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Quantum Chemical Consideration of Substituent Effects on Tautomeric Properties of 2-Pyridones–2-Pyridinols

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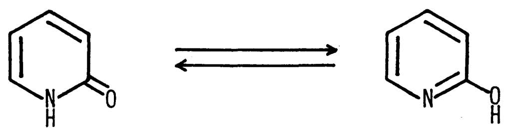
The tautomeric properties of 2-pyridones–2-pyridinols exerted by the substituent effect were discussed on the basis of quantum chemical quantities deduced from molecular orbital (MO) calculations. A substituent at the 6-position has the greatest stabilizing effect. The magnitude of this effect was greater on the 2-pyridinol form than the 2-pyridone form, irrespective of the nature of the substituent. This led to a large predominance of the 2-pyridinol form on the 6-polar-substituted derivatives to such an extent that it was observed by conventional UV measurements at ambient temperature. In the 6-methyl derivative, the 2-pyridinol form was not observed by a similar measurement due to the weak substituent effect. The association ability is still an important factor in determining tautomeric equilibrium in a solution, resulting in a strong lability to the molecular environment. The substituent effects on the stabilities of both tautomers were shown to be correlated with the N-atomic charges and ring structural modifications of the tautomers.

2-Pyridone–2-pyridinol (**1**) has been one of the basic tools in a number of studies on tautomeric equilibria, the properties of which are of interest regarding the structure-reactivity relationship and is of potential biological significance for understanding mutation due to base mispairing and enzymic reactions related to the bifunctional catalysis.[1,2] Thus, the study of 2-pyridone (**1**) has been attracting many investigators from more than one area.



1a **1b**

Scheme 1.

It has now become well established that **1** exists very largely in the 2-pyridone tautomeric form (**1a**) in solution[1] and in the solid state,[3] but that there is no significant difference in the fundamental stabilities of the tautomers in the gas phase (ΔH=1.3±10 kJ mol^{-1}).[2] It was also been shown that self-association and/or solvation significantly affect tautomeric equilibria.[2,4]

A number of quantum chemical studies on the energetics of the tautomeric properties for **1** have already been published, but those studies have led to various diverse results regarding the energetics of tautomeric equilibria.[5] This may be mainly due to the differences in the method of calculation and the molecular geometric parameters employed. Recently, *ab initio* studies with extended basis sets, including full geometry optimization, were reported and the calculated tautomeric energy difference was shown to be in good agreement with experimental values related to the gas phase.[5k,5l,5m] The details of the substituent effects on the tautomeric properties of **1**, however, have yet been fully elucidated.

We felt it would be important and useful to investigate the substituent effect in order to achieve a full understanding of the factors which influence tautomeric equilibria. In fact, several derivatives of **1** which bear a polar substituent at the 6-position are known to favor the 2-pyridinol form over the 2-pyridone form,[1,6] and the substituent effects have been ascribed to the electron-withdrawing property.

Molecular orbital calculations are particularly useful for such studies since they can provide much information about less-abundant tautomeric species. It is now apparent that nonempirical *ab initio* calculations with extended basis sets must be used to achieve a high accuracy regarding the energetics of tautomeric equilibria.[5k,5l,5m] A large amount of computational time, however, is neccessary for such calculations for a large molecule. Thus, we systematically performed molecular orbital calculations supported by the CNDO/2 and MINDO/3 methods on various substituted 2-pyridones. We believe that the semiempirical method can provide a sufficient fundamental insight into the substituent effects on the relative stability and electronic structure of each tautomeric form.

In this paper, we present the special features disclosed by the calculations and discussed the substituent effects with the quantum chemical quantities derived from such calculations.

In order to obtain experimental data to support the calculated quantities, the IR spectra of several methyl derivatives of 2-pyridones were also measured in a CCl_4 solution.

Experimental

2-Pyridone was commercially available. The preparation of other substituted 2-pyridones is described in the literature.[7]

The infrared spectra were recorded with a JASCO 403G infrared spectrophotometer. The solvent of carbon tetrachloride (spectroscopic grade) was dried over molecular sieves. Solute concentrations were 5×10^{-4} M† (20 mm NaCl cells). The cell was heated with a heat gun (PLAJET PJ-206,

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† 1M=1 mol dm^{-3}.

