

Selected Paper

Gas-Phase Acidities of Acetophenone Oximes. Substituent Effect and Solvent Effects

Md. Mizanur Rahman Badal and Masaaki Mishima*

Institute for Materials Chemistry and Engineering, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812-8581

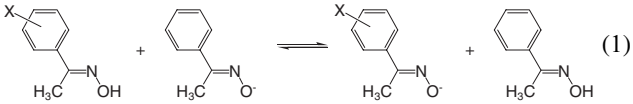
Received September 15, 2009; E-mail: mishima@ms.ifoc.kyushu-u.ac.jp

Gas-phase acidities (GA) of ring-substituted (*E*)-acetophenone oximes, $XC_6H_4C(CH_3)$=NOH, were determined by measuring proton-transfer equilibria using an FT-ICR mass spectrometer. The magnitude of the substituent effect on the acidity was found to be smaller than that of corresponding phenols by a factor of 0.70. The effects of strong *para* π-acceptors such as *p*-NO_2 and *p*-CN are somewhat enhanced compared with those of phenols, indicating that the negative charge on oxygen atom of the conjugate anion of the oxime is significantly delocalized into the aromatic π-system. In addition, it was found that there is a good linear relationship between acidities in gas phase and in DMSO with a slope of 0.26, indicating that the solvation stabilization reduces consistently the effects of substituents without any significant specific solvent effect on a particular substituent. This is in contrast to the phenol acidities in which the effects of electron-rich *para* +R substituents in DMSO and water were enhanced significantly due to the substituent solvation-assisted resonance (SSAR) effects. These results were consistent with computational studies at the B3LYP/6-311+G(d,p) level of theory.

Oximes have received continuous attention in various fields because they possess interesting biological activities and high potential as starting materials for the synthesis of a variety of N-containing compounds.[1–7] The conjugate anions, oximates, represent a class of nucleophilic catalysts which has proven to be very efficient in promoting processes such as acyl, phosphoryl, and sulfuryl transfers which are important processes in biological reactions as well as proton transfers. In particular, the reactivity of oximate anions has considerably received attention in the last two decades, because the oximates are referred to as α-nucleophiles which exhibit a high nucleophilic reactivity compared to common nucleophiles of similar basicities.[8–14] Recent work suggests that the solvent effects in addition to differential ground-state destabilization and transition-state stabilization effects play an important role in determining the enhanced reactivity of α-nucleophiles.[15,16] Bordwell and co-workers measured the acidities of acetophenone oximes and benzaldehyde oximes in DMSO and found that these acidities fall within a narrow range of 3.8 pK_a units for the change from *p*-NO_2 to *p*-MeO.[17] Contrary to this, the large substituent effect was observed for the pK_a values of phenols, where the *p*-NO_2 group enhances the acidity by 7.2 pK_a units.[18] The small substituent effect in the oxime acidity was attributed to a remote anion center from the substituent. They reported further that a Hammett plot of the pK_a values is linear with σ_p values rather than σ_p^- values for *p*-NO_2 and *p*-CN. These results suggested that the negative charge in the oximate anion remains primarily on oxygen atom with little or no π-delocalization to the benzene ring. The localized negative charge at the oxygen atom would cause stronger interaction with solvent than that in phenoxides. This may also be one of the causes for small substituent effects observed for the acidity of acetophenone oxime and benzaldehyde oxime in DMSO. Thus, it is important to elucidate the intrinsic stabilities of oximates free from solvent effects for understanding fundamental properties and developing applications for various fields. Such information can be obtained from acidities in the gas phase.[19,20] In this study, the substituent effect on the gas-phase acidity of (*E*)-acetophenone oxime, $XC_6H_4C(CH_3)$=NOH, have been investigated. The gas-phase acidities were determined based on proton-transfer equilibria using a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer. Theoretical calculations were also conducted for acetophenone oximes, phenols, and a related system, (*E*)-2-phenylpropen-1-ol, of which acidities cannot be determined experimentally.

Results

Gas-Phase Acidities. The free energy changes determined by measuring the equilibrium constant of the proton-transfer reaction between acetophenone oximes of interest and a reference acid (AH) of known acidity[21] are summarized in Table 1.



(1)

The gas-phase acidity of the unsubstituted acetophenone oxime is found to be 53.4 and 54.5 kJ mol^{-1} stronger than formaldehyde oxime and acetaldehyde oxime, respectively. The increased acidity is explained by an electron-withdrawing effect of the phenyl group through inductive and resonance effects which stabilize the conjugate anions. The acidity of acetophenone oxime is 15.5[19] or 21.5[20] kJ mol^{-1} weaker than phenol, being consistent with the difference in DMSO (17.6 kJ mol^{-1}).[17,18] The relative gas-phase acidities of acetophenone oximes are summarized in Table 2 along with the

Published on the web December 23, 2009; doi:10.1246/bcsj.20090246

Table 1. Free Energy Changes of Proton-Transfer Equilibrium and Gas-Phase Acidities (GA)[a)]

Subst.	Reference acid	[GA][b)]	ΔG^{o} [c)]	$GA_{selected}$
p-OCH_3	*m*-$CF_3C_6H_4NH_2$	[1460]	−4.9	1459.0
	CH_3NO_2	[1463]	−4.0	
	p-$CF_3C_6H_4NH_2$	[1448]	11.0	
p-CH_3	CH_3NO_2	[1463]	−8.9	1454.1
	p-$CF_3C_6H_4NH_2$	[1448]	6.1	
H	CH_3NO_2	[1463]	−15.0	1447.5
	p-$CF_3C_6H_4NH_2$	[1448]	−1.2	
	p-$CH_3C_6H_4CH_2CN$	[1443]	4.7	
m-F	CH_3COOH	[1429]	6.8	1434.3
	m-$CH_3C_6H_4CH_2CN$	[1440]	−7.3	
p-Cl	C_6H_5OH	[1437]	−8.4	1429.1
	m-$CH_3C_6H_4CH_2CN$	[1440]	−10.5	
m-Cl	*p*-$FC_6H_4CH_2CN$	[1433]	−3.8	1428.6
	m-$CH_3C_6H_4CH_2CN$	[1440]	−12.0	
m-CF_3	CH_3COOH	[1429]	−10.0	1419.0
	m-FC_6H_4OH	[1410]	7.6	
	o-FC_6H_4OH	[1418]	1.3	
p-CF_3	*m*-FC_6H_4OH	[1410]	2.6	1413.8
	o-FC_6H_4OH	[1418]	−2.9	
m-NO_2	*p*-$CF_3C_6H_4CH_2CN$	[1393]	10.8	1404.8
	m-ClC_6H_5OH	[1402]	3.8	
3,5-$(CF_3)_2$	*p*-$CF_3C_6H_4CH_2CN$	[1393]	0.6	1393.5
	m-$CF_3C_6H_4CH_2CN$	[1403]	−9.6	
p-CN	*p*-$CF_3C_6H_4CH_2CN$	[1393]	0.0	1393.0
p-NO_2	$ClCH_2COOH$	[1377]	2.5	1379.5
	m-FC_6H_4COOH	[1377]	6.7	

a) Units of $kJ\,mol^{-1}$. b) Gas-phase acidity of reference compounds, Ref. 21. c) Free energy changes of respective proton-transfer equilibria.

