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Effect of Solvent on the α-Effect: Nucleophilic Substitution Reactions of *p*-Nitrophenyl Acetate with *m*-Chlorophenoxide and Benzohydroxamates in $MeCN-H_2O$ Mixtures of Varying Compositions

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Second-order rate constants have been measured spectrophotometrically for the reactions of *p*-nitrophenyl acetate (PNPA) with three α-effect nucleophiles, benzohydroxamate (BHA^-), *p*-methylbenzohydroxamate ($MBHA^-$), and *p*-methyl-*N*-methylbenzohydroxamate (M_2BHA^-), and a corresponding normal nucleophile, *m*-chlorophenoxide ($ClPhO^-$), in $MeCN-H_2O$ mixtures of varying compositions at 25.0 °C. The reactivity of $ClPhO^-$ and M_2BHA^- toward PNPA decreases upon additions of MeCN into the reaction medium up to near 30−40 mol % MeCN and is followed by a gradual increase upon further additions of MeCN. BHA^- and $MBHA^-$ also exhibit initial rate decreases upon the addition of MeCN up to near 40 mol % MeCN. However, unlike the $ClPhO^-$ and M_2BHA^- systems, the rate enhancement beyond 40 mol % MeCN is negligible for the BHA^- and $MBHA^-$ systems. The present benzohydroxamates exert a large α-effect in H_2O. Interestingly, BHA^- and $MBHA^-$ show a decreasing α-effect trend with increasing mol % MeCN, while M_2BHA^- exhibits an increasing α-effect trend, indicating that the magnitude of the α-effect is significantly solvent dependent. Based on the results of the kinetic study and relative basicity measurements, the decreasing α-effect trend shown by BHA^- and $MBHA^-$ has been attributed to an equilibrium shift of these hydroxamates (I) toward their isomeric structures (II or III) upon the addition of MeCN. The solvent dependent α-effect has led a conclusion that the solvent effect on the α-effect is significant; however, the ground state contribution is not solely responsible for the α-effect in the present system.

Introduction

The basicity of nucleophiles has most commonly been used as a measure of nucleophilicity. However, a certain group of nucleophiles has been found to exhibit abnormally higher nucleophilic reactivity than would be predicted from their respective basicity. A common feature of these nucleophiles is the possession of one or more nonbonding electron pairs at the α-position of the nucleophilic center. Therefore, the abnormally enhanced nucleophilic reactivity was termed the α-effect in 1962 by Edwards and Pearson.[1] Since then, numerous studies have been performed to account for the origin of the α-effect.[2] Some suggested origins of the α-effect are electronic repulsion between the nonbonding electron pairs in the α-position,[3] stabilization of transition state,[4] enhanced stability of the α-product,[5] and solvent effects.[6,7] However, none of these alone is conclusive. Particularly, the theory concerning solvent effect has been a subject of controversy.[6,7] Some studies performed in H_2O and in organic solvents suggested that solvent effect is unimportant for the α-effect,[6] but other studies including gas phase experiments and *ab initio* calculations claimed that solvent effect is significant.[7]

We have initiated a systematic study to obtain more conclusive information on the effect of solvent on the α-effect. We recently reported that the magnitude of the α-effect for the reaction of *p*-nitrophenyl acetate (PNPA) with *p*-chlorophenoxide (p-$ClPhO^-$ as a normal nucleophile, $pK_a = 9.35$) and 2,3-butanedione monoximate (Ox^-, as an α-nucleophile, $pK_a = 9.44$) is very sensitive to the solvent composition in $DMSO-H_2O$ mixtures of varying compositions.[8] The magnitude of the α-effect $k^{Ox^-}/k^{p-ClPhO^-}$ increased with increasing mol % DMSO up to near 50 mol % DMSO and then decreased upon further additions of DMSO into the reaction medium, resulting in a bell-shaped α-effect trend.[8] However, the corresponding reactions run in $MeCN-H_2O$ mixtures showed an increasing α-effect trend with increasing mol % MeCN.[9]

We have now extended our study to a different set of nucleophiles, *m*-chlorophenoxide ($ClPhO^-$), as a normal nucleophile, and benzohydroxamate (BHA^-), *p*-methylbenzohydroxamate ($MBHA^-$), and *p*-methyl-*N*-methylbenzohydroxamate (M_2BHA^-), as corresponding α-nucleophiles as shown in eq 1.

