On Tautomerism and Self-Association of 2-Pyridinol/2-Pyridone System

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The semiempirical "Effective Pair Correlation Energy" method of Sinanoglu et al. has been employed to investigate the role of the electron correlation energy in the cis-trans, protomeric and dimerization equilibria in the 2-pyridinol (HP2)/2-pyridone (P2) system. CNDO/2 wave functions were used throughly. Preliminary calculations on test cases formic acid, water dimer, and ammonia-water dimer gave acceptable figures in comparison with more accurate literature data. The results show that in HP2 the N-C-O-H cis isomer is more stable than the trans isomer by 2.7 kJ mol^{-1}. Correlation energy favors the trans isomer by 2.9 kJ mol^{-1} and the keto P2 form over the HP2 form by 11.3 kJ mol^{-1}, in qualitative agreement with results of ab initio calculations. The correlation energy term is stabilizing for the associative process of both tautomers. The numerical data are greatly dependent on the intermolecular equilibrium distance, the best results being obtained at experimental equilibrium distances. $(P2)_2$ dimer is correctly predict to be more stable than $(HP2)_2$ dimer. The correlation energy contribution amounts to 22 and 12.4 kJ mol^{-1} per hydrogen bond in $(HP2)_2$ and $(P2)_2$, respectively.

The 2-pyridone(P2)/2-pyridinol(HP2) tautomeric equilibrium is of leading importance in heterocyclic chemistry and has been investigated by a variety of experimental[1–5] and theoretical methods.[6–8] Spectroscopic measurements in the gas phase indicate that the hydroxy form is more stable than the keto form by 1.3±10.4 kJ mol^{-1}. Ab initio 6-31G*calculations[6] reproduced this figure well. They pointed out that the electron correlation energy (E_c) contributes significantly to define the equilibrium position by favoring by 3.3 kJ mol^{-1} the P2 form. By contrast, most recent more advanced ab initio coupled cluster calculations[8] predict an energy difference of 14.6 kJ mol^{-1} in favor of HP2, with E_c being destabilizing for P2 by about 4.2 kJ mol^{-1}. No correlation energy calculations have been so far reported on the P2 and HP2 dimerization equilibria. The computation of the correlation energy by very accurate methods is highly expensive and for the dimers which we are dealing with at all impracticable, so it is of interest to investigate whether acceptable E_c values may be obtained by means of semiempirical methods. The present work is concerned with a semiempirical evaluation of E_c for the tautomeric and dimerization equilibria of Fig. 1. E_c is computed according to the semiempirical "Effective Pair correlation Energy" (EPCE-2σ) method of Sinanoglu et al.[9] by using CNDO/2 wave functions to calculate density matrix elements. The method has been reviewed[10] and implemented in the HAM/4 formalism;[11] it has been previously applied to calculate intermolecular interactions,[12–15] electron affinities[16] and ionization potentials.[17]

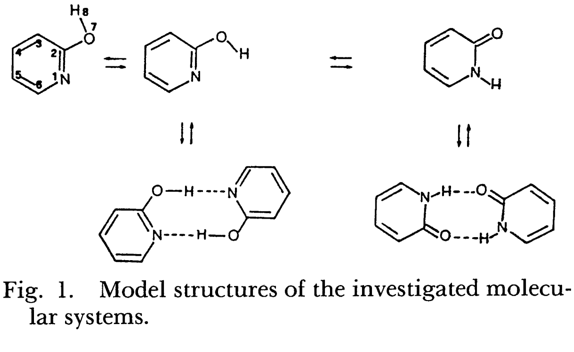


Fig. 1. Model structures of the investigated molecular systems.

Computational Details

According to the EPCE-2σ method[9] the molecular electron correlation energy for a closed shell system is computed as

$$E_c = 1/4 \sum_{A}\sum_{\mu}\sum_{B}\sum_{\nu} P_{\mu A\nu A} P_{\mu B\nu B} \times \bar{\varepsilon}_{\mu A\nu B},$$

where $\bar{\varepsilon}_{\mu A\nu B}$ is the "Effective Pair Correlation Energy" between the electron in the orbital μ of the atom A and the electron in the orbital ν of the atom B. Terms P are the diagonal elements of the density matrix. One-center terms $\bar{\varepsilon}_{\mu A\nu A}$ are given by the many electron theory of Sinanoglu;[9a] two-center terms $\bar{\varepsilon}_{\mu A\nu B}$ are determined empirically[9e] from the one-center terms by the relation

$$\bar{\varepsilon}_{\mu A\nu B} = (0.75F^{(1)}{}_{\mu A\nu B} + 0.25F^{(2)}{}_{\mu A\nu B})(\bar{\varepsilon}_{\mu A\nu A} + \bar{\varepsilon}_{\mu B\nu B})$$

where $F^{(1)}$ and $F^{(2)}$ are empirical functions expressed in terms of overlap integrals S

$$F^{(1)} = (K_1 R_{AB} + 0.1)S^2{}_{\mu A\nu B}$$
$$F^{(2)} = [0.5K_2(\tau_{\mu A} + \tau_{\nu B})R_{AB} - 0.08]S^2{}_{\mu A\nu B}$$

