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Ab Initio MO Study of Hydrogen Bonded Complex: Noradrenaline — Formic Acid*

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The ionic complex ethanolammonium-carboxylate serves as a model of the interaction between the noradrenaline side chain and anionic sites in the biophase. Proton transfer properties and the influence of water on this process were investigated using an ab initio MO method. In all cases considered the proton transfer from the side chain nitrogen to the carboxylate oxygen is energetically preferable and inclusion of a water hydration shell by the addition of 2 or 4 water molecules is not sufficient to stabilize the ionic form. The degree of covalency of hydrogen bonds was estimated to be rather large by considering MO energy levels, Mulliken population analysis and molecular electron density difference plots.

INTRODUCTION

The amino group is most probably involved in interactions of catecholamines and related compounds with receptor sites in the biophase.[1–3] It is usually assumed that catecholamines are bound at the receptor site in the protonated form because at physiological pH ~ 7.4 this form predominates. The ionic form is stabilized by the hydration shell as shown by mass spectrometric studies of acid-base equilibria and ab-initio calculations.[4,5] However, it is questionable if there is sufficient space at the receptor to accomodate the whole hydration shell. It is also possible that the electric field of the nearby polar groups is functional in this respect. In our previous work[6,7] we investigated theoretically the interaction energies of amine ionic complex formation. Due to the lack of structural data on the receptor binding sites one has to rely upon the choice of the most probable model. There is some indirect evidence that the carboxylate anion may be the anionogenic site of the adrenergic receptor.[2,8] We have recently studied the ionic complex protonated ethanol-amine-carboxylate anion with the ab initio method in various geometrical arrangements.[7] The geometry of Figure 1. with two nearly parallel hydrogen bonds emerged as being energetically most favourable. Energy decomposition[9] of the interac-

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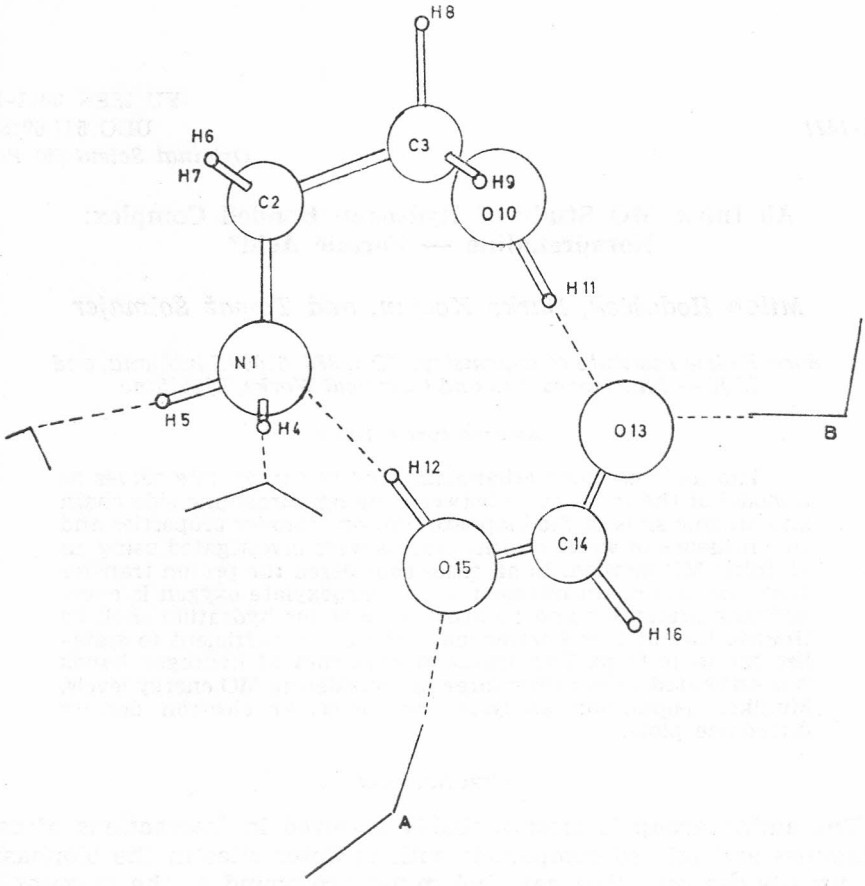

Figure 1. Geometry of the ethanolamine-formic acid complex. Four water molecules are placed at molecular electrostatic potential minima

tion energy of this complex showed[10] that charge transfer was the second largest contribution (14%) to the total interaction energy of the complex, the electrostatic part being the largest (83%). The polarization contribution was found to be negligible (2%).

