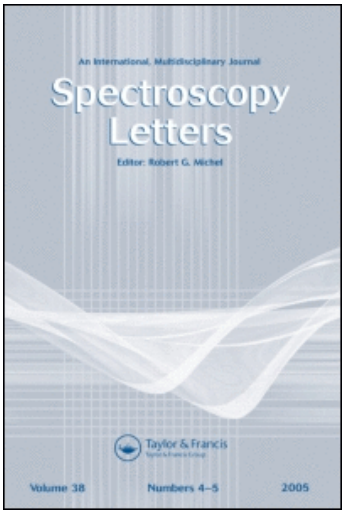

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KETO-ENOL TAUTOMERISM OF MONO-SUBSTITUTED PHENYLPYRUVIC ACIDS AS STUDIED BY NMR AND PM3 CALCULATION

Key Words : phenylpyruvic acids, keto-enol tautomerism, NMR spectra, PM3 calculation

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ABSTRACT

Keto-enol tautomerism of mono-substituted phenylpyruvic acids has been studied by the ^{1}H and ^{13}C NMR spectra. The equilibrium constants and the kinetic parameters for the tautomerism were obtained from the spectral data. The equilibrium constants are strongly dependent on the position of the substitution; the values for the *o*-substituted PPAs are several times greater than those of the *m*- or *p*-substituted derivatives. The PM3 calculations have been carried out to obtain the information on the preferred conformations of the tautomers and on the mechanism for the tautomerism. The results suggest the involvement of a solvent molecule in the equilibrium process.

INTRODUCTION

Biological importance of α-keto acids such as phenylpyruvic acid (PPA) has been well recognized. PPA is known as a metabolite of phenylalanine found in the urine of patients afflicted with phenylketonuria [1]. Besides their biological roles, PPA has aroused many research interests in structural chemistry. Owing to the chemical nature of the α-keto carbonyl group, PPA can exist in the

keto and the enol form. The tautomeric behavior of PPA has been extensively studied by spectroscopic methods both in solution and in the solid state. Sciacovelli et al. reported on the existence of the hydrated keto form on the basis of the NMR, IR and UV data.[2-3] We have investigated the molecular structures of PPA in solution and in the solid state by IR, Raman and solid state NMR spectra.[4-7]

Tautomeric equilibria of organic compounds are presumed to be sensitive to various kinds of factors.[8] Introduction of substituent groups into the phenyl ring affects the electronic and steric environments in the PPA system and causes shifts in the position of the equilibrium. In the present work, we have investigated the tautomeric behavior of mono-substituted PPAs carrying various substituents. Equilibrium constants and kinetic parameters were obtained from the ^1H NMR data. Semiempirical MO calculations were carried out in order to confirm the tautomeric and conformational preferences and obtain information on the reaction mechanism.

EXPERIMENTAL

Materials

PPA was prepared by acidification of sodium phenylpyruvate monohydrate (PPA-Na · H_2O) purchased from

Tokyo Kasei Kogyo, Jpn. A series of *o*-, *m*- and *p*-substituted PPAs were prepared by three step procedures using the corresponding mono-substituted benzaldehydes and N-acetylglycine as starting materials.[9] The purities of PPA and mono-substituted PPAs were checked by elemental analyses and ^{1}H NMR spectra.

Measurement

^{1}H NMR spectra in solution were recorded on a JEOL JNM-LA 400 spectrometer. The samples were dissolved either in CD_3CN or in $CDCl_3$. In determining the equilibrium constants, the spectra were taken in 72 hours after the sample preparation so as to allow equilibrium to reach. Kinetic parameters were calculated from the ^{1}H NMR data obtained at 25, 40 and 55 °C. The elemental analyses were carried out on a Yanaco CHN Corder MT-3.