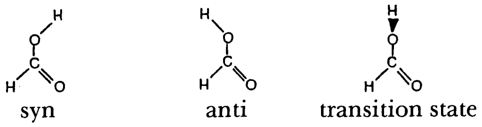
where K_1 and K_2 are empirical parameters and $\tau_{\mu A}$ and $\tau_{\nu B}$ are the Slater-type orbital exponent for atom A and B, respectively.

The method was computerized and interfaced to a CNDO/2 program. Ab initio and MNDO calculations were carried out by means of Gaussian 80[18] and AMPAC[19] programs, respectively.

Results and Discussion

Preliminary Computations. EPCE-2σ computations were preliminary carried out on some test case appropriate to the present work. They include formic acid isomers, water dimer and mixed ammonia-water dimer.

Zirz and Ahlrichs[20] have reported CEPA-2(SD) calculations on syn, anti, and transition state (ts) conformers of formic acid.



Scheme 1.

They found that the inclusion of valence shell correlation lowers E(syn-anti) by 1.7 kJ mol^{-1} and E(ts-syn) by 5.9 kJ mol^{-1}. Our EPCE-2σ calculations on the molecular geometries reported by these authors gave E_c(syn-anti)=2.1 kJ mol^{-1} and E_c(ts-syn)=9.1 kJ mol^{-1}. The first figure compares well with the corresponding value of Zirz and Ahlrichs, while E_c(ts-syn) appears to be somewhat overestimated.

Configuration interaction calculations on $(H_2O)_2$ gave ΔE_c values [E_c(dimer)$-2E_c$(monomer)] of -3.8[21] and 4.5[22] kJ mol^{-1}. For ammonia-water dimer second order pertubation computations gave[23] ΔE_c values in the range -2.9—-8.4 kJ mol^{-1}. Our results relative to the water dimer and ammonia-water dimer are shown in Fig. 2. In the calculations the experimental monomer geometries of H_2O[24] and NH_3[25] were used.

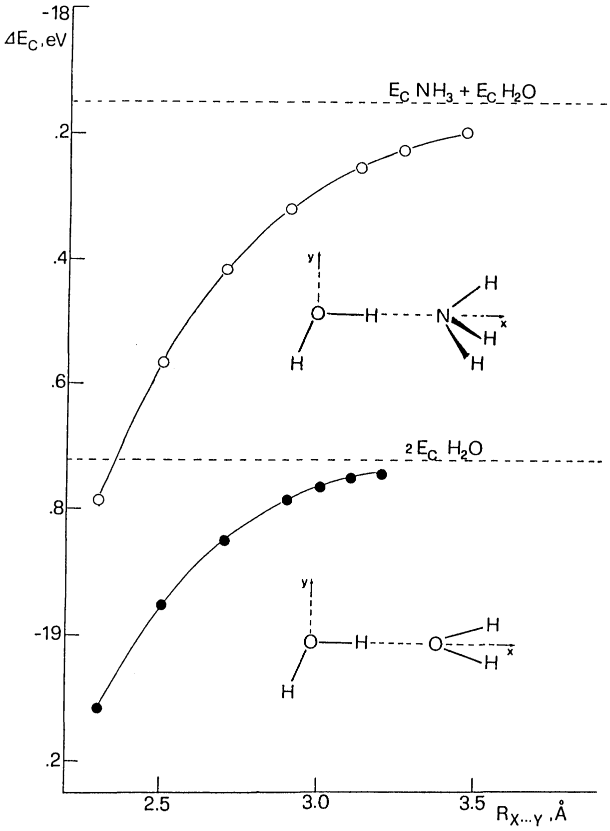


Fig. 2. Dependence of ΔE_c [E_c(dimer)$-2E_c$(monomer)] on the heavy atoms distance in water dimer and ammonia-water dimer.

Figure 2 shows that E_c has a stabilizing effect for the dimerization process and appears to be greatly dependent on the heavy atom distance. At CNDO/2 equilibrium distance of water dimer (2.52 Å) and ammonia-water dimer (2.65 Å) ΔE_c is greatly overestimated: -22.5 and -31.4 kJ mol^{-1}, respectively. This is mostly due to the known tendence of the CNDO/2 approximation wich in intermolecularly hydrogen bonded complexes underestimates equilibrium distances.[26] Indeed, at ab initio equilibrium distances (3.00 Å for $(H_2O)_2$ and 3.12 Å for $(NH_3)_2$)[25] ΔE_c for water dimer and ammonia-water dimer is estimated to be -4.6 and -9.6 kJ mol^{-1}, respectively. These values are comparable with the results of configuration interaction and pertubation calculations and, on the whole, indicate that a prudent application of the EPCE-2 method to the topics which we are here concerning may be made.