In this work we have focussed our attention on the influence of water molecules on proton transfer and on electron density properties of the complex as described by Mulliken population analysis and molecular electron density difference (MEDD) plots.[11–16] The energetics of the proton transfer forms the basis for studies of proton transport kinetics[17–19] and has been the subject of numerous investigations at ab-initio and semiempirical levels. Cooperativity of proton transfers has been found to be energetically favourable. However, in view of the importance of a properly oriented C hydroxyl group of the catecholamine side chain for bin-

oriented Cβ hydroxyl group of the catecholamine side chain for binding[3,6,7] we tried to consider its influence on proton transfer of the amine head proton to the anionic site and on the charge distribution of the complex. The actual existence of such a molecular complex in the adrenergic ligand-receptor interaction process is only tentative at present: the details of such a process in a ring clusure hydrogen bonded system are, moreover, of a general interest.

METHODS AND GEOMETRIES

Two levels of ab-initio single-determinant MO theory were employed. First, the minimal STO-4G basis set was used[20] together with standard molecular scaling factors for geometry optimization. Following STO-4G geometry optimizations, single calculations were carried out at the extended 4—31 G level. Because these basis sets differ so greatly in the degree of bond polarity they predict, any results we derive, which are consistent with both basis sets, are more likely to be correct than if we were to rely only on one.[21] Drawings of molecules were made using the PLUTO program[22] and a graphic set of programs was used for drawing contours.[23] Standard bond lengths and bond angles were adopted for the ethanolamine moiety[24] and optimized values were used for the carboxylate.[12] The prefered sites for water fixation were obtained as minima in molecular electrostatic potential.[25] They correlate well with water attachment sites obtained with the SCF »supermolecular« energy optimization procedure.[26] Maximum structural changes caused by hydration in the free acid were shown[26] to be of the order of magnitude of 0.03 A and 3°, for bond distances and bond angles, respectively. Therefore we have kept the geometry of the complex as frozen when we added water molecules. Molecular electron density difference maps were computed using the simple expression[15]

$$\rho(\vec{r}) = \rho_c(\vec{r}) - \rho_L(\vec{r})$$

where $\rho_c(\vec{r})$ is the electron density of the complex at point $\vec{r}$ and $\rho_L(\vec{r})$ is the density of the ligands.

RESULTS AND DISCUSSION

In Figure 2 the energies of proton transfer in the ethanol-ammonium--carboxylate complex are presented. The intermolecular separation was optimized in case (a). In case (b) two water molecules were attached at positions A and B in Figure 1, and in case (c) two additional water molecules were added near the amine nitrogen. In all three cases the optimal position of the bridging hydrogen is near oxygen 015 of the hydrogen bond N1-H12 ... 015. It was observed earlier[27] that the minimal basis set calculations underestimated the intermolecular distance (case (a) and that experimental geometry (cases (b) and (c)) may be a better choice for proton transfer studies. The addition of two or four water molecules lowers the energy minimum near the nitrogen but this is not sufficient to stabilize the ionic form. From an experiment on a similar system (pyridine--acetic acid) it was estimated that as many as 30 water molecules would be neseccary to do this.[28] The results of the more expensive double zeta plus polarization and large scale CI calculations using generalized valence bond wave function[29] confirm the correctness of the qualitative trends of energy equilibria for proton transfer obtained by smaller basis sets.