Quantum Mechanical Calculations

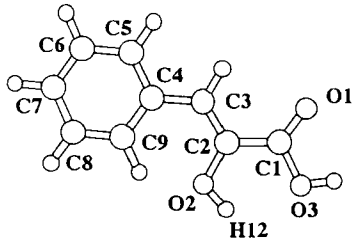
Molecular mechanics and semiempirical PM3 MO calculations were carried out by using MM2 and MOPAC implemented in CAChe programs[10] run on an IBM RISC 6000 computer.

The atom numbering scheme is shown in Fig. 1. The *(Z)*- and *(E)*-forms were considered as possible configurations for the enol form. Rotational isomers about the three torsional angles τ_1-τ_3 were taken into account. As a first step, low energy conformations are searched for by changing the torsional angles, τ_1-τ_3, using the sequential search option of the CAChe MM2. The carbonyl oxygen atom in the carboxylic acid, O=C—O—H, was fixed at the *cis*- position to the hydroxyl hydrogen atom, because this conformation is proven to be the most stable in carboxylic acids.[11] Ten to twelve of the lowest energy conformers are taken up and the molecular structures were optimized by the MOPAC PM3 method. In all cases, the PRECISE option was used to provide higher accuracy within this calculation. The transition state structure and the activation energy for the enol-to-keto interconversion were also calculated by the IRC (Intrinsic Reaction Coordinate) procedure implemented in the CAChe MOPAC.

RESULTS AND DISCUSSION

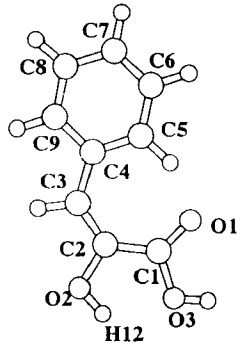
Tautomeric behavior of mono-substituted PPAs

PPA and all the mono-substituted PPAs exhibit exclusively the enol ^{1}H NMR features in $CDCl_3$. When



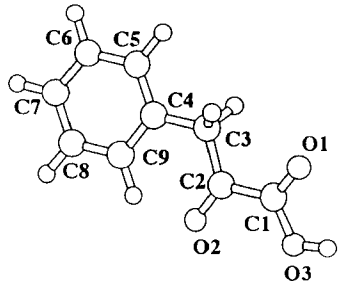
(Z)-enol

τ_1 = O1-C1-C2-C3
τ_2 = H12-O2-C2-C3
τ_3 = C2-C3-C4-C5



(E)-enol

τ_1 = O1-C1-C2-C3
τ_2 = H12-O2-C2-C3
τ_3 = C2-C3-C4-C5



keto

τ_1 = O1-C1-C2-C3
τ_2 = O2-C2-C3-C4
τ_3 = C2-C3-C4-C5

FIG. 1 Numbering scheme and torsional angles τ_1-τ_3 for the *(Z)*-enol, the *(E)*-enol, and the keto form of PPA. Hydrogen atoms except the hydroxy group are omitted for clarity.

dissolved in CD_3CN, the resonances due to the keto form appear and increase in intensity with time at the expense of the enol form. Table 1 summarizes some NMR data of these compounds. This time-dependent enol-to-keto interconversion can be followed by analyzing the intensity change in the enolic –CH= and the ketonic $-CH_2-$ signals. The keto-enol equilibrium appears to be reached in about 72 hours after the sample preparation. A small amount of degradation products was also detected, which was not taken account of in the calculation of the equilibrium constant. Figure 2 depicts the dependence of the equilibrium constants on the mono-substitution at the phenyl ring of PPA. It is noteworthy that the *o*-substituted PPAs generally have much larger equilibrium constants than the *m*- or *p*- substituted PPAs. Furthermore, they tend to increase with the order of bulkiness of the substituents. The equilibrium constants appear to be little dependent on the electronic nature of the substituents. This finding suggests that the steric factor is more important than the electronic nature of the substituents in determining the position of the keto-enol equilibrium. The steric repulsion between the *o*-substituent and the –CH= proton may hinder the co-planarity

TABLE 1

Some NMR data of PPA and its mono-substituted derivatives in CD_3CN solution

		Keto			Enol		
		$\delta(-C\underline{H}_2-)$	$\delta(-\underline{C}H_2-)$	$^1J_{-CH2-}$	$\delta(-C\underline{H}=)$	$\delta(-\underline{C}H=)$	$^1J_{-CH=}$
Subst.		/ppm	/ppm	/Hz	/ppm	/ppm	/Hz
CH_3O-	*o*-	4.09	40.5	130	6.91	104.9	161
	m-	4.13	45.3	129	6.49	110.6	157
	p-	4.09	44.4	129	6.49	111.5	160
CH_3-	*o*-	4.24	43.5	129	6.69	108.3	159
	m-	4.12	45.2	129	6.49	111.7	159
	p-	4.11	45.5	129	6.50	111.6	156
H-		4.18	45.4	129	6.53	111.5	158
F-	*o*-	4.24	39.4	129	6.69	101.8	159
	m-	4.21	44.9	130	6.52	110.2	160
	p-	4.17	44.4	129	6.52	110.4	160
Cl-	*o*-	4.34	43.7	129	6.87	105.9	165
	m-	4.19	44.8	129	6.48	109.8	160
	p-	4.18	44.6	129	6.50	110.1	160
Br-	*o*-	4.36	46.1	129	6.84	108.8	162
	m-	4.18	44.8	130	6.47	109.6	161
	p-	4.16	44.6	130	6.68	110.1	160

of the conjugated system and reduce the stability of the enol form.

The enol and the keto content may be connected with the *s*- and *p*-characters of the bond. As the *s*-character of the enol =CH— bond and the keto $-CH_2-$ bond increases, PPAs have

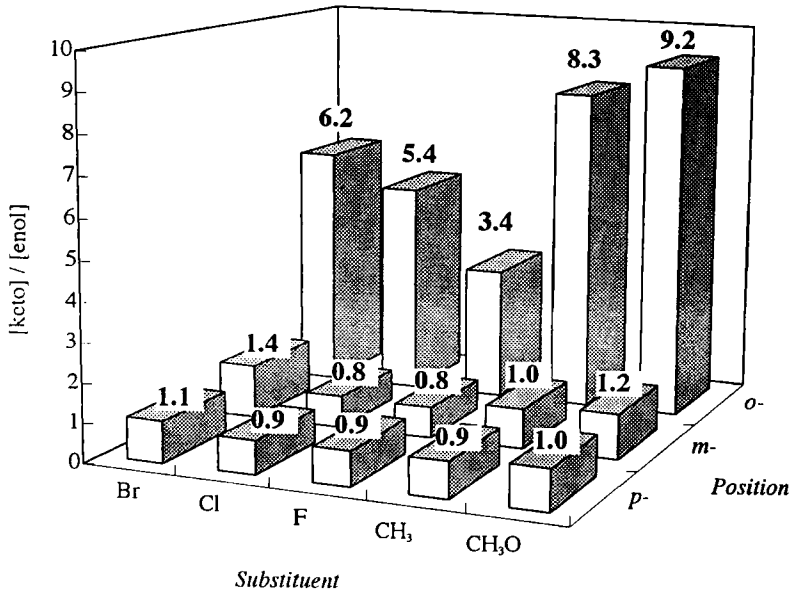


FIG. 2 Equilibrium constants K, [keto]/[enol] of mono-substituted PPAs in CD_3CN, at 298K.

greater propensities toward the enol form. The bond *s*- and *p*-characters may be reflected in the NMR chemical shifts and the $^1J_{CH}$ values. Bassetti et al. surveyed the effect of substituents on the tautomeric equilibria of β-diketones[12]. They found a linear correlation between the enolic $^1J_{-CH-}$ coupling constants and the equilibrium free energies of the tautomerism. We expected a similar correlation for the tautomerism of mono-substituted PPAs. However, the $^1J_{-CH-}$

and the $^1J_{-CH_2-}$ values are little affected by the electronic nature and the position of the substituents. The considerable dependence on the substitution position are observed for the enol -CH= and the keto $-CH_2-$ carbon chemical shifts. The values for the *o*-substituted PPAs are observed at a higher field by a few ppms than those for the *m*- or *p*-substituted PPAs except for the data of the bromo derivatives. Such higher field shift is connected with an decreased *s*-character of the carbon atoms and an increased propensity toward the keto form.

