCF) MO formalism described by Roothaan (1951) has been applied to two classical physical models of a molecule in solution.   A conformational study of noradrenaline (protonated) has then been made, incorporating each of the two

solvent interaction models, and the results compared to those obtained by means of the usual unmodified H-F MO method.

In the H-F SCF MO formalism described by Roothaan (1951), it is assumed that a closed-shell molecular system of M electrons and N nuclei is adequately described by a wave function consisting of a single asymmetric product of molecular orbitals, ϕ_i. The energy of the molecular system is then given by

$$E = 2 \sum_{i=1}^{M/2} \int_v \phi_i^* H \phi_i d\tau + \sum_{i=1}^{M/2} \sum_{j=1}^{M/2} \left[2 \int_{v_2} \int_{v_1} \frac{\phi_i^*(1)\phi_j^*(2)\phi_i(1)\phi_j(2)d\tau_1 d\tau_2}{r_{12}} \right. $$
$$\left. - \int_{v_2} \int_{v_1} \frac{\phi_i^*(1)\phi_j^*(2)\phi_j(1)\phi_i(2)d\tau_1 d\tau_2}{r_{12}} \right] + \frac{1}{2} \sum_{i}^{N} \sum_{\substack{j \\ i \neq j}}^{N} \frac{z_i z_j}{r_{1j}} \qquad (1)$$

where E is the energy, H is the one-electron Hamiltonian, and the volume integrals are overall space. In the first solvent interaction model (Model I), the molecule is pictured as a charge distribution within an infinite dielectric continuum of dielectric constant ϵ. This model has been used by Jortner (1962) and Newton (1973) in studies on the solvated electron. The total energy of the system is assumed to be the sum of the molecular energy (self-energy of the charge distribution), given by equation (1), and the reversible work required to charge the dielectric medium (Marcus, 1956):

$$U = -(1/8\pi)(1-1/\epsilon) \int_v \hat{D} . \hat{D} \, d\tau \qquad .. \qquad .. \qquad .. \qquad (2)$$

where $\hat{D}$ is the electric displacement vector. Since $\hat{D}$ can be expressed in terms of the system MO's (charge density), the total energy expression may be used in the usual variational treatment (Roothaan, 1951), an appropriate Fock operator derived, and the MO solutions determined by the usual iteration method.

The second model (Model II) is based on the Onsager concept of a molecule in solution (Onsager, 1936). The molecule is now pictured as a point dipole contained within a spherical cavity of radius 1 in an infinite dielectric medium with dielectric constant ϵ and refractive index n. By electrostatic and inductive polarization of the dielectric, a reaction field (MacRae, 1957; Mataga & Kubota, 1970)

$$\hat{R} = (2\hat{\mu}/l^3) [(\epsilon-1)/(\epsilon + 2) - (n^2-1)/(n^2+2)] \qquad .. \qquad .. \qquad (3)$$

is created within the cavity, $\hat{\mu}$ being the resultant molecular dipole. The total energy of the system is assumed to be the sum of the molecular energy, equation (1), and the solute-solvent interaction energy given by

$$U = -\hat{\mu} . \hat{R} \qquad .. \qquad .. \qquad .. \qquad (4)$$

Since the dipole moment can be expressed in terms of the system MO's, the total energy expression may be used in the variational treatment (Roothaan, 1951), and an appropriate Fock operator derived to be used for obtaining the MO solutions.

Parameters introduced in Model I are the solvent dielectric constant, ϵ, and the Van der Waal's radii of the constituent atoms which are used to specify a molecular cavity assumed to be a series of small spherical cavities, one centered at each atomic centre and having a radius equal to the Van der Waal's radius of the appropriate atom. In Model II, the dielectric constant, ϵ, and refractive index, n, of the solvent, as well as a cavity radius, 1, equal to the maximum length of the molecule, are introduced. Both of the theoretical models, as used in the present study, would be inappropriate to

Table 1. *Comparison of CNDO/2 conformational studies of noradrenaline (protonated) made with each of two solvent interaction models and in the usual (no solvent interaction) manner.* Relative molecular energy for a given method of calculation is relative to the absolute value obtained for the low energy configuration using that particular method. CNDO/2 molecular energies, dipole moments, and net charges on the β-hydroxyl oxygen and onium nitrogen at the low energy configuration ($\theta = 180°$) are also given.