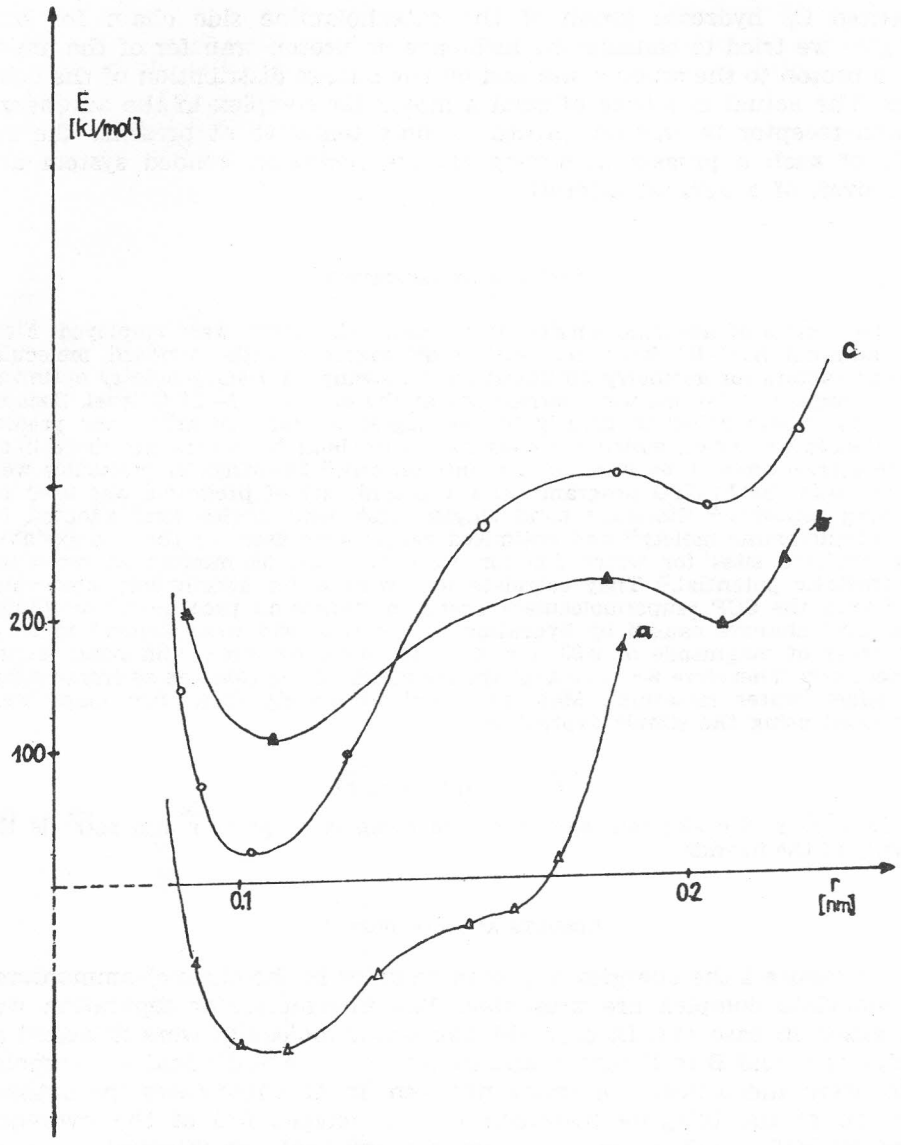

Figure 2. Hydrogen bond potential curves for the ethanolamine-formic acid ionic complex. r denotes the distance of the bridging hydrogen H12 from the oxygen atom 015

a) optimized bond lengths and bond angles

b) two water molecules (A and B) attached to carboxylate oxygen atoms lone pairs

c) four water molecules attached to the complex (see Figure 1)

Proton transfer in similar systems with ring closure through the formation of pairs of hydrogen bonds is well documented.[27,30] But in the particular case of catecholamines with side chain OH groups we propose that this feature may lead to a possible implication in relevant processes of biological importance. In the water solution the amines are nearly 100% protonated at the physiological pH ~ 7.4. However, at the receptor, the situation may be different. There may not be sufficient space at the binding site of the amine ligand to accomodate the bulky hydration shell. Hence it may be possible in such an environment that proton transfer actually takes place, which seems to be of importance for the mechanims of binding of protonated receptor ligands. The Cβ hydroxyl group of the side chain (if present) may serve not only as a stereoselectivity determining factor[2,3,7] but also as a mediator of the charge transfer between monomer moieties.

Therefore, we tried to estimate the degree of covalency of hydrogen bonds N-H...O and OH...O. First, molecular orbital energy levels of monomer moieties were compared to energy levels of the complex (numbers in paranthesis denote 4-31G results). The energy level of the highest occupied molecular orbital (HOMO) of the complex, -0.2877 a.u. (-0.3930 a.u.), indicates that it contains a high component of highest occupied MO electron density donor with an energy level of -0.1525 a.u. (-0.1526 a.u.). Since the combined MO energy level is considerably less than the donor energy level it does include a large amount of originally vacant acceptor orbital and results in the net donation of electron density. In fact, it has been shown[13] that in a similar system with the same donor and $C(NH_2)_3$ serving as the proton acceptor, charge transfer is occuring from highest occupied orbitals of $HCOO^-$ to the unoccupied MO's in the acceptor and valence MO's of $HCOO^-$. This feature can be described in terms of Mulliken population analysis. Atomic charges of the monomer moieties and charges when a complex is formed are shown in Table I. Changes in atomic charges if two of four water molecules are attached to the molecular complex (Figure 1.) are also presented. Both, minimal and extended basis sets give very similar changes in electron population. All atoms of the carboxylate moiety involved in this hydrogen bonded complex lose their electrons while the amino group of the ethanolamine and, to a lesser extent, other atoms gain electrons. It is interesting to note that the electron density difference on hydrogen H16 is as large in absolute value as that of oxygen atoms 011 and 013 which are directly affected by the interaction. From charges in the ethanolamine moiety it can be concluded that the net donated electron density is spread over the whole molecule. Change in the most distant atom from the site of interaction hydrogen H9, is nearly 60% as large as in the nitrogen of the amino group. Water molecules do not modify this picture to a significant extent except for atoms directly participating in hydrogen bond to water.

Since in general the Mulliken population analysis is by definition basis set dependent we shall now examine the MEDD plots, in order to see how the perturbation of electron density of one ion with another is reflected in the electron density of complex. We have plotted MEDD plots of a single ligand (Figure 3a) and both ligands substracted from the complex (Figure 3b) in the molecular planes. We note a decrease in elec-

TABLE I

Mulliken Charges (STO-4G) for the Ionic Complex Ethanolammonium-carboxylate. All Values in a.u. Values in Parenthesis are the Results for 4-31G Basis Set

	Atom	monomer	C	C.2H_2O	C.4H_2O	C_{FO}[a]
ETHANOLAMINE	N1	7.3039 (7.7642)	0.1119 (0.1039)	0.1165 (0.1141)	0.1957	0.1045 (0.0949)
	C2	6.0140 (6.1815)	0.0119(-0.0530)	0.0117(-0.0536)	0.0188	0.0119(-0.0446)
	C3	5.9555 (5.9109)	0.0102(-0.0191)	0.0098(-0.0175)	0.0481	0.0467(-0.0197)
	H4	0.7181 (0.5732)	0.1231 (0.1026)	0.1217 (0.0995)	0.0687	0.0858 (0.0946)
	H5	0.7129 (0.5636)	0.1243 (0.1033)	0.1230 (0.1001)	0.0809	0.1010 (0.1016)
	H6	0.6218 (0.7333)	0.0907 (0.0761)	0.0735 (0.0709)	0.0630	0.0892 (0.0894)
	H7	0.8673 (0.7545)	0.0593 (0.1062)	0.0567 (0.0983)	0.0742	0.0591 (0.0808)
	H8	0.8725 (0.7523)	0.0781 (0.0829)	0.0795 (0.0751)	0.0751	0.0579 (0.0820)
	H9	0.8723 (0.8150)	0.0610 (0.0518)	0.0567 (0.0476)	0.0817	0.0658 (0.0253)
	H10	0.9177 (0.8311)	0.0362 (0.0653)	0.0343 (0.0658)	0.0363	0.0234 (0.0651)
	O11	8.3749 (8.8311)	0.0626 (0.0756)	0.0606 (0.0764)	-0.0317	-0.0297(-0.0685)
	H12	0.7691 (0.5716)	-0.0303(-0.0739)	-0.0247(-0.0912)	0.0166	-0.0007(-0.1197)
CARBOXYLATE	C13	5.8353 (5.3961)	-0.1272(-0.0165)	-0.1496(-0.0808)	-0.1431	-0.1116(-0.0425)
	O14	8.5207 (8.7911)	-0.2210(-0.1444)	-0.2256(-0.1003)	-0.2066	-0.1950(-0.0991)
	O15	8.5207 (8.7911)	-0.2010(-0.0969)	-0.2034(-0.0342)	-0.1678	-0.1427(-0.0561)
	H16	1.1233 (1.0217)	-0.1901(-0.2337)	-0.2196(-0.2794)	-0.2029	-0.1657(-0.2040)