Thermodynamic and Kinetic Aspects of the Tautomerism

Thermodynamic and kinetic parameters for the keto-enol tautomerism were obtained by measuring the ^1H NMR spectra of PPA in CD_3CN at three different temperatures (25, 40, 55 °C). A reversible first-order reaction was postulated as shown in Scheme 1, and the data were fitted to the rate equation.

The logarithm of difference in the enol concentration between the time, *t*, and the equilibrium point was plotted against time to give an approximate straight line. The effective rate constant, $(k + k')$ was obtained as a slope of the line (2). The rate constant k, for the forward

$$\text{Enol} \underset{k'}{\overset{k}{\rightleftharpoons}} \text{Keto} \qquad \cdots (1)$$

$$\ln \frac{[\text{Enol}]_o - [\text{Enol}]_e}{[\text{Enol}]_t - [\text{Enol}]_e} = (k + k')\, t \qquad \cdots (2)$$

$$k = \frac{k + k'}{1 + 1/K} \qquad \cdots (3)$$

$$\ln k = -\frac{Ea}{R} T^{-1} + \ln A \qquad \cdots (4)$$

Scheme 1 The rate equation for the keto-enol equilibrium of PPA.

k, k'	: rate constants of the forward and the backward reaction
$[\text{Enol}]_t$	: the enol concentration at time t
$[\text{Enol}]_o$	: the initial enol concentration
$[\text{Enol}]_e$	: the enol concentration at equilibrium
K	: the equilibrium constant
E_a	: activation energy
A	: pre-exponential factor
R	: gas constant

reaction was calculated from the equation (3), using the (k + k') and the equilibrium constant value, K. The activation energies for the forward and the backward reaction, Ea and Ea', respectively, were estimated by using the Arrhenius plot (4). The calculated rate and equilibrium constants and the activation energies are given in Table 2. The Ea and Ea' were obtained as 32.7 and 36.4 kcal mol^{-1}, respectively, indicating that the keto form is thermodynamically more stable than the enol form.

TABLE 2

The kinetic constants for the tautomerism of PPA

Temperature / K	$k + k'$ / min^{-1}	K	k / min^{-1}	Number of data
298	2.48×10^{-5}	0.84	1.11×10^{-5}	9
313	5.53×10^{-4}	1.14	2.95×10^{-4}	10
328	2.96×10^{-3}	1.39	1.72×10^{-3}	6

Quantum Mechanical Calculations

The semiempirical PM3 method was chosen for the molecular orbital calculations, because this Hamiltonian has been shown to be quite reliable for the present purpose.[13] Table 3 summarizes the results of the PM3 optimizations on the keto, the (*Z*)-enol and the (*E*)-enol form of PPA. The four of the lowest energy conformers (numbered from (I) to (IV)) are listed for each form. Inspection of Table 3 indicates that the keto forms give lower heats of formation by 7-8 kcal/mol than the enol forms. The dipole moments for the keto forms are generally greater than those of the enol forms. These results are consistent with the fact that the keto form increases at equilibrium in CD_3CN. In comparing the (*Z*)-geometry of the enol form with that of the (*E*)-geometry, the structural preference

TABLE 3

PM3 optimized parameters of PPA (heats of formation ΔH_f^0, dipole moment μ, and torsional angles τ_1-τ_3)