corresponding gas-phase acidities of phenols collected from the literature.[19]

Computations of Gas-Phase Acidity. The geometries of neutral acetophenone oximes and the corresponding conjugate anions were optimized at the B3LYP/6-311+G(d,p) level of theory. The harmonic vibrational frequencies were also evaluated at the same level of theory to ensure that each optimized structure was a true minimum on the potential energy surface and to calculate thermochemical quantities. Although the calculated acidity values of acetophenone oximes are consistently 10–20 $kJ\,mol^{-1}$ lower than those observed, there is a good linear relationship between experimental and calculated acidities covering a wide range from *p*-MeO to *p*-NO_2. The slope is somewhat larger than unity for an ideal fit.

acetophenone oxime:

$$\Delta G^{o}_{acid}(calc) = 1.08\Delta G^{o}_{acid}(exp) - 1.5 (R^2 = 0.996) \quad (2)$$

phenol:

$$\Delta G^{o}_{acid}(calc) = 1.14\Delta G^{o}_{acid}(exp) + 2.3 (R^2 = 0.995) \quad (3)$$

The good linearity of the correlations indicates that the substituent effects for the calculated acidities could be used for comparisons of substituent effects among related substrates. The calculated acidities of acetophenone oximes and phenols are given in Table 2. The calculated acidities of (*E*)-2-phenylpropen-1-ols are available in Table S1 (Supporting Information).

Table 2. Relative Gas-Phase Acidities of Acetophenone Oximes and Phenols[a)]

Subst.	Acetophenone oxime		Phenol	
	$-\Delta GA_{exp}$	$-\Delta GA_{calc}$ [b)]	$-\Delta GA_{exp}$ [c)]	$-\Delta GA_{calc}$ [b)]
p-NMe_2		−15.3	−8.8	−2.5
p-MeO	−11.5	−10.1	−5.0	−4.7
p-Me	−6.6	−4.8	−4.6	−3.0
H	0.0	0.0	0.0	0.0
m-F	13.2	16.2	22.2	28.2
p-Cl	18.4	19.5	24.7	28.4
m-Cl	18.9	22.2	29.7	36.4
m-CF_3	28.5	30.8	40.2	47.7
p-CF_3	33.7	40.4	49.8	60.7
m-NO_2	42.7	47.6	60.2	67.2
3,5-$(CF_3)_2$	54.0	61.5	79.1	90.3
p-CN	54.5	56.8	69.5	79.4
p-NO_2	68.8	76.4	87.4	102.8

a) Units of $kJ\,mol^{-1}$. b) Calculated at B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p). c) Ref. 19.

Chart 1. Optimized structures of *p*-MeO- and *p*-NMe_2-substituted acetophenone oximates.

Discussion

Substituent Effect. Figure 1 shows a plot of the relative gas-phase acidities of acetophenone oximes against the corresponding acidities of benzoic acids which can be considered to be a standard σ^{o}-type substituent effect in the gas phase.[22] One can find a good linear relationship for non-conjugative substituents such as *meta* substituents with a slope of 0.91. On the other hand, the strongly π-electron accepting *p*-NO_2 and *p*-CN groups show significant upward deviations from the line. Such deviations for strong *para* π-acceptors suggest that these conjugate anions are stabilized more significantly by the π-delocalization of the negative charge into the π-aryl group compared with that in the benzoate anion. In Figure 2 are plotted the gas-phase acidities of acetophenone oximes against the acidities of phenols where the effects of *para* π-acceptors are well-known to be enhanced by strong π-interaction between these substituents and the anion center.[19] There exists a fairly linear relationship with a slope of 0.70, indicating clearly that the negative charge on oxygen atom of the oximate anion is significantly delocalized into the aromatic π-system in the same manner as that in the phenoxide. Closer examination

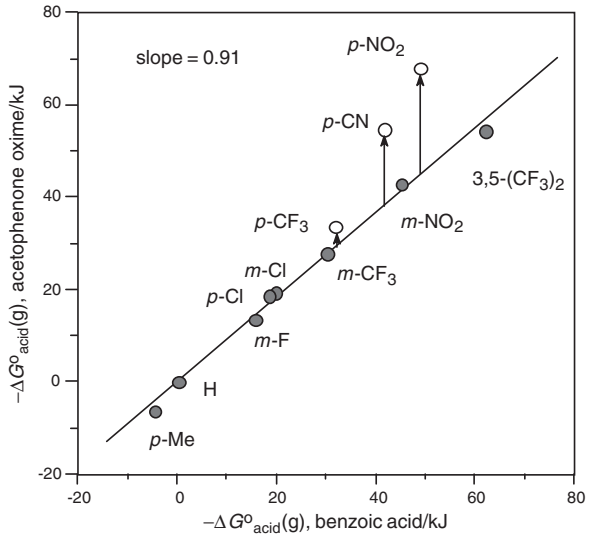


Figure 1. Plot of gas-phase acidities of acetophenone oximes against the corresponding benzoic acids.[22]