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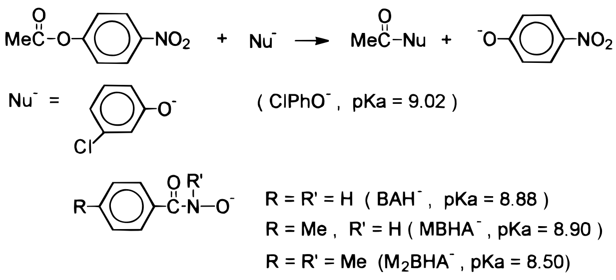

(1)

Results

Pseudo-first-order rate constants were measured spectrophotometrically for the reactions of PNPA with three α-effect nucleophiles (BHA^-, $MBHA^-$, and M_2BHA^-) and the corresponding normal nucleophile ($ClPhO^-$) in $MeCN-H_2O$ mixtures of varying compositions at 25.0 ± 0.1 °C. All the kinetic reactions in the present study obeyed pseudo-first-order kinetics. Pseudo-first-order rate constants (k_{obs}) were obtained from the well-known equation: $\ln(A_\infty - A_t) = -k_{obs}t + C$. Generally five different concentrations of nucleophile solutions were used to obtain second-order rate constants from the slope of the plot of k_{obs} vs concentration of nucleophile. Correlation coefficient of the plot was usually higher than 0.9995 in all solvents studied, indicating that the ion-pairing problem was absent in the present kinetic conditions. It is estimated from replicate runs that the error in any particular measured rate constant is less than ±3%. The second-order rate constants obtained in this way are summarized in Table 1. The kinetic results are also demonstrated graphically in Figures 1−3.

Product analysis for the reaction of PNPA with BHA^- was performed by comparison of the HPLC peak area with that of the authentic compound. The result indicated that the reaction of PNPA with BHA^- yielded only the O-acylated product ($C_6H_5CONHOCOMe$) quantitatively but no N-acylated product ($C_6H_5CON(OH)COMe$) in the kinetic condition for all the solvent compositions studied.

Relative basicities of the present nucleophiles ($\Delta pK_a = pK_a$ of conjugate acids of nucleophiles − pK_a of conjugate acid of a reference base) were determined spectrophotometrically using the relationship: $\Delta pK_a = \log [HA]_{eq}[NO_2PhO^-]_{eq}/([NO_2PhO^-]_0 - [NO_2PhO^-]_{eq})^2$, in which $[HA]_{eq}$ and $[NO_2PhO^-]_{eq}$ represent the equilibrium concentration of the conjugate acid of the nucleophile and the reference base, *m*-nitrophenoxide (NO_2PhO^-), respectively, and $[NO_2PhO^-]_0$ represents the initial concentration of the reference base. The equilibrium concentration of the reference base in a given solvent was determined from the equation: $[NO_2PhO^-]_{eq} = A/\epsilon$, in which A and ϵ represent the absorbance and molar absorptivity of NO_2PhO^- at 430 nm in a given solvent, respectively. The advantages of NO_2PhO^- as a reference base are as follows. (1) The basicity of NO_2PhO^- has been known to be similar to the present nucleophiles in H_2O (pK_a of *m*-nitrophenol = 8.38).[22] (2) The pK_a values of the conjugate acid of $ClPhO^-$ and NO_2PhO^- in pure MeCN are known (25.04 and 23.85, respectively).[22] (3) NO_2PhO^- is stable in the experimental condition and absorbs visible light, while the other species ($ClPhO^-$, BHA^-, $MBHA^-$, and M_2BHA^-) are transparent. (4) NO_2PhO^- obeys Beer's law in basic solution of $MeCN-H_2O$ mixtures. (5) The ϵ value of NO_2PhO^- at 430 nm in all the solvents used is in the range of 1050−1460 cm^{-1} M^{-1}, which permits absorbance measurements possible at near the kinetic condition (*e.g.*, 1.5−2.0 mM of the conjugate acids of the nucleophiles and the reference base). The ΔpK_a values of the present nucleophiles obtained in this way are summarized in Table 2 and demonstrated graphically in Figure 4.

Table 1. Summary of the Second-Order Rate Constants (k, M^{-1} s^{-1}) for the Reactions of PNPA with OH^-, *m*-Chlorophenoxide ($ClPhO^-$), Benzohydroxamate (BHA^-), *p*-Methylbenzohydroxamate ($MBHA^-$), and *p*-Methyl-*N*-methylbenzohydroxamate (M_2BHA^-) in $MeCN-H_2O$ Mixtures of Varying Compositions at 25.0 ± 0.1 °C[a]

mol %	k, M^{-1} s^{-1}				
MeCN	OH^- [b]	$ClPhO^-$	BHA^-	$MBHA^-$	M_2BHA^-
0	11.6	0.362	58.3	63.8	15.3
10	7.29	0.202	30.1	40.0	15.4
20	4.84	0.131	18.7	24.6	13.1
30	4.68	0.109	12.9	19.1	12.0
40	4.66	0.103	12.0	16.5	13.7
50	5.56	0.107	12.1	16.6	18.5
60	8.43	0.124	12.2	16.6	27.4
70	15.7	0.161	12.5	17.4	47.5
80	36.3	0.235	13.9	19.9	133
90		0.483	14.0	20.1	574

[a] The error in rate constants is estimated to be less than ±3%. [b] The rate constants for OH^- were taken from ref 10.

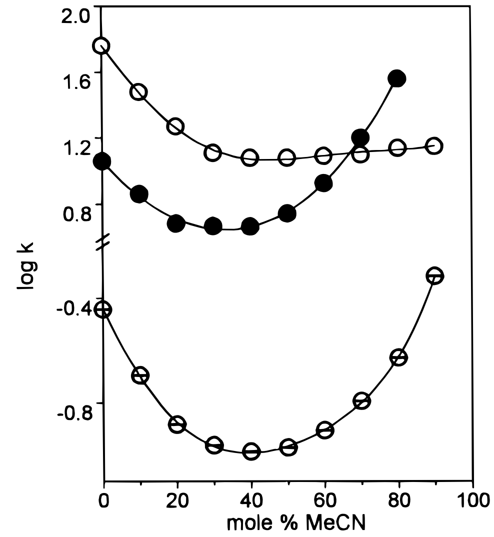

Figure 1. Plots showing dependence of log k on solvent composition for the reactions of PNPA with $ClPhO^-$ (⊖), BHA^- (○), and OH^- (●) in $MeCN-H_2O$ mixtures of varying compositions at 25.0 ± 0.1 °C.

Discussion

Solvent Effect on Reactivity. As shown in Table 1 and Figure 1, the reactivity of $ClPhO^-$ toward PNPA decreases upon the initial addition of MeCN into the reaction medium up to near 30−40 mol % MeCN and is followed by a gradual rate increase upon further additions of MeCN. A similar result has been reported for the reaction of PNPA with OH^-.[10] As shown in Figure 1 for a comparison purpose, the reaction of PNPA with OH^- shows two distinctive reactivity zones, one in the H_2O-rich zone and one in the MeCN-rich zone, resulting in a rate minimum near 30−40 mol % MeCN. Such an observation of rate minima near 33 mol % MeCN is not

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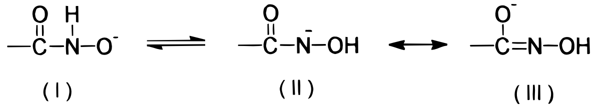
Scheme 1



specific to the present reactions but is considered to be rather a characteristic feature of MeCN−H_2O mixtures. Studies of some physicochemical properties of aqueous MeCN have also showed extrema at 33 mol % MeCN, such as excess entropy of mixing,[11] energy−volume coefficient, isothermal compressibility,[12] and enthalpies of transfer for various anions.[13] The extrema observed at this solvent composition have been attributed to the strong tendency of MeCN to form complexes with two H_2O molecules, since the stoichiometric ratio of 1:2 for MeCN:H_2O is reached at 33.3 mol % MeCN.[13]

As shown in Figure 1, BHA^- also exhibits initial rate decreases upon the additions of MeCN up to near 40 mol % MeCN. However, interestingly, the rate trend beyond 40 mol % MeCN is significantly different from the ones obtained from $ClPhO^-$ and OH^- systems *i.e.*, the BHA^- system shows almost no rate enhancement compared with the others beyond 40 mol % MeCN. It is well known that the negative end of the dipole in MeCN is exposed whereas the positive one is buried in the middle of the molecule. Accordingly, the anionic nucleophiles in the present system would be strongly destabilized upon the additions of MeCN into H_2O, and one might expect significant rate enhancements upon the addition of MeCN into the reaction medium. Therefore, the rate trend obtained for the BHA^- system is quite an unexpected result based on the Hughes and Ingold rules of solvent effect in a qualitative manner.[14]

Hydroxamic acids have been suggested to behave either as NH or OH acids depending on solvents.[15−17] Numerous studies indicate that hydroxamic acids are OH, rather than NH acids in H_2O.[15,16] However, on the basis of IR and UV spectroscopic data and acidity measurements, hydroxamic acids have been suggested to be NH acids in the gas phase[15] or in solvents such as dioxane, aqueous methyl cellosolve,[15] methanol,[16] and DMSO.[17] In accordance, the structure of hydroxamates has been also under active investigation. It has been suggested that hydroxamates form an equilibrium of I with their isