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## On the Ability of the CNDO/2 and INDO MO Methods to Cope with Nonbonded Interactions

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**Abstract:** Results are presented which show that the popular CNDO/2 and INDO closed-shell restricted Hartree-Fock MO methods are unable to account properly for nonbonded interactions. Potential energy curves which should be strongly repulsive are predicted to be either weakly repulsive or attractive. The more sophisticated of the two methods, the INDO method, gives significantly worse results. In contrast, the extended Hückel method, the simplest full-overlap all-valence electron MO method, predicts the correct nature of the curves.

The ready availability of computer programs for calculating electronic wave functions and energies by single determinantal molecular orbital (MO) methods has resulted in a large increase in the number of applications of these methods to problems in organic chemistry and biology. One only has to look through recent issues of this journal to see how important and popular a tool they have become in these fields for rationalizing the results of experiments and for guiding new ones.

The methods currently enjoying the greatest popularity amongst experimentalists are the approximate, all-valence electron, neglect of differential overlap (NDO) variants of the Hartree-Fock (HF) model. The complete (C) NDO/2 and intermediate (I) NDO schemes that were introduced by Pople and his co-workers<sup>2</sup> are the two most often used. Most specialists in MO calculations are aware, however, that these two schemes overemphasize bonding effects in molecules. Thus they tend, for example, to favor more highly connected structures.<sup>3,4</sup> However, this particular defect is one that is shared in many systems by minimal basis ab initio HF theory.<sup>3</sup> Hence it is not always wholly due to the NDO approximations or to the choice of parameters, but is sometimes due in part to the use of a minimal basis.

Other failures of the CNDO/2 and INDO methods which have the same origin, but are not shared by minimal basis ab initio HF theory, have been reported.<sup>2,3a,4</sup> There is, however, one such failure that has not yet been properly documented. The purpose of this paper is to correct that situation by presenting the results of some simple test calculations, which show unequivocally that the CNDO/2 and INDO methods are unable to account properly for nonbonded lone pair/lone pair and lone pair/ $\pi$ -bond interactions. Applications of these methods to conformational problems where such interactions play a nonnegligible role are therefore of uncertain value.

Our work stems from a CNDO/2 and INDO closed shell (CS) restricted (R) HF investigation of intramolecular hydrogen bonding between alcohols and unsaturated linkages.<sup>3a,5</sup> Calculations on a model system consisting of a methanol molecule suitably oriented with respect to an ethylene molecule correctly predicted the existence of weak OH... $\pi$  bonds, but also implied that alcohols can interact with double bonds so

as to form "oxygen- $\pi$ " bonds. We argued that the latter bonds could derive their stability from the mixing of the nonbonding atomic orbitals (AO's) of the oxygen and the  $\pi$  MO's of the double bond and turned to a simpler and more convenient system to test this hypothesis. Our results are reported in the next section.

### Water/Ethylene System

Potential energy curves were calculated by the CNDO/2 and INDO CS RHF methods for the four approaches of a water molecule to an ethylene molecule, shown in Figure 1.<sup>6</sup>

The geometries of both molecules were held fixed. The CC and CH bond lengths in the ethylene molecule were set at 1.339 and 1.086 Å, respectively, and the HCH bond angles at 117.5°. The OH bond lengths in water were set at 0.98 Å, the HOH angle at 104.2°.

Orbital interaction diagrams for the lone pair orbitals,  $n_1$  and  $n_2$ , of the oxygen and the  $\pi$  and  $\pi^*$  MO's of the double bond are also shown schematically in Figure 1. The symmetry classifications S (symmetric) and A (antisymmetric) refer to the symmetry planes indicated at the bottom of each diagram. The symmetry inherent in approaches 2-4 was not available to us in the methanol/ethylene system because of the presence of the methyl group. Case 1 corresponds to the methanol/ethylene approach which led to the most stable symmetrical "oxygen- $\pi$ " bond. Cases 2 and 4 are the most interesting because, at the level of approximation implied by the diagrams, there can be little doubt as to the outcome of orbital mixing: destabilization and a repulsive potential energy curve.