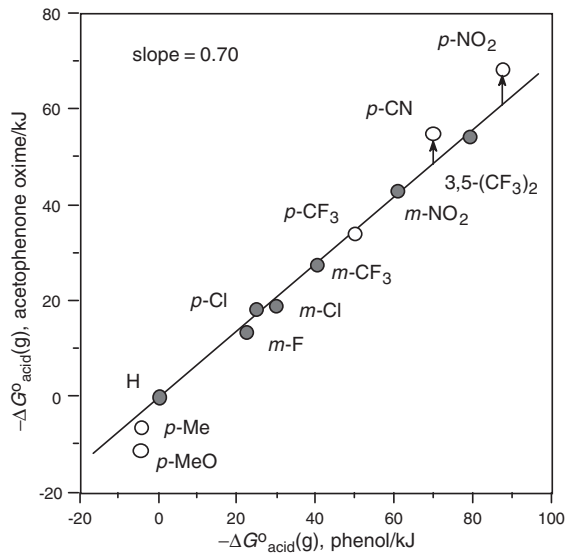


Figure 2. Plot of gas-phase acidities, acetophenone oximes vs. phenols.[19]

of Figure 2 reveals that the *p*-NO_2 and *p*-CN groups tend to deviate slightly upward from the line determined by non-conjugative substituents, suggesting that the degree of π-delocalization of a negative charge is even larger in the oximate than in the phenoxide. Similar deviations of strong π-acceptors were observed for the calculated acidities in Figure S1 (Supporting Information) though the magnitude of the deviations is somewhat smaller than the experimental results. Contrary to strong *para* π-acceptors, the strong *para* π-donor *p*-MeO shows downward deviation from the line (Figure 2). The same trend is also observed for the calculated acidities including *p*-NMe_2 (Figure S1). This result may be explained as follows. In the neutral acetophenone oximes there exists the π-interaction between these π-donor substituents and the electron-withdrawing C(Me)=NOH moiety,[23] while there is no such resonance interaction in the conjugate anions. Indeed, the optimized geometries at B3LYP/6-311+G(d,p) indicate that *p*-NMe_2 and *p*-MeO in the conjugate anion are perpendicular to the π-plane of the benzene ring as shown in Chart 1. Contrary to this, there is no increased resonance interaction of the π-donor substituents in the neutral phenols because the hydroxy group is a π-electron donor. As a result, the acidity-weakening effect of a *para* π-donor is more effective in the acidity of acetophenone oxime compared with that in phenol.

To describe quantitatively the contribution of the resonance effect of *para* π-acceptors involved in the substituent effect of acidity, a correlation analysis using the Yukawa–Tsuno (Y–T) equation (eq 4)[24,25] is useful.

$$\Delta G^{o} = \rho(\sigma^{o} + r^{-}\Delta\bar{\sigma}_{R}^{-}) \quad (4)$$

where σ^{o} and $\Delta\bar{\sigma}_{R}^{-}$ are the normal substituent constant and the resonance substituent constant, respectively, and r^{-} is the resonance demand parameter representing the degree of the π-delocalization of the negative charge into the aryl π-system. Application of the Y–T equation to acidities of acetophenone oximes and phenols gave $\rho = -56.7$, $r^{-} = 0.86$ ($R^2 = 0.986$) and $\rho = -78.8$, $r^{-} = 0.62$ ($R^2 = 0.992$), respectively, when *p*-MeO was excluded.[26] Although the reliability of the present correlation result may be insufficient because of the limited number of substituents involved in the correlation in addition to the lack of suitable substituent parameters in gas phase, the r^{-} value of 0.86 for acidities of acetophenone oximes is meaningfully larger than that for phenol, indicating that the contribution of resonance effect relative to the polar effect is larger in the oximate than in the phenoxide. This is consistent with a graphical analysis shown in Figure 2. A large contribution of resonance effect in the oximate may be related to the larger group natural charge of the benzene ring moiety ($\Sigma q_{ph} = -0.265$) than that of -0.212 in the phenoxide. In conclusion, the substituent effect on the gas-phase acidity of acetophenone oxime is characterized by a large π-delocalization of the negative charge on oxygen into the π-aromatic system in a manner similar to that in the phenoxide. The only significant difference in the substituent effect is a small susceptibility for the oxime acidity compared to the phenol acidity. That is, the intervening –C(Me)=N– moiety reduces the transmission of the substituent effect by a factor of 0.70. A similar attenuation factor of 0.7 was observed for the calculated acidities of (*E*)-2-phenylpropen-1-ol (calculated acidity values are given in Table S1). Figure 3 shows a plot of gas-phase acidities between 2-phenylpropen-1-ol and phenol. The upward deviations of strong π-acceptors, *p*-NO_2 and *p*-CN, from the line determined by the non-conjugative substituents are significantly larger than those in the corresponding plot for acetophenone oximes (Figure S1), indicating the larger π-delocalization effect of strong π-acceptor in the conjugate anion of 2-phenylpropen-1-ol than acetophenone oximate. This is also consistent with the group natural charge (Σq_{ph}) of the phenyl moiety (-0.340) calculated at B3LYP/6-311+G(d,p) larger than that of acetophenone oximate (-0.265). In conclusion, the intervening –C(Me)=N– moiety reduces the transmission of the inductive/field effect but the transmission of the resonance effect is not reduced. As a result of this difference in the transmission of substituent effects, a larger r^{-} value was observed for the acetophenone oximate compared to that for the phenoxide.

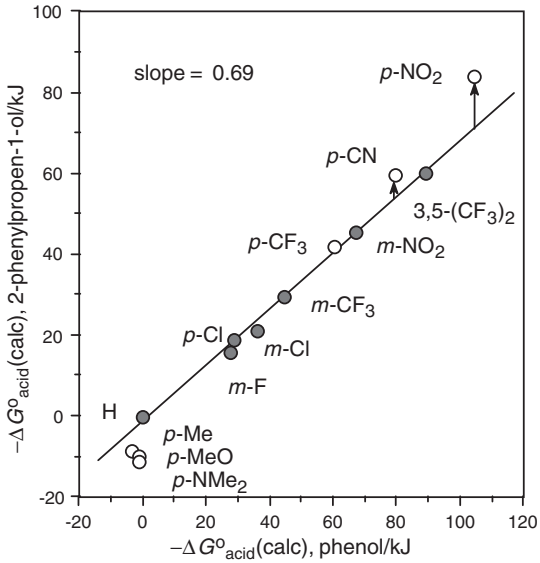


Figure 3. Plot of calculated acidities, 2-phenylpropen-1-ols vs. phenols.

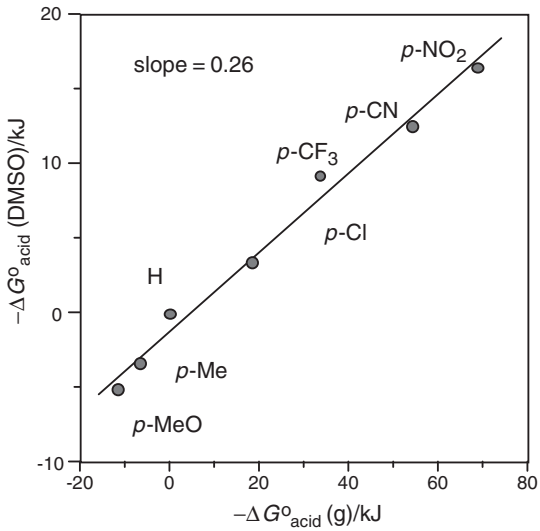


Figure 4. Plot of acidities of acetophenone oximes, DMSO vs. gas phase.

Solvent Effects. In Figure 4 are plotted acidities of acetophenone oximes in DMSO[17] against the corresponding values in gas phase. There exists a linear relationship with a slope of 0.26 ($R^2 = 0.988$) covering a wide range of substituents. This indicates that the solvation stabilization reduces consistently the effects of substituents, leading to a suggestion that the negative charge in the oximate is dispersed into the solvent without any significant specific solvent effect on a particular substituent. This is contrast to the result observed for phenol acidities in DMSO where enhanced substituent effects were observed for strongly conjugative *para* +R substituents such as *p*-NO_2 and *p*-NO groups compared with the effects of non-conjugative substituents in addition to the reduced substituent effect in DMSO by a factor of 0.35 relative to in the gas phase.[19,22,27] Indeed, a plot of acetophenone oxime acidities against phenol acidities in DMSO (Figure 5) shows that the

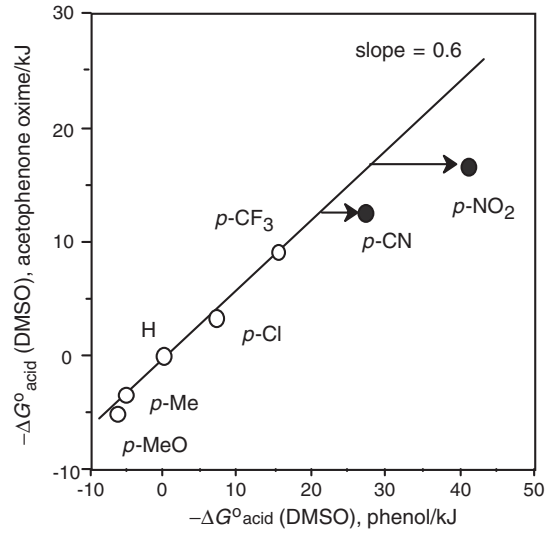


Figure 5. Plot of acidities in DMSO, acetophenone oximes vs. phenols.

acidities of *p*-NO_2 and *p*-CN groups are enhanced in the phenol compared to those expected from the acidities of acetophenone oximes. This is remarkably different from the corresponding plot of the gas-phase acidities in Figure 2, indicating that the deviations for *p*-NO_2 and *p*-cyano in DMSO must result from differences in solvent effect between two systems. In the acidities of phenoxides, the enhanced effects of these strongly conjugative *para* +R substituents in DMSO were considered to be due to attractive interactions of the π-electron-rich substituent with DMSO by which the enhanced effects were termed the substituent solvation-assisted resonance (SSAR) effects by Taft.[19,22] Similar but larger SSAR effects were observed for the acidities of toluenes and anilines where the π-delocalization of the conjugate anions is more significant than phenoxide.[22,27] Taking these results into consideration, the magnitude of the SSAR effects seems to be related to the negative charge on the electron-rich substituent. Indeed, the group natural charge of the *para*-nitro group increases in order of acetophenone oximate (−0.484) < phenoxide (−0.538) < anilide (−0.585) < benzyl anion (−0.639), being consistent with the increase in the SSAR effect.[22] Accordingly, the deviations of *p*-NO_2 and *p*-CN in Figure 5 suggest the smaller SSAR effect in the acetophenone oximate than in the phenoxide.

It is interesting to examine the solvent effects on the acidity of acetophenone oxime on the basis of the theoretical calculations. In general, reaction field models of solvation have been used for describing the properties of molecules in solution. In Figure 6 are plotted the relative acidities in DMSO calculated by using Tomasi's polarized continuum model (PCM)[28] at B3LYP/6-311+G(d,p) against the corresponding values calculated in gas phase. Excluding strong π-acceptor *p*-NO_2 and strong π-donors, *p*-NMe_2 and *p*-MeO, there exists a good linear relationship with a slope of 0.40 and 0.46 for acetophenone oxime and phenol, respectively. The downward deviations of *p*-NMe_2 and *p*-MeO in the acetophenone oxime are easily understood because the optimized structures of these conjugate anions reveal that these substituents are coplanar to

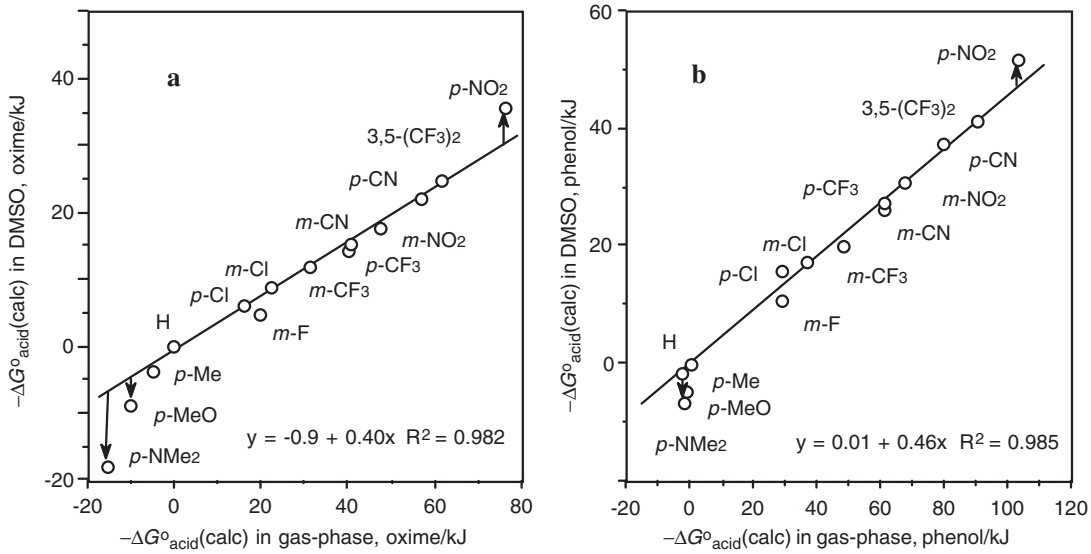


Figure 6. Comparison of calculated acidities between gas phase and DMSO (SCRF-PCM) for acetophenone oximes (**a**) and phenols (**b**).

the benzene ring in DMSO while they are perpendicular in gas phase as mentioned already. A smaller deviation of *p*-NMe_2 observed for the phenol acidity may be attributed to the twisted structure of the *p*-NMe_2 group in the phenoxide in DMSO as well as in gas phase. The upward deviations observed for *p*-NO_2 of the phenol acidity are consistent with the experimental observation. On the other hand, the upward deviations in the acetophenone oxime are inconsistent with the present experimental results as shown in Figure 4. This suggests that though the reaction field model of solvation using the SCRF-PCM model describes the reduced substituent effect in DMSO the specific solvent effects observed for the electron-rich substituents in DMSO are not described properly. Recently, Nakata et al.[29] reported theoretical calculations that the acidity-strengthening effects of *para* π-acceptors of phenols were enhanced compared with the acidities expected from *meta* substituents when these substituents were associated with two water molecules. Theoretical calculations were therefore conducted for the binding energies of neutral acids and the conjugate anions with DMSO molecules at B3LYP/6-311+G(d,p). We considered here two DMSO molecules as a minimum solvation model. Since the oxygen atom of the polar S=O group of DMSO is a good hydrogen-bond acceptor and the acidic hydrogen of the CH_3 group of DMSO will behave as a hydrogen-bond donor, the first DMSO molecule binds with a hydrogen atom of the OH group of a neutral acid or an oxygen atom of the conjugate anion. The second DMSO molecule would bind with an electron-rich substituent such as NO_2 or CN groups. The optimized structures of the complexes associated with two DMSO molecules are shown in Chart 2. The binding energies of DMSO with neutral acids and the corresponding anions are summarized in Table 3.

The first binding energy ($\Delta H^o_{0,1}$) of the OH group with a DMSO molecule in phenols is larger than that in acetophenone oximes, and the $\Delta H^o_{0,1}$ value increases when the substituent is changed to a strong electron-withdrawing group, indicating that the higher acidity of the OH group should have stronger interaction with a DMSO molecule. Contrary to this, the $\Delta H^o_{0,1}$ value of conjugate anions having an electron-withdrawing group is smaller than the unsubstituted one and decreases with increasing electron-withdrawing ability of the substituent. This is also consistent with the order of the decreasing basicity of the oxygen atom of a conjugate anion. The binding energy of the second DMSO molecule ($\Delta H^o_{1,2}$) with an electron-rich substituent of the neutral acid is significantly smaller than the first binding energy ($\Delta H^o_{0,1}$) with the OH group. The $\Delta H^o_{1,2}$ values of the acetophenone oximes are close to the $\Delta H^o_{0,1}$ values of benzonitrile and nitrobenzene.[30] While the $\Delta H^o_{1,2}$ value for a neutral acid increases only by 2–4 kJ mol^{-1} when the substituent is changed from *m*-CN to *p*-NO_2, the $\Delta H^o_{1,2}$ for the conjugate anion significantly increases by 8 and 10 kJ mol^{-1} for acetophenone oximate and phenolate, respectively, indicating that conjugate anions with an electron-rich substituent are stabilized by strong interaction with DMSO. Since the solvent effects on the acidity should be related to the differences in the solvation energy between a neutral and a conjugate anion, it is interesting to consider the difference in the binding energy ($\Delta H^o_{1,2}$) between a neutral and a conjugate anion. The differential binding energies ($\Delta\Delta H^o_{1,2}$) given in Table 3 reveal that the values for *m*-CN and *m*-NO_2 of the acetophenone oxime system are practically identical to the values for the respective *para* derivatives, indicating the similarity in solvent effect between *meta* and *para* substituents. Contrary to this, in the phenol system the $\Delta\Delta H^o_{1,2}$ values for the *para* substituents are clearly larger than the values for the corresponding *meta* substituents. In addition, it was found that the difference between *para* and *meta* substituents is larger for NO_2 than CN, being consistent with the order of the π-electron-withdrawing ability. This suggests that the resonance effects of *para* substituents of phenol are enhanced by binding with DMSO. In conclusion, the present theoretical calculations for the binding energies of the substituent with DMSO molecule are consistent with the concept of the SSAR effects which result from a strong interaction of a solvent molecule and an electron-

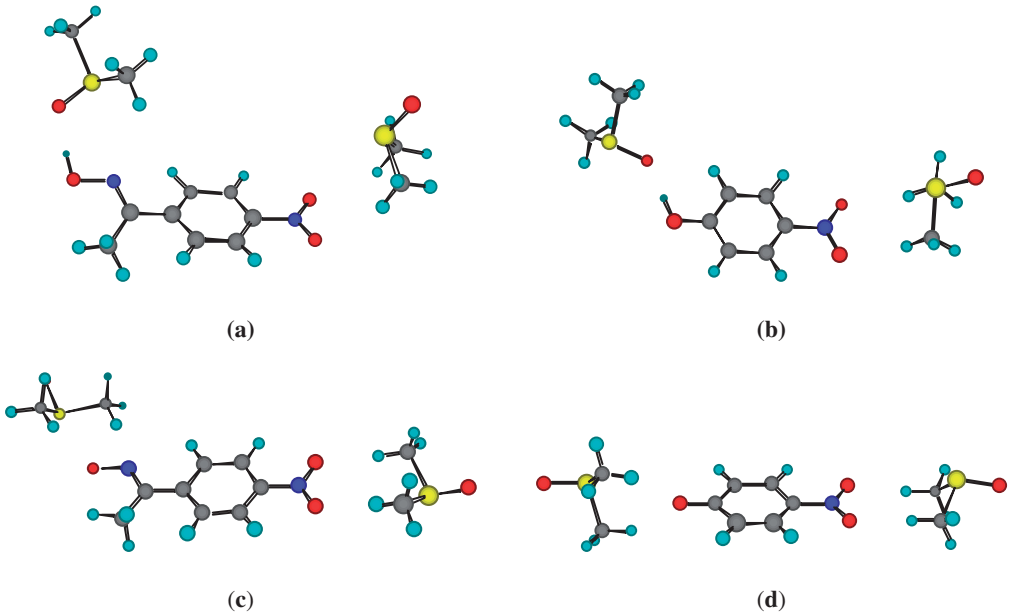


Chart 2. Optimized structures of complexes associated with two DMSO molecules. (**a**) *p*-Nitroacetophenone oxime, (**b**) *p*-nitrophenol, (**c**) *p*-nitroacetophenone oximate, and (**d**) *p*-nitrophenoxide.