Ishizaki-Denki Co. Ltd.) to above 60 °C. Then, heating was discontinued and the spectra in the 3200—3800 cm^{-1} region were measured at *ca.* 50 °C. The temperature, measured by a digital thermometer with a thermocouple directly fixed to the cell, was constant during the measurement. The intensities were determined to be given by $\log_{10}(T_0/T)$, where T_0 and T are the apparent intensities of the incident and transmitted radiation at the maximum wave number, respectively.

Calculations

All calculations were carried out on a FACOM M-382 computer at the Computation Center of Nagoya University. The CNDO/2,[8] MINDO/3,[9] MNDO,[10] and MNDOC[11] calculations were performed with the original standard parametrizations, respectively. Geometrical parameters were taken from the results of X-ray crystallographic studies on 2-pyridone[12] and 6-bromo-2-pyridinol[13] for the CNDO/2 and the MINDO/3 calculations with a fixed geometry. Standard bond lengths and bond angles[14] were used as the geometrical parameters of the substituents. The MINDO/3 calculation, with full geometry optimization, was carried out on the structures within C_s symmetry by the RPI/MINDO/3 which contains a convergence-forcing procedure.[15]

Results and Discussion

The molecular-orbital calculations were carried out for a set of 2-pyridones and 2-pyridinols substituted at various positions with methyl, cyano, and methoxy groups.

The computed results by the CNDO/2 method (with a fixed geometry) did not afford satisfactory substituent effects for the relative stability of the two tautomeric forms of the 6-substituted derivatives, which is experimentally known to favor the pyridinol form.[1,6] In contrast, the MINDO/3 method did afford satisfactory results for the substituent effect on the 6-position (*vide infra*). The introduction of substituents can also be expected to alter the ring geometries of both tautomeric forms. Thus, to obtain more precise information on the nature of substituent effects on tautomeric properties, MINDO/3 calculations (with full geometry optimization) were carried out. Details of the results, thus obtained, are presented and discussed in the following subsections.

Energetic Features. The heat-of-formation values (H_f) of a parent compound (**1**) were calculated to be −142.9 and −127.3 kJ mol^{-1} for the pyridone form and the pyridinol form, respectively. The calculated energy difference between the two tautomeric forms (15.6 kJ mol^{-1}) was somewhat greater than the experimental value (1.3±10 kJ mol^{-1}).[2]

However, the calculated relative energies (ΔH_f) compared to that of a parent compound (**1**) are a measure of the net substituent effect and are presented in Table 1.

The relative energies, thus obtained, clearly indicate that the 6-substituted derivatives in each tautomeric form are the most stable among the ones bearing the same substituent irrespective of the nature of the substituent. This fact might be rationalized in terms of the *ortho*-position relative to the nitrogen atom, which has a greater electron-accepting property. Thus, the 6-substituent has the greatest interaction with the ring system. Also, the greater stabilizing effect of the 6-substituents on the 2-pyridinol form than on the 2-pyridone form was also shown. This can be understood from the larger C_6–N double-bond character of the former as compared with that of the latter.

As for the effect of the substituent at the 5-position, the 5-methoxy substituent is as effective as 6-polar substituents in a shift of the tautomeric equilibria leading to the predominance of the 2-pyridinol form.

The 5- and 6-chloro derivatives have been shown by IR spectra to favor the 2-pyridinol form over the 2-pyridone form, compared with the 3- and 4-chloro derivatives.[6d] A similar effect of the ortho substituent

TABLE 1. SUBSTITUENT EFFECTS ON THE HEAT OF FORMATION (H_f) OF 2-PYRIDONES AND 2-PYRIDINOLS CALCULATED BY MINDO/3 WITH GEOMETRY OPTIMIZATION

Substituent	ΔH_f[a]/kJ mol^{-1}		$\Delta\Delta H_f$[b]/kJ mol^{-1}
	2-Pyridones	2-Pyridinols	
3-Me	−24.2	−26.6	−2.4
4-Me	−25.8	−25.1	0.7
5-Me	−29.6	−29.4	0.2
6-Me	−45.4	−48.6	−3.2
3-, 4-Me	−32.6	−33.8	−1.2
5-, 6-Me	−63.2	−67.9	−4.7
3-CN	78.5	73.6	−4.9
4-CN	88.1	87.2	−0.9
5-CN	79.6	78.3	−1.3
6-CN	61.2	52.9	−8.3
3-OMe	−173.5	−174.1	−0.6
4-OMe	−215.2	−211.9	3.3
5-OMe	−176.2	−186.3	−10.1
6-OMe	−227.6	−235.8	−8.2

a) H_f (substituted)−H_f (parent). b) ΔH_f (2-pyridinols)−ΔH_f (2-pyridones).

to the nitrogen atom has also been shown for 4-pyridones.[6c] Due to the similarity of the net electronic-substituent effect between the methoxy group and the halogen atom (σ-inductive and π-donative), the calculated substituent effects of the methoxy derivatives on the relative stabilities between the two tautomeric forms seem to be in accord with the experimental evidence.

The methyl-substituent effect on the relative energetics of the tautomers has been calculated to be not so strong. In fact, it is the 2-pyridone form that is observed in the UV spectral measurement of these derivatives in a nonpolar solvent. However, some supportive experimental data for such an effect were obtained by IR spectral measurements of several methyl derivatives in a CCl_4 solution (5×10^{-4} M) at *ca.* 50 °C, although, in the solutions, these derivatives exist largely as the self-associated 2-pyridone form and the intensities of the nonassociated species are fairly weak. The observed intensity ratio (I_{OH}/I_{NH}) of the O–H and N–H stretching bands (around 3580 and 3410cm , respectively) of the nonassociated species were 0.08, 0.06, 0.14, 0.10, and 0.19 for unsubstituted-, 4-methyl-, 5-methyl-, 6-methyl-, and 5,6-dimethyl-2-pyridones, respectively. Although the absorption coefficient for the same type of vibration may vary from one molecule to another, the difference in the observed intensity ratio could qualitatively represent the greater stabilization of the corresponding 2-pyridinol form in that order.

Electronic Features. It is known that the introduction of electron-donating substituents at the 2- and 4-positions of pyridine, especially at the 2-position, renders a stabilizing effect. Such effects were ascribed to be the consequence of an increase in the N-atomic electron densities.[16]

Thus, the redistributions of atomic electron densities, resulting from the introduction of substituents, were examined. The differential electron densities of substituted 2-pyridones and 2-pyridinols relative to parent compounds are shown in Fig. 1.

An interesting point regarding Fig. 1 is that the largest increments of electron density on the nitrogen atom were shown on each tautomeric form of the 6-substituted derivatives regardless of the nature of the substituent. This is atributable to the lower core potential (large electronegativity) of the nitrogen atom and the ortho-position against the nitrogen atom. On the other hand, the substituents at the 3-, 4-, 5-positions in both tautomeric forms are primarily explained in terms of the general electronic effects for an aromatic system, that is, the *ortho*- and *para*-orientation for electron-donating substituents and the *meta*-orientation for electron withdrawing substituents. As a result, the 4-cyano and 3- and 5-methoxy substituents lead to the smallest electron densities on the nitrogen atom.

The relationship between the relative N-atomic electron densities (ΔQ_N) and the relative energies (ΔH_f) was examined for each substituent (Fig. 2).

It is clear from Fig. 2 that the increments of the electron densities on the nitrogen atom are in parallel to the trend of the relative total energy gain.[17] The magnitude of this increment was greater for the 2-pyridinol form in the case of methyl and methoxy derivatives. However, the nature of the electron density on the nitrogen atom differs from each other between the tautomeric forms, and also between the substituents. Based on an analysis which divided the electron charge increments into the σ- and π-electron character, the contribution of the σ-electron was found to be greater in methyl derivatives, while in the methoxy and cyano derivatives some greater contributions of the π-electron were found. These differences in the contribution of the σ- and π-electron may cause some deviations from

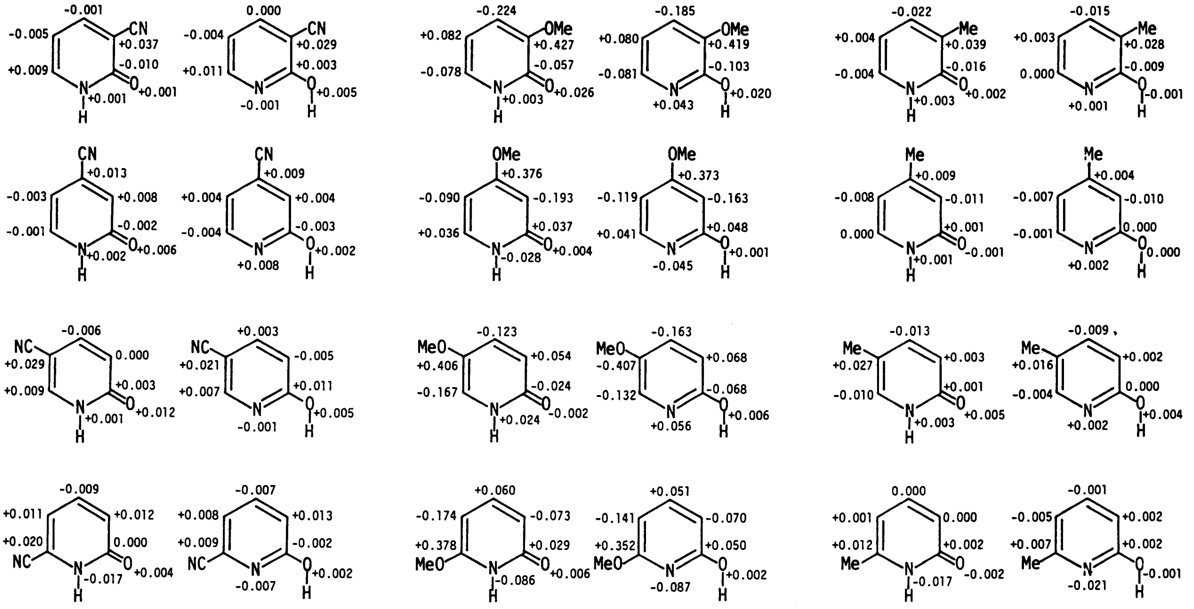


Fig. 1. Differential atomic electron densities of 2-pyridone and 2-pyridinol forms relative to those of the parent compounds.

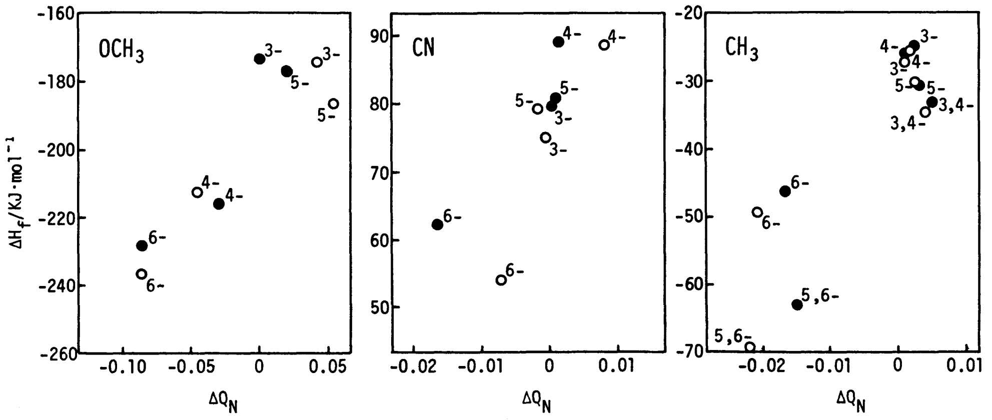


Fig. 2. Plots of the differential heat of formation (ΔH_f) *vs.* the differential N-atomic electron density (ΔQ_N) exerted by substituents. Filled and open symbols represent 2-pyridone and 2-pyridinol forms, respectively.

TABLE 2. CALCULATED BOND LENGTHS OF 2-PYRIDONES[a)]

Substituent	N-H	C_2-O	N-C_2	C_2-C_3	C_3-C_4	C_4-C_5	C_5-C_6	C_6-N
H	1.030	1.218	1.399	1.467	1.369	1.439	1.373	1.364
3-Me	1.031	1.218	1.398	1.489	1.386	1.435	1.372	1.362
4-Me	1.030	1.218	1.397	1.465	1.388	1.459	1.372	1.362
5-Me	1.033	1.217	1.398	1.464	1.368	1.460	1.390	1.363
6-Me	1.033	1.218	1.400	1.464	1.369	1.435	1.391	1.379
3-, 4-Me	1.031	1.219	1.394	1.489	1.408	1.459	1.370	1.359
5-, 6-Me	1.034	1.217	1.398	1.460	1.366	1.457	1.411	1.377
3-CN	1.031	1.216	1.399	1.485	1.387	1.435	1.374	1.361
4-CN	1.030	1.217	1.397	1.467	1.385	1.458	1.372	1.362
5-CN	1.031	1.215	1.402	1.464	1.368	1.458	1.392	1.358
6-CN	1.032	1.217	1.400	1.464	1.367	1.439	1.388	1.379
3-OMe	1.031	1.219	1.387	1.502	1.377	1.446	1.364	1.374
4-OMe	1.030	1.217	1.407	1.455	1.389	1.456	1.373	1.359
5-OMe	1.031	1.220	1.385	1.467	1.368	1.453	1.384	1.375
6-OMe	1.033	1.215	1.414	1.457	1.373	1.429	1.395	1.371

a) Bond lengths are given in Å.

TABLE 3. CALCULATED BOND LENGTHS OF 2-PYRIDINOLS[a)]

Substituent	O-H	C_2-O	N-C_2	C_2-C_3	C_3-C_4	C_4-C_5	C_5-C_6	C_6-N
H	0.952	1.321	1.341	1.424	1.400	1.410	1.402	1.334
3-Me	0.951	1.321	1.338	1.446	1.417	1.407	1.400	1.333
4-Me	0.951	1.322	1.340	1.424	1.420	1.427	1.400	1.333
5-Me	0.951	1.320	1.340	1.421	1.397	1.429	1.421	1.328
6-Me	0.951	1.322	1.338	1.422	1.399	1.407	1.420	1.346
3-, 4-Me	0.952	1.323	1.337	1.443	1.444	1.427	1.398	1.330
5-, 6-Me	0.951	1.320	1.336	1.420	1.398	1.426	1.443	1.342
3-CN	0.952	1.318	1.339	1.443	1.418	1.407	1.403	1.333
4-CN	0.952	1.321	1.339	1.424	1.418	1.427	1.400	1.334
5-CN	0.952	1.318	1.341	1.423	1.398	1.428	1.422	1.329
6-CN	0.951	1.320	1.338	1.425	1.398	1.410	1.416	1.346
3-OMe	0.952	1.328	1.326	1.453	1.406	1.418	1.391	1.342
4-OMe	0.952	1.319	1.341	1.423	1.415	1.431	1.398	1.336
5-OMe	0.951	1.326	1.340	1.417	1.404	1.419	1.423	1.331
6-OMe	0.951	1.317	1.335	1.423	1.400	1.407	1.419	1.342

a) Bond lengths are given in Å.

the correlations in cyano and methoxy derivatives in Fig. 2.

Structural Features. The experimental geometries of 2-pyridones and 2-pyridinols have been reported for 2-pyridone,[3,12)] 5-chloro-2-pyridone,[18)] 6-chloro-2-pyridinol,[12,19)] and 6-bromo-2-pyridinol[13)] by the X-ray crystal structure analyses. The optimized geometries derived by the MINDO/3 method show good agreement with experimental facts. The optimized geometric parameters for the ring part of 2-pyridinol were nearly identical with the result for pyridine by the same method.[20)]

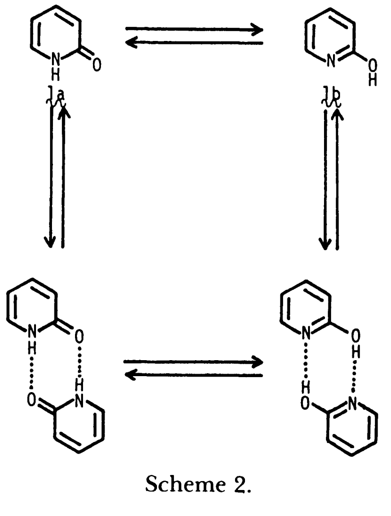
The computed bond lengths of the various substituted 2-pyridones and 2-pyridinols obtained by the MINDO/3 method with geometry optimization are summarized in Tables 2 and 3, respectively.

The ring structural perturbation due to an introduction of the substituents can be understood, on the whole, by an increase in bond lengths, including that of the atom attached to the substituent by about 2.0 pm. Also, the O–H bond lengths are nearly constant and variations in the C–O and C–N bond lengths are small. They seemed not to be associated with the tautomeric properties.

Here, it may be interesting to inspect the substituent effects, combining the structural features with the electronic effects described in a previous subsection. The geometric perturbations indicated that the C_3–C_4 bond length had a greater effect on the stabilities of the 2-pyridone and 2-pyridinol forms than the other bond length, considering that the energy gains by the geometrical optimizations in the 3-, or 4-substituted derivatives were greater than those in 5-, or 6-substitution. But, when a comparison between the energy gains in the two forms was made, it was found that the lengthening of the C_5–C_6 bond had an effect on stabilizing the 2-pyridinol form more than the 2-pyridone form (Table 1) (*vide supra*).

As a result of the C_5–C_6 bond lengthening, some parts of the electron density forming the C_5–C_6 bond must be transferred to the rest of the molecule. Among those, the nitrogen atom would naturally gain the greater part of the electron, resulting in the increment in the N-atomic electron densities.

Self-association. The hydrogen-bonded dimeric structure of 2-pyridones is well known from crystallographic[3,12,18] and thermodynamic studies.[21] The dimeric structure of the 2-pyridinol form with a centrosymmetry is also known through X-ray studies of 6-halo-2-pyridinols.[13,19] Thermodynamic parameters, such as the association constant, have been studied for 6-chloro-2-pyridinol[4] and results indicate that the association energies of the 2-pyridinol form are relatively smaller than those for the 2-pyridone form. The importance of self-association in the tautomeric equilibria of 2-pyridones (**1**) has also been stressed by P. Beak *et al.*[2,4] and O. Bensaude *et al.*,[22] and the mechanism by which the tautomerism occurs is widely accepted to be through the dimer. Although the OH proton in the pyridinol form is more acidic than the NH-proton in the pyridone form, based on both charge densities and bond-order terms, the relevant site for the self-association in the pyridone form is more sterically favorable over that in pyridinol form. The net effect of this may be that the pyridone-pyridone dimer is more feasible. Accordingly, the larger association energies of the 2-pyridone form result in a shift in the tautomeric equilibria of **1**, leading to the predominance of the 2-pyridone form (**1a**).



Scheme 2.

Thus, the substituent effect on the association energy of each tautomeric form is considered to be directly related to tautomeric equilibria. However, there is very little experimental or theoretical in formation available on this matter.

The defects of the MINDO/3 and MNDO methods for the evaluation of intermolecular interactions, particularly in the case of hydrogen-bonding interactions, have already been pointed out.[23,24] In fact, attempts to reproduce the self-association energies of the 2-pyridone (**1a**) and 2-pyridinol (**1b**) form by the MINDO/3 method (employing geometries based on the crystalline structures) resulted in the destabilization of 53.1 kJ mol^{-1} in the former and 74.4 kJ mol^{-1} in the latter.

Furthermore, in calculations related to the optimization of intermolecular distances, including those of NH and OH, energy minima were found at unrealistic interatomic distance between the nitrogen and the oxygen: 4.87 Å in 2-pyridone and 7.80 Å in 2-pyridinol, respectively.[25]

Although there are also documented failures of the CNDO/2 scheme's ability to acount correctly for hydrogen bonding or nonbonded interaction,[26] for certain limited structures set on specific association orientations, one can evaluate the relative energetics by the CNDO/2 method.

In fact, it has been reported that the CNDO/2 method has given the correct self-association energy values for formamide[27] and for several other cases of intermolecular systems such as those involving large contribution due to electrostatic interactions.[28]

Recently, Inuzuka *et al.* have reported the self-association energy of 2-pyridone supported by the CNDO/2 method with a geometry optimization, but without referring to the interrelation to the tautomerism.[29] The reported self-association energy was 147.7 KJ mol^{-1}. They deduced a corrected value of 68.2 kJ mol^{-1}, based on comparisons with several organic compounds. This was compatible with the experimental value (65.3 kJ mol^{-1}) obtained by the NMR technique.[29]

We have also evaluated the self-association energies of various substituted 2-pyridone forms and 2-pyridinol forms on the dimeric structure experimentally determined by X-ray analyses[13,18] (Table 4).

In the present calculations, the self-association energy of the 2-pyridone form (**1a**) was 71.6 kJ mol^{-1}, which is in fairly satisfactory agreement with the above-mentioned experimental value (65.3 kJ mol^{-1}).[30] This value was greater than that of the 2-pyridinol form (**1b**) by 7.6 kJ mol^{-1}, proving a qualitative validity of this method.

However, when comparisons are made of the values between the 2-pyridone form and the 2-pyridinol form of such derivatives (as shown in Table 4), those of the former value were all greater than those of the latter by about 2.9—10.5 kJ mol^{-1}. This was even true for the case of the derivatives which exist very largely in the 2-pyridinol form (to such an extent as can be observed in conventional UV measurements). Therefore, the association ability seems not to be closely related to the tautomerism of the derivatives bearing a polar substituent at the 6-position, although the tautomerism is well known to occur *via* the dimer. On the other hand, parent and methylated derivatives exist largely in the 2-pyridone form due to the greater association energies compared to the tautomeric-energy differences.

Table 4. Dimerization energies calculated by the CNDO/2 method

Substituent	E_{dim}/kJ mol^{-1}	
	2-Pyridones	2-Pyridinols
H	71.7	64.1
3-Me	69.0	64.0
4-Me	74.7	64.9
5-Me	71.1	64.1
6-Me	74.4	64.8
3-CN	73.1	62.5
4-CN	72.7	63.1
5-CN	72.2	62.2
6-CN	70.2	61.8
3-OMe	70.3	62.9
4-OMe	74.2	66.4
5-OMe	70.7	62.5
6-OMe	69.6	66.4

Conclusion

It is often observed that the substituent effect on stability and reactivity can not be easily predicted and interpreted in a simple manner since the factors at play (steric, inductive, conjugative and others) may act in opposing ways. Nevertheless, the present studies considerably enhanced our understanding of the nature of the substituent effect on the tautomeric properties of 2-pyridone–2-pyridinol.

The conclusion reached from the present studies may be represented as follows: From calculations, the substituent at the 6-position have been shown to exert the strongest influence on the relative energetics of the tautomers, irrespective of the nature of the substituents. The introduction of polar substituents at this position stabilized the 2-pyridinol form much more than the 2-pyridone form. This effect is well correlated by N-atomic electron densities and ring structural modifications of the tautomers.

Thus, in this type of derivative, the association ability is not an important factor in controlling the tautomeric euilibria in solution, unlike unsubstituted 2-pyridone, although the association energies have been shown to vary with such substituents.

The introductin of a 6-alkyl substituent, such as a methyl group, also similarly resulted in a greater stabilization of the 2-pyridinol form than of the 2-pyridone form. However, due to the small difference in such a relative energetic of the tautomers, the 2-pyridinol forms were not observed by conventional UV spectral measurements, and the association abilities still play an important role in determining the tautomeric equilibria in solution. The tautomerism of these derivatives, therefore, can be considered to be more susceptible to their environmental conditions than that of unsubstituted 2-pyridone.

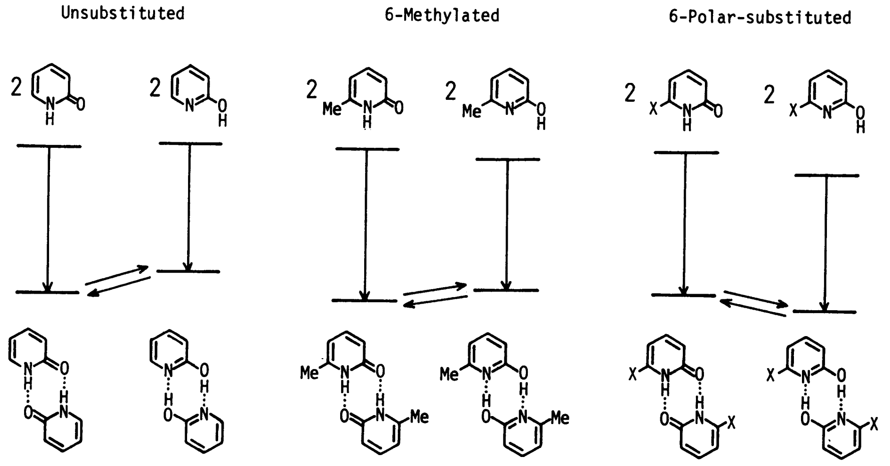


Fig. 3. Qualitative representations for 6-substituent effect on the relative stability of the two tautomers. 6-Polar substituent, **X**, denotes strong electron-withdrawing and donating substituents.

A comparison of the qualitative energy diagrams in the interrelation of the tautomer and dimer forms in solution is illustrated in Fig. 3.

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