Relative Molecular Energy† vs –CH(OH)–CH₂– rotation angle‡						Calculated Parameters at $\theta = 180°$			
0°	60°	120°	180°	240°	300°	Energy	Dipl. Mom.§	QN*	Qo*
CNDO/2 No solvent interaction									
11·4214	6·0433	0·8673	0·00	3·2212	8·7124	−1324·9651	10·026	−0·0113	−0·2725
CNDO/2 Model I interaction									
Acetonitrile									
11·2723	5·9618	0·8639	0·00	3·1836	8·6221	−1325·7665	12·107	+0·1122	−0·2573
Water									
11·2718	5·9600	0·8637	0·00	3·1829	8·6202	−1325·7776	12·145	+0·1140	−0·2571
CNDO/2 Model II interaction									
Acetonitrile									
11·4158	6·0391	0·8649	0·00	3·2208	8·7072	−1324·9580	10·297	−0·0122	−0·2707
Water									
11·4153	6·0387	0·8647	0·00	3·2207	8·7068	−1324·9575	10·314	−0·0123	−0·2706

† Energies given in Hartree units (1 Hartree = 27·21 eV).
‡ Bond rotation angle θ defined in Fig. 1.
§ Dipole moment in Debye units.
* Calculated net charges on β-hydroxyl oxygen and onium nitrogen in units of electronic charge, *e*.

situations of actual solute-solvent molecular complexing and high solute concentrations.

The more technical aspects of the theoretical methods, including calculations on *N*-nitrosodimethylamine and *NN*-dimethylformamide using a full overlap Mulliken MO method (Germer, 1973), will be presented elsewhere. In the present study of noradrenaline, the zero-differential overlap (ZDO) approximation was applied to the theoretical expressions. The appropriate expressions were then incorporated into the otherwise unmodified CNDO/2 method of Pople & Segal (1966). The CNDO/2 method is, of course, a highly approximated form of the basic H–F SCF MO method.

Calculations on the protonated form of noradrenaline were made with both the unmodified CNDO/2 method and CNDO/2 programs incorporating the above two solute-solvent interaction models. In the calculations with solvent interaction, solvent parameters for acetonitrile ($\epsilon = 38\cdot8$, n = 1·3441) and water ($\epsilon = 78\cdot54$, n = 1·3329) were used. Results of the conformational study are given in Table 1. The –CH(OH)–CH₂– bond rotation angle, θ, is defined in Fig. 1. The so-called *trans* form ($\theta = 180°$) is found to be the low energy conformation in all cases. This is in general agreement with the previous results of Kier (1969) and Pedersen, Hoskins & Cable (1971). Specific differences in the rotation angle versus energy function may be attributed to the use of a generalized molecular geometry (Table 2) in the present study instead of the crystal geometry of Carlstrom & Bergin (1967) used in the earlier
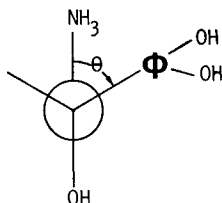

FIG. 1. Definition of –CH(OH)–CH₂– bond rotation angle θ.

Table 2. *Bond lengths and bond angles of noradrenaline molecular geometry used in study.*

Atoms	Bond length (Å)	Bond angle
C (*tetrahedral*)		109·4712°
C–C (tet.)	1·541	
C–C (pla.)	1·530	
C–N	1·472	
C–O	1·427	
C–H	1·091	
C (*planar*)		120·0°
C–C	1·395	
C–O	1·360	
C–H	1·084	
N (*tetrahedral*)		109·4712°
N–H	1·014	
O (*hydroxyl*)		108·9°
O–H	0·956	

work. Also shown in Table 1 is a comparison of the calculated molecular dipole moments and charges on the beta hydroxyl oxygen and onium nitrogen for the molecule in its low energy configuration. The dipole moment increases when the presence of the solvent is taken into account as would be predicted from simple electrostatic considerations. The charge on the oxygen becomes less negative with both interaction models, while the nitrogen becomes significantly more positive with Model I and slightly more negative with Model II. The important point of this study, however, is that while changes in charge distribution which are assumed to occur in the presence of a solvent can, in fact, be seen in the calculated results, the conclusions drawn from the conformational study with no provision for solvent interaction are not altered by the inclusion of solvent interaction.

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