Table 3. Stepwise Binding Energies (ΔH^o) with DMSO Calculated at B3LYP/6-311+G(d,p)[a]

X	Acid (XAH)		Conjugate anion (XA^-)		$\Delta\Delta H^o_{1,2}$[f]
	$\Delta H^o_{0,1}$[b]	$\Delta H^o_{1,2}$[c]	$\Delta H^o_{0,1}$[d]	$\Delta H^o_{1,2}$[e]	
Acetophenone oximes					
H	−36.3		−65.0		
m-CN	−40.7	−6.0	−59.0	−23.3	−17.2
m-NO_2	−39.9	−7.2	−52.2	−29.0	−21.8
p-CN	−41.2	−9.1	−52.6	−26.4	−17.2
p-NO_2	−42.4	−9.7	−48.1	−31.3	−21.6
Phenols					
H	−40.3		−68.5		
m-CN	−46.7	−11.4	−59.1	−27.9	−16.5
m-NO_2	−48.2	−11.0	−57.7	−30.3	−19.3
p-CN	−48.2	−12.2	−55.0	−31.6	−19.4
p-NO_2	−51.3	−12.8	−49.2	−37.6	−24.8

a) Units of kJ mol^{-1}. b) XAH + DMSO = XAH:DMSO. c) XAH:DMSO + DMSO = DMSO:XAH:DMSO. d) XA^- + DMSO = XA^-:DMSO. e) XA^-:DMSO + DMSO = DMSO:XA^-:DMSO. f) Difference in the binding energy of the second DMSO between anion and neutral molecule, $\Delta\Delta H^o_{1,2} = \Delta H^o_{1,2}$(conjugate anion) − $\Delta H^o_{1,2}$(neutral).

rich substituent. Negligible SSAR effect observed for the acidity of acetophenone oxime as shown in Figure 4 is also consistent with the present calculations.

From the present results it is concluded that the substituent effect on the acidity of acetophenone oxime is influenced significantly by the resonance effects of *para* π-acceptors in both DMSO and gas phase. Therefore, it is necessary to re-examine Bordwell's observation[17] that the substituent effect on the acidity of acetophenone oxime in DMSO was linearly correlated with σ_p values rather than σ_p^- values for *p*-NO_2 and *p*-CN. Since there is a contribution of the resonance effects of the π-donors to stabilize the neutral acetophenone oxime as mentioned above, the substituent effects on the acidity of acetophenone oxime must be analyzed individually for *para* π-donors and *para* π-acceptors. In fact, excluding *para* π-donors, least-squares calculation provides an excellent linear relationship of the acidities in DMSO with σ_p^-, $\Delta G^o(\text{DMSO}) = -0.1 + 13.2\sigma_p^-$ ($R^2 = 1.00$, $n = 5$), indicating the significant contribution of the resonance effect of π-acceptors. This is consistent with the result that the acidities in DMSO is correlated linearly with the gas-phase acidities of which substituent effect is described by the Y–T equation with an r^- of 0.84 ($r^- = 1.00$ for σ_p^- by definition[25]).

Conclusion

The substituent effect on the gas-phase acidity of acetophenone oxime is characterized by a large π-delocalization of the negative charge on oxygen into the π-aromatic system in a manner similar to that in phenoxide. The intervening –C(Me)=N– moiety reduces the transmission of the substituent effect (inductive/field effect) by a factor of 0.70 compared with the acidities of phenol but the transmission of the resonance effect is not reduced. As a result of this, a larger r^- value was observed for the acetophenone oximate compared to that for the phenoxide. It was found that there is a good linear relationship between acidities in gas phase and in DMSO with a slope of 0.26, indicating that the solvation stabilization reduces consistently the effects of substituents without any significant specific solvent effect on a particular substituent. This is in contrast to the phenol acidities in which the effects of electron-rich *para* +R substituents in DMSO and water were enhanced significantly due to the substituent solvation-assisted resonance (SSAR) effects. These results are consistent with computational studies at the B3LYP/6-311+G(d,p) level of theory.

Experimental

Chemicals. The substituted (*E*)-acetophenone oximes used in this work were prepared according to the literature.[31] Acetophenone oxime was purchased from Tokyo Kasei Co., Tokyo.

General Procedure. A mixture of substituted acetophenone (1 mmol) and fine powder of CaO (0.5 g, 8.9 mmol) was heated to 60–130 °C for a few minutes. Then, hydroxylamine hydrochloride (0.208 g, 3 mmol) was added and the mixture was stirred about 2 to 12 h. Afterward, ethyl acetate (50 mL) was added to the reaction mixture, filtered to remove CaO, then mixed with water and extracted. The ethyl acetate solution was dried over $MgSO_4$. The solvent was removed in vacuo and then recrystallized from hexane to give the oximes. These oximes were characterized by ^{1}H NMR (500 MHz). *p*-$CH_3OC_6H_4C(CH_3)$=NOH, mp 82–83 °C, ^{1}H NMR ($CDCl_3$): δ 2.26 (3H, s, CH_3), 3.83 (3H, s, OCH_3), 6.90 (2H, d, J = 8.8 Hz, Ar), 7.58 (2H, d, J = 8.8 Hz, Ar). *p*-$CH_3C_6H_4C(CH_3)$=NOH, mp 88–89 °C, ^{1}H NMR ($CDCl_3$): δ 2.27 (3H, s, CH_3), 2.37 (3H, s, Ar-C*H*$_3$), 7.18 (2H, d, J = 8.3 Hz, Ar), 7.52 (2H, d, J = 8.0 Hz, Ar). *m*-$FC_6H_4C(CH_3)$=NOH, mp 43–44 °C, ^{1}H NMR ($CDCl_3$): δ 2.28 (3H, s, CH_3), 7.05–7.09 (1H, m, Ar), 7.32–7.41 (3H, m, Ar). *p*-$ClC_6H_4C(CH_3)$=NOH, mp 89–90 °C, ^{1}H NMR ($CDCl_3$): δ 2.26 (3H, s, CH_3), 7.35 (2H, d, J = 8.6 Hz, Ar), 7.57 (2H, d, J = 8.6 Hz, Ar). *m*-$ClC_6H_4C(CH_3)$=NOH, mp 87–88 °C, ^{1}H NMR ($CDCl_3$): δ 2.26 (3H, s, CH_3), 7.30–7.36 (2H, m, Ar), 7.50–7.52 (1H, m, Ar), 7.62–7.63 (1H, m, Ar). *m*-$CF_3C_6H_4C(CH_3)$=NOH, mp 66–68 °C, ^{1}H NMR ($CDCl_3$): δ 2.28 (3H, s, CH_3), 7.47–7.50 (1H, m, Ar), 7.58–7.60 (1H, m, Ar), 7.81–7.83 (1H, m, Ar), 7.94–7.95 (1H, m, Ar). *p*-$CF_3C_6H_4C(CH_3)$=NOH, mp 107–108 °C, ^{1}H NMR ($CDCl_3$): δ 2.30 (3H, s, CH_3), 7.63 (2H, d, J = 10.5 Hz, Ar), 7.75 (2H, d, J = 10.5 Hz, Ar). *m*-$NO_2C_6H_4C(CH_3)$=NOH, mp 135–136 °C, ^{1}H NMR ($CDCl_3$): δ 2.33 (3H, s, CH_3), 7.54–7.58 (1H, m, Ar), 7.99–8.00 (1H, m, Ar), 8.21–8.22 (1H, m, Ar), 8.50–8.51 (1H, m, Ar). 3,5-$(CF_3)_2C_6H_3C(CH_3)$=NOH, mp 88–89 °C, ^{1}H NMR ($CDCl_3$): δ 2.32 (3H, s, CH_3), 7.53 (1H, s, Ar), 7.87 (1H, s, Ar), 8.00 (1H, s, Ar). *p*-$CNC_6H_4C(CH_3)$=NOH, mp 140–142 °C, ^{1}H NMR ($CDCl_3$): δ 2.30 (3H, s, CH_3), 7.66 (2H, d, J = 10.5 Hz, Ar), 7.77 (2H, d, J = 10.5 Hz, Ar). *p*-$NO_2C_6H_4C(CH_3)$=NOH, mp 178–179 °C, ^{1}H NMR ($CDCl_3$): δ 2.32 (3H, s, CH_3), 7.23 (2H, d, J = 9.1 Hz, Ar), 7.81 (2H, d, J = 9.1 Hz, Ar). All reference acids were obtained from commercial sources. They were purified by recrystallization or distillation prior to use. Their purities were checked by ICR mass spectra at positive ion mode.

Gas-Phase Acidity Measurement. The gas-phase acidity measurements were performed on an Extrel FTMS 2001 Fourier transform mass spectrometer. Most of the experimental techniques used for the measurements of the equilibrium constants of the reversible proton-transfer reactions are the same as procedures reported previously.[32] The following schemes describe the sequence of reactions which occur in a typical experiment where AH and A_oH are the measured acid and the reference acid, respectively.

$$CH_3ONO + e^- \rightarrow CH_3O^- + NO \quad (5)$$

$$CH_3O^- + A_oH \rightarrow A_o^- + CH_3OH \quad (6)$$

$$CH_3O^- + AH \rightarrow A^- + CH_3OH \quad (7)$$

$$A_o^- + AH \rightleftharpoons A^- + A_oH \quad (8)$$

An experiment is initiated by a 5 ms pulse of a low-energy electron beam (0.3–0.5 eV) through the ICR cell. The electrons are captured by methyl nitrite at a partial pressure of 1.2×10^{-7} Torr, and CH_3O^- is produced (eq 5). The acids AH and A_oH react rapidly with CH_3O^- to yield M − 1 negative ions (eqs 6 and 7). The partial pressures of the oximes and the reference acids were maintained at lower than 4×10^{-7} Torr. The proton-transfer equilibrium (eq 8) was achieved within 5–40 s of initiation of the reaction (depending on the pressure of neutrals) as shown in Figure 7. The equilibrium constant and free energy change for the reaction were evaluated by using the expression (eq 9).

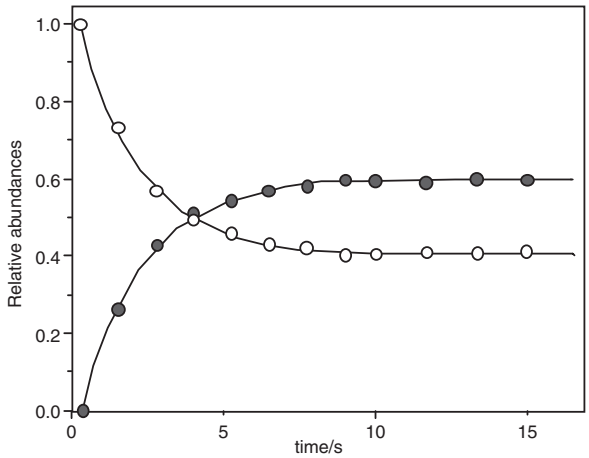


Figure 7. Time profile of anions formed from the binary mixture of *m*-$CF_3C_6H_4C(CH_3)$=NOH (1.61×10^{-7} Torr) and *o*-FC_6H_4OH (2.27×10^{-7} Torr). Closed circles; m/z 111 (*o*-FC_6H_4OH), open circles; m/z 202 (*m*-$CF_3C_6H_4C(CH_3)$=NOH).

$$K = \frac{I(A^-)p(A_oH)}{I(A_o^-)p(AH)}$$

$$\Delta GA = -RT \ln K \quad (9)$$

The relative abundances of ions A^- and A_o^- were determined by the relative intensities of ICR mass spectra signals when equilibrium was attained. The pressures of the neutral reactants were measured by means of a Bayard–Alpert type ionization gauge applying appropriate correction factors to correct the gauge reading for the different ionization cross sections of various compounds.[33] Each experiment was performed at several ratios of partial pressures and at different overall pressures. The proton-transfer reactions were examined by ion-eject experiments. Equilibrium constants measured in this way can be used to calculate ΔG^o_{acid} at 340 K (eq 9). The average uncertainty is ± 0.8 kJ mol^{-1} in most of these cases. Each value was measured with more than two reference acids. The gas-phase acidity values for the reference compounds were taken from the literature.[21] The ionization gauge shielded from strong magnetic field by use of a magnetic shield foil (Fe–Ni alloy) was directly set at the main vacuum chamber to read the precise pressure in the ICR cell, because the ionization gauge that was originally set at the small pipe connected with the main chamber gave a lower reading of the pressure. In addition, the pumping speed was also reduced by use of the gate valve, which was set between the main chamber and a turbo-molecular pump. The blank pressure was kept at less than 10^{-9} Torr.