[a] ionic complex with geometry of Figure 1, fully optimized bond angles and bond lengths and hydrogen atoms H12 and H6 relaxed to potential well minima.

tron density at the nitrogen due to proton transfer towards carboxylate oxygens. Correspondingly, we note a decrease in electron density at the bridge hydrogen of the NH...O hydrogen bond and an increase in electron density of the carboxylate oxygen. On the O-H...O hydrogen bond, however, the resulting picture is somewhat different. At the ethanolamine oxygen 011 electron density is increased while at the bridge hydrogen H10 and carboxylate oxygen 014 it is decreased. The bonding characteristic of the latter hydrogen bond is relatively weak and this is revealed by the small difference in electron density in the space between oxygens 011 and 013.

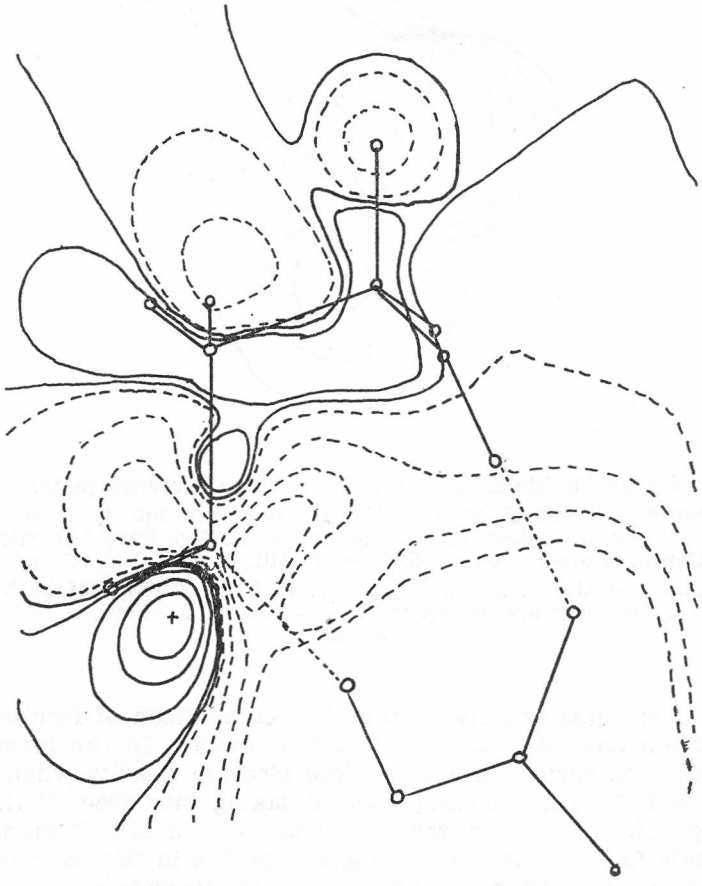

Figure 3a.

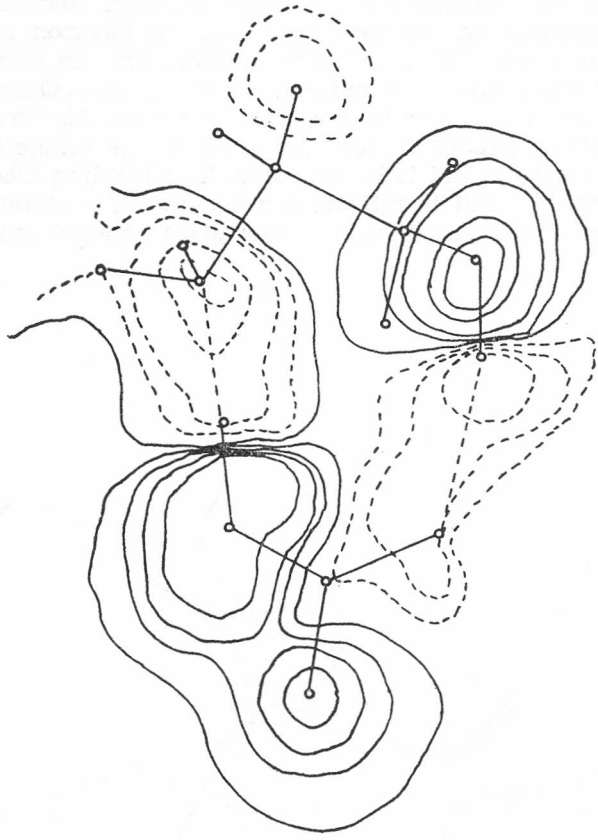

Figure 3b. Molecular electron density difference plots:

a) in the plane of N1-C2-C3 atom of the ethanolamine moiety. Positive contours are marked by unbroken line, negative by dotted line. Logarithmic scale. Contours are drawn at -0.10, -0.05, 0.01, 0., 0.01, 0.05, 0.10 e^-/a_0^3

b) in the plane of the formic acid moiety. Electron density of both ligands is subtracted. Contours are drawn at -0.05, -0.02, -0.01, -0.005, 0., 0.005, 0.01, 0.02 e^-/a_0^3

There is an apparent discrepancy if a comparison of results of Mulliken population analysis and MEDD plots is made.[31] In the former all the atoms of the the carboxylate anion lose electron density when the complex is formed. This is a consequence of taking into account the average total charge difference localized on an atom. The MEDD maps show in a more subtle fashion the electron density profile in the bond region. The build up of the overlap population results in descreening of both heavy nuclei when the complex is formed ionic moieties.

CONCLUSION

In the cases considered the proton of the amino head tends to localize nearer to the acid moiety, i.e., the neutral complex is more stable. The addition of water changes the proton potential curves: the potential minimum on the acid site is lowered and the barrier is also lower. Thus the Cβ-OH not only helps in fixing the ligand in a definite spatial relation to the putative receptor site, but may also facilitate proton transfer.[7] The covalent character of the hydrogen bonds of this complex seems to be greater than its polarization nature: from the electron density difference plots and from MO energy levels of the complex when compared to separated moieties, charge transfer emerged as an important contribution.

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IZVLEČEK

Študij kompleksa noradrenalin-mravlja kiselina

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Ionski kompleks etanolamonijum-karboksilat nam služi kot model za interakcijo stranske verige noradrenalina z anionskimi vezavnimi mesti v biofazi. Raziskovali smo lastnosti protonskega transfera in vpliv vode na proces z ab-initio metodo molekularnih orbital. V vseh obravnavanih primerih je protonski transfer z dušikovega atoma stranske verige proti karboksilatnemu kisiku energijsko ugodnejši in vključitev hidratacijske luske z dvema ali štirimi molekulami vode ne zadostuje za stabilizacijo ionske oblike. Ocenili smo, da je stopnja kovalentnosti obeh vodikovih vezi precejšnja, in sicer iz energijskih nivojev, Mullikenove populacijske analize in diferenčnih map elektronske gostote.