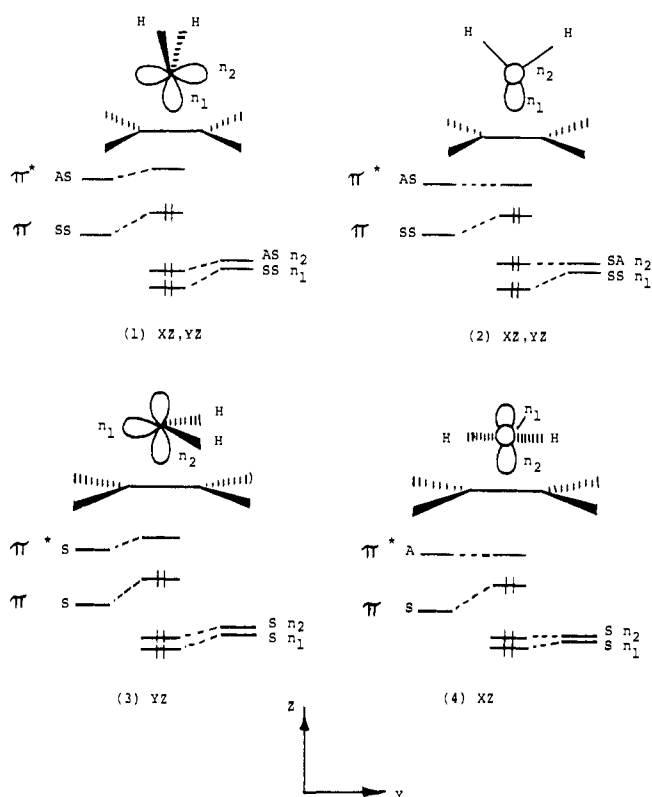
The CNDO/2 and INDO calculations led, however, to attractive potential curves for all four approaches. The approximate distances between the oxygen atom and the midpoint of the CC bond of the ethylene at the minima and the corresponding stabilization energies are shown in Table I. Approach 1 leads to the deepest minimum, but approach 2, which one expects to be repulsive from simple orbital interaction considerations, is also associated with strong stabilization at distances not too far removed from ordinary bonding distances. The other two approaches are associated with potential curves with very shallow minima at much larger distances; here rising electronic stability is nearly offset by the internuclear repulsion

**Table I.** Potential Minima and Stabilization Energies for Various Symmetric Approaches of Water to Ethylene (Figure 1)

Approach	CNDO/2		INDO	
	$(Z_0)_{\min}$ , Å	Stabilization energy, eV	$(Z_0)_{\min}$ , Å	Stabilization energy, eV
1	1.75	0.32	1.6	0.87
2	1.5	0.20	1.7	0.40
3	2.5	0.01	2.35	0.07
4	2.5	0.03	2.5	0.05

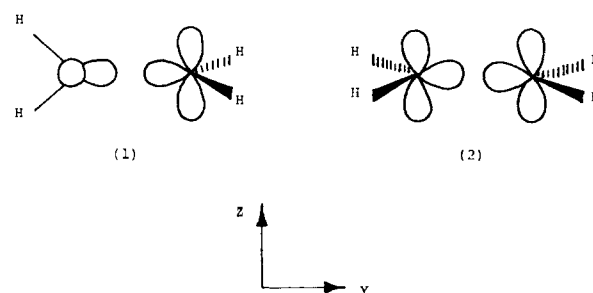
**Table II.** Potential Minima and Stabilization Energies for the Two Water/Water Approaches of Figure 2

Approach	CNDO/2		INDO	
	$Y_{\min}$ , Å	Stabilization energy, eV	$Y_{\min}$ , Å	Stabilization energy, eV
1	1.6	0.35	1.4	1.05
2	1.6	0.31	1.45	0.91

**Figure 1.** The four approaches of a water molecule to an ethylene molecule.

energy which increases more rapidly than in the case of the other two approaches. We also note that inclusion of one-center exchange integrals in the calculation results in a two- to threefold increase in the stabilization energy. Following the eigenvectors along each path, one sees the mixing pictorialized by the interaction diagrams of Figure 1 taking place in what appears to be a manner consistent with the diagrams. The most striking feature of the variation of the energies of the other occupied MO's is the rapid increase in the stability of the lowest energy MO when the approaching water molecule enters the region of high AO overlap. This change is far from offset by the destabilization of other filled MO's.

For the purpose of comparison, we repeated the calculations using the simplest all-valence electron MO method available, the extended Hückel (EH) method.<sup>7</sup> This method, unlike the

**Figure 2.** The two approaches of a water molecule to another water molecule.

CNDO/2 and INDO schemes, is a full-overlap method. Despite its many well-known deficiencies and limitations, Hoffmann and his co-workers have shown that the EH model is often capable of providing sound qualitative insights into chemical bonding. In our EH calculations<sup>8</sup> the 2s and 2p coulomb integrals of oxygen were taken to be  $-35.3$  and  $-17.7$  eV, respectively. The other parameters were set at the values currently being used by Hoffmann.<sup>9</sup>

The EH potential energy curves are repulsive for all four water/ethylene approaches and very much so in those regions of high overlap, where for approaches 1 and 2 the CNDO/2 and INDO calculations predict greatest stabilization. In the EH calculations, the stability of the lowest energy MO increases in the high overlap region, but at the same time the next lowest energy MO destabilizes to a greater extent, so that their combined effect is a destabilizing one. The same picture emerges from minimal basis ab initio CS RHF calculations.<sup>10</sup>

### Water/Water System

Having found an "oxygen- $\pi$ " bond, we wondered if we would also discover an "oxygen-oxygen" bond when we calculated CNDO/2 and INDO potential energy curves for the approach of two water molecules orientated so that their oxygen atoms are closest to one another. With the geometries of the water molecules held fixed, we calculated potential curves for the two approaches shown in Figure 2 by the CNDO/2, INDO, and EH methods. The CNDO/2 and INDO calculations led to attractive potential curves for both approaches. The approximate distances between the oxygen atoms at the minima and the corresponding stabilization energies are shown in Table II. The EH method gave strongly repulsive curves; for example, for  $y = 1.5$  Å in approach 1, the

EH stabilization energy is ca.  $-11$  eV. Once again the CNDO/2 and INDO minima occur in regions of high overlap and the inclusion of one-center exchange integrals serves only to increase the stabilization energy. Similar CNDO/2 and INDO calculations on the approach of two eclipsed molecules of ammonia led to weakly repulsive potential curves, whereas EH calculations led to strongly repulsive curves.

### Concluding Remarks

The model calculations reported here show that the popular CNDO/2 and INDO CS RHF methods impart too much stability to systems containing nitrogen and/or oxygen atoms separated from one another or from  $\pi$  bonds by less than  $4 \text{ \AA}$ . As the separation in question decreases and the AO overlap increases, the total electronic energy is further underestimated with the result that the potential energy surface becomes increasingly unrealistic. These observations should be useful for assessing the significance of many of the CNDO/2 and INDO calculations that are being reported in growing numbers alongside experimental results.

Our results provide unequivocal evidence that one cannot be sure at the outset of a project that a semiempirical MO theory will give results that are qualitatively correct or that a more sophisticated theory will generally give better results.<sup>11</sup> However, assumptions of this type still have wide currency. One should establish their validity each time a new application of a theory is envisaged, either by careful reference to the literature or by a preliminary series of carefully designed numerical tests. The direct  $\sigma$ -type interaction between two lone pairs is a very simple, but conclusive test of theory that has with few exceptions<sup>12</sup> been overlooked.

Finally, it should be noted that our calculations complement recent work by other authors. Veillard<sup>13</sup> has reviewed the literature and established that the CNDO/2 method fails to predict correctly the conformational preferences of molecules

$H_mA-BH_n$  and their substituted derivatives, when both atoms A and B bear one or two lone pairs. And Giessner-Prette and Pullman<sup>14</sup> have concluded from the calculation of molecular electrostatic potentials that the CNDO method makes oxygen too attractive (as a site for protonation) compared to nitrogen.

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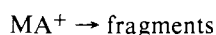
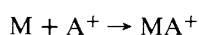
## Theoretical Study of the Protonation of Glycine in Gas-Phase Ion-Molecule Reactions

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**Abstract:** The electronic structure of glycine and its ion-molecule association reaction with  $H^+$  have been studied using a semiempirical INDO-type molecular orbital computation. The results indicate that the association reaction of glycine with  $H^+$  produces a quasi-molecular ion possessing two functional groups,  $NH_2$  and  $COOH$ , interacting through  $N\cdots HO$  type hydrogen bonding. However, a wide range of conformations is suggested due to the low energy barriers among the several different configurations.

The low yield of parent ion of amino acids produced by electron impact has prompted the mass spectrometric studies of the biological molecules with more gentle means of ionization. Examples include chemical ionization,<sup>1</sup> field desorption,<sup>2</sup> and  $^{252}Cf$ -Plasma desorption,<sup>3</sup> which have been found to form relatively stable products by the ion-molecule association reaction,



Among quasi-molecular (QM) ion products, the  $MH^+$  formed by protonation appears as a major component for most ion-molecule association reactions occurring in mass spectrometry. To understand the condition and mechanisms of the ion production by this method, theoretical investigation of the interaction of the simplest  $\alpha$ -amino acid, glycine, with free  $H^+$  ions was undertaken using semiempirical INDO molecular orbital theory.<sup>4</sup>

Glycine is known to exist in a variety of structures depending on its environment. In solution, it exists either as the zwitterion,