Calculations. Conformational searches were carried out using Spartan '03 (Wavefunction, Inc.), and several conformers of the lowest energy were further optimized at the RHF/3-21G* level of theory to search the lowest energy conformer (global minimum). Finally, the geometries were fully optimized at the B3LYP/6-311+G** level of theory with normal convergence using the Gaussian 03 program.[34] Vibrational normal mode analyses were

performed at the same level to ensure that each optimized structure was a true minimum on the potential energy surface and to calculate the thermal correction needed to obtain the Gibbs free energies. The zero point energies used for the thermal correction were unscaled. Acidities in DMSO were calculated using Tomasi's polarized continuum model (SCRF-PCM)[28] with United Atom for Hartree–Fock (UAHF) Model to build the cavity.

This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, Japan and by Joint Project of Chemical Synthesis Core Research Institutes.

Supporting Information

The calculated energies (H, G, S) of acetophenone oximes, the corresponding conjugate anions, and the related species and Cartesian coordinates for the optimized structures are available in Supporting Information (Tables S1–S16 and Figure S1). This material is available free of charge on the Web at: http//www.csj.jp/journals/bcsj/.

References

1 R. T. Delfino, T. S. Ribeiro, J. D. Figueroa-Villar, *J. Braz. Chem. Soc.* **2009**, *20*, 407.

2 G. M. Robertson, in *Comprehensive Organic Functional Group Transformation*, ed. by A. R. Kartrizky, O. Meth-Cohn, C. W. Rees, Elsevier, Oxford, **1995**, Vol. 3, p. 425.

3 S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069.

4 E. Abele, E. Lukevics, in *Synthesis of Heteocycles from Oximes*, ed. by Z. Rappoport, J. F. Liebman, Willey, Chichester, **2009**, Chap. 7. p. 223.

5 D. A. Pratt, J. A. Blake, P. Mulder, J. C. Walton, H.-G. Korth, K. U. Ingold, *J. Am. Chem. Soc.* **2004**, *126*, 10667.

6 D. D. M. Wayner, V. D. Parker, *Acc. Chem. Res.* **1993**, *26*, 287.

7 S.-S. Chong, Y. Fu, L. Liu, Q.-X. Guo, *J. Phys. Chem. A* **2007**, *111*, 13112.

8 K. B. Wiberg, *J. Am. Chem. Soc.* **1953**, *75*, 3961.

9 J. O. Edwards, R. G. Pearson, *J. Am. Chem. Soc.* **1962**, *84*, 16.

10 E. Buncel, S. Hoz, *Isr. J. Chem.* **1985**, *26*, 33.

11 K. R. Fountain, K. D. Patel, *J. Org. Chem.* **1997**, *62*, 4795.

12 D. Herschlag, W. P. Jencks, *J. Am. Chem. Soc.* **1990**, *112*, 1951.

13 C. H. Depuy, E. W. Della, J. Filley, J. J. Grabowski, V. M. Bierbaum, *J. Am. Chem. Soc.* **1983**, *105*, 2481.

14 F. Terrier, P. Rodringuez-Dafonte, E. L. Guével, G. Moutiers, *Org. Biomol. Chem.* **2006**, *4*, 4352.

15 E. Buncel, S. Hoz, *Tetrahedron Lett.* **1983**, *24*, 4777.

16 E. Buncel, I.-H. Um, *J. Chem. Soc., Chem. Commun.* **1986**, 595; I.-H. Um, E.-K. Jung, S.-M. Lee, *Can. J. Chem.* **1998**, *76*, 729; I.-H. Um, E. Buncel, *J. Org. Chem.* **2000**, *65*, 577; I.-H. Um, E. Buncel, *J. Am. Chem. Soc.* **2001**, *123*, 11111; E. Buncel, I.-H. Um, *Tetrahedron* **2004**, *60*, 7801; I.-H. Um, Y.-H. Shin, J.-Y. Han, E. Buncel, *Can. J. Chem.* **2006**, *84*, 1550.

17 F. G. Bordwell, Y. Zhao, J.-P. Cheng, *J. Phys. Org. Chem.* **1998**, *11*, 10.

18 F. G. Bordwell, R. J. McCallum, W. N. Olmstead, *J. Org. Chem.* **1984**, *49*, 1424; F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456.

19 M. Fujio, R. T. McIver, Jr., R. W. Taft, *J. Am. Chem. Soc.* **1981**, *103*, 4017.

20 L. A. Angel, K. M. Ervin, *J. Phys. Chem. A* **2004**, *108*, 8346.

21 J. E. Bartmess, in *Negative Ion Energetics Data*, ed. by W. G. Mallard, P. J. Linstrom, NIST Chemistry WebBook, NIST Standard Reference Database Number 69, National Institute of Standards and Technology, Gaithersburg MD, **2005**, 20899, http://webbook.nist.gov.

22 R. W. Taft, R. D. Topsom, *Prog. Phys. Org. Chem.* **1987**, *16*, 1.

23 The $^{13}C_{para}$ chemical shift of acetophenone oxime was found to be 1.00 ppm lower than benzene in $CDCl_3$, indicating that the C(Me)=NOH group is a π-acceptor. The σ_p of 0.10 was reported for CH=NHOH. C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165.

24 Y. Tsuno, M. Fujio, *Adv. Phys. Org. Chem.* **1999**, *32*, 267; Y. Tsuno, M. Fujio, *Chem. Soc. Rev.* **1996**, *25*, 129.

25 Y. Tsuno, M. Fujio, Y. Takai, Y. Yukawa, *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1519; M. Fujio, M. Mishima, Y. Tsuno, Y. Yukawa, Y. Takai, *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2127.

26 The substituent constants used for the present analysis were determined in solution, Ref. 25.

27 M. Mashima, R. T. McIver, Jr., R. W. Taft, F. G. Bordwell, W. N. Olmstead, *J. Am. Chem. Soc.* **1984**, *106*, 2717.

28 a) J. Tomasi, M. Persico, *Chem. Rev.* **1994**, *94*, 2027. b) V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995.

29 K. Nakata, M. Fujio, K. Nishimoto, Y. Tsuno, *SEC Annual Report, Hosei Univ* **2004**, *1*, 2.

30 The binding energies ($\Delta H^o_{0,1}$) of benzonitrile and nitrobenzene with DMSO are -8.4 and $-7.9\,kJ\,mol^{-1}$, respectively.

31 H. Sharghi, M. H. Sarvari, *J. Chem. Res., Synop.* **2000**, 24.

32 M. Matsuoka, Mustanir, S. Than, M. Mishima, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 147.

33 a) J. E. Bartmess, R. M. Georgiadis, *Vacuum* **1983**, *33*, 149. b) K. J. Miller, *J. Am. Chem. Soc.* **1990**, *112*, 8533.

34 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03, Revision E.01*, Gaussian, Inc., Wallingford CT, **2004**.