Cis-Trans and Tautomeric Equilibria. CNDO/2 calculations on P2 and HP2 were firstly carried out on the X-ray experimental geometry of the ring heavy atoms[27,28] together with an assumed C-H bond length of 1.08 Å, while the C=O (1.29 Å), C-O (1.37 Å), N-H (1.07 Å), O-H (0.99 Å) and δ_{COH} (110°) parameters are CNDO/2 optimized values. The calculations predict that in HP2 the N-C-O-H cis isomer is more stable than the trans isomer by 11.2 kJ mol^{-1}, by reflecting the occurrence of an intramolecular hydrogen bond, as was also inferred by ab initio calculations.[8] The correlation energies of the cis and trans isomers are -54.51 and -54.54 eV, respectively. Thus E_c favors the trans structure by 2.9 kJ mol^{-1}, i.e. by an amount comparable with that found in the formic acid syn-anti equilibrium. The correlation energy of P2 is computed to be -54.17 eV. It follows that E_c, like ab initio coupled cluster calculations,[8] is stabilizing for HP2 by 32.7 kJ mol^{-1}, although the semiempirical figure appears to be considerably overestimated. Since E_c is expected to depend on the molecular geometry of the tautomers, EPCE-2σ calculations were also carried out on molecular geometry fully optimized at various theoretical levels: ab initio 3-21G,[6] CNDO2/GEOMO,[29] NNDO. The results are collected in Table 1. It can be seen that ΔE_c(HP2−P2) is greatly dependent on the optimization method. The discrepancy with respect to the results of ab initio calculations[8] decreases on going from the ab initio to the GEOMO geometry.

Table 1. EPCE-2σ Correlation Energies for 2-Pyridinol (HP2) and 2-Pyridone (P2) as a Function of the Geometry Optimization Method

	AB INITIO[6]	MNDO	GEOMO[29]
E_c(HP2)/eV	-54.34	-54.64	-54.66
E_c(P2)/eV	-53.98	-54.37	-54.54
E_c(HP2-P2)/kJ mol^{-1}	34.7	25.5	11.3

This is at first sight rather surprising. However, it must be noted that the accuracy of the CNDO/2 calculations on the same geometries in predicting the SCF energy difference between the tautomers increases in the same order. It follows that it is preferable to use in the calculations an internally consistent procedure: to compute EPCE-2σ data from CNDO/2 optimum geometry. The best present estimate of ΔE_c, 11.3 kJ mol^{-1}, may be considered of qualitative utility in comparison with the corresponding ab initio results[8] of 4.2 kJ mol^{-1}.

Dimerization Equilibria. Self-association of HP2 and P2 is intimately connected with the protomeric HP2/P2 equilibrium constant[1,30]. The dimerization enthalpy of P2 has been determined in benzene solution by calorimetry[31] as 35.9 kJ mol^{-1}. UV absorption measurements in $CHCl_3$[32] and ^{1}H NMR spectroscopy in benzene[33] gave 24.7 and 65.3 kJ mol^{-1}, respectively. Thus the P2 dimerization constant is sensibly solvent dependent, although different kinds of experiments in the same solvent (benzene) lead to rather different results. Thermodynamic studies[34,35] have indicated that the self-association energy of the enol tautomer is smaller than that of the keto form. In agreement with this result recent CNDO/2 dimerization energy calculations on a series of substituted pyridinols and pyridones[7] have indicated that the HP2 dimerization energy in the former are smaller by 2.9—10.2 kJ mol^{-1} than in the latter. In agreement with these results the HP2 dimer has not been observed by conventional spectroscopic methods.

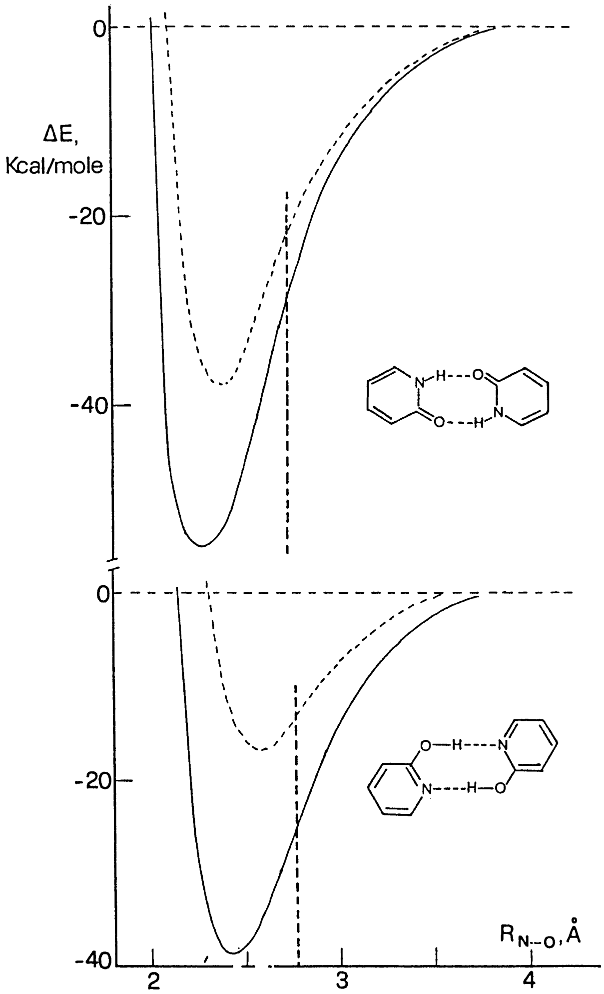
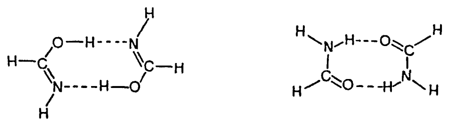


Fig. 3. Potential energy curves for the formation of 2-pyridone and 2-pyridinol dimers. The dashed vertical line is drawn at the ab initio STO-3G equilibrium N···O distance in the corresponding model compounds formamide and 2-formimidic acid dimers (see text). The solid curves include ΔE_c contributions.

Our potential energy curve calculations for the movement of the monomer unit along the N···O coordinate with and without the inclusion of the correlation energy contribution is reported in Fig. 3. An energy minimum is found at 2.60 and 2.40 Å for $(HP2)_2$ and $(P2)_2$, respectively. The corresponding dimerization energies are 70.2 and 157.2 kJ mol^{-1}. The correlation energy is stabilizing for the associative process, as found for water dimer and ammonia-water dimer. ΔE_c makes to decrease the N···O equilibrium distance by 0.15 and 0.10 Å in $(HP2)_2$ and $(P2)_2$, respectively, and makes to increase the corresponding dimerization energies by 87.8 and 71.1 kJ mol^{-1}. These figures are clearly very high, so, as experienced in $(H_2O)_2$ and NH_3-H_2O dimers ΔE_c cannot be evaluated at the CNDO/2 equilibrium distance. This indeed is significantly overestimated with respect to the corresponding experimental value of 2.756 Å in the 6-bromo-2-pyridinol dimer in the solids[36] and 2.77 Å in the P2 dimer in the solid.[27] The use of these N···O experimental distances in the calculations leads to SCF dimerization energies of 58.5 and 83.5 kJ mol^{-1} in (HP2) and (P2), respectively. They correctly indicate $(P2)_2$ to be more stable than $(HP2)_2$ in agreement with experimental data and with the results of the most recent semiempirical calculations.[7] In particular the $(P2)_2$ dimerization energy is comparable with the ^{1}H NMR experimental value[33] of 65.3 kJ mol^{-1}. Now the E_c estimate amounts to 22 and 12.4 kJ mol^{-1} per hydrogen bond in $(HP2)_2$ and $(P2)_2$, respectively. It represents an important fraction of the total dimerization energy process, as generally found in intermolecular hydrogen bonded complexes.[22,23] ΔE_c is more favorable for the HP2 than for the P2 dimerization process. By recalling that the correlation energy of the monomer unit is greater in HP2 than in P2, this behavior indicates that the OH···N interaction is much more correlated than the NH···O interaction. However this effect is not enough to upset the SCF energy difference between the two dimers. The numerical ΔE_c data are in line with the results on $(H_2O)_2$ and NH_3-H_2O dimers and can be considered as useful qualitative estimate of electron correlation energy in large intermolecular hydrogen bonded complexes.

In the absence of experimental intermolecular distances the obvious choice is their evaluation by means of ab initio calculations. It is of interest to test this procedure in the present case. To minimize the computational effort ab initio calculations have been carried out at the minimal STO-3G basis set on *cis*-formimidic acid and formamide dimers, as model compounds for $(HP2)_2$ and $(P2)_2$ dimers, respectively, by using the corresponding geometrical parameters of the monomer unit.



Scheme 2.

The calculated N···O distance in the *cis*-formamidic acid dimer (2.76 Å) reproduces perfectly (perhaps somewhat fortuitously) the corresponding experimental figure (2.756 Å).[36] In the formamide dimer the N···O distance is underestimated by 0.04 Å (which is between the performance limits of the STO-3G calculations), leading in $(P2)_2$ to a ΔE_c value of about 15 kJ mol^{-1} per hydrogen bond, only slight smaller than the previously calculated one.

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