Conformation	ΔH_f^0 /kcal mol^{-1}	μ /debye	τ_1 /°	τ_2 /°	τ_3 /°
keto (I)	-101.3	2.46	-69.5	111.4	103.5
keto (II)	-101.2	2.48	71.0	-105.1	-103.6
keto (III)	-101.0	2.70	-102.4	-111.0	-106.9
keto (IV)	-101.0	2.38	-80.9	12.8	90.0
Z-enol (I)	-93.9	2.40	-1.6	3.6	57.5
Z-enol (II)	-93.1	3.16	174.1	-3.8	-58.0
Z-enol (III)	-92.7	1.25	177.0	-176.8	-44.8
Z-enol (IV)	-92.3	1.19	-1.8	176.0	45.9
E-enol (I)	-92.1	2.26	90.8	0.1	-60.3
E-enol (II)	-92.0	2.23	-87.8	0.5	84.9
E-enol (III)	-91.5	1.21	127.6	-147.8	-63.2
E-enol (IV)	-91.1	1.57	55.1	143.2	88.1

is observed for the former, although the energy difference is very small (1-2 kcal).

We have attempted to reproduce the observed trend that the *o*-substitution favors the keto form in the tautomeric equilibrium by the calculation. However, no systematic trend was not drawn from the calculation.

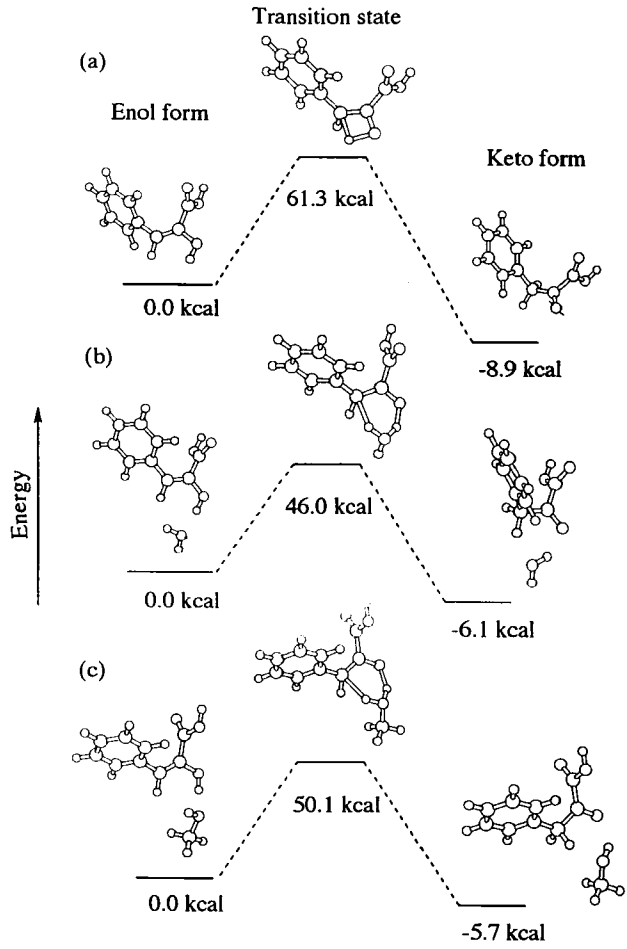


FIG. 3 Reaction mechanisms for the keto-enol tautomerism.

(a) direct migration mechanism

(b) water assisted mechanism

(c) methanol assisted mechanism

The transition state structures for the keto-enol tautomerism were calculated by using the IRC option of the PM3 method. We assumed that the keto-enol tautomerism occurs through the direct proton migration from the methylene group to the α-keto oxygen in the keto form (direct migration mechanism). However, as shown in the NMR results, the enol-to-keto transformation proceeds much more rapidly in polar solvents such as water, methanol and acetonitrile. Therefore, involvement of the solvent molecule was suggested for the keto-enol tautomerism of monochloroacetyl chloride.[14] Thus we have also studied the solvent-assisted mechanism where the solvent molecule is involved in the transition state structure. The reasonable transition state structures have been obtained for the water- and the methanol-assisted mechanism. The results of the calculations are summarized in Fig. 3. It is noted that the solvent-assisted mechanisms result in lower activation energies than the direct migration mechanism by 15.3 and 11.2 kcal mol^{-1} for the water assisted and methanol-assisted mechanisms, respectively. This finding suggests that the solvent molecule plays an important role in the keto-enol tautomerism of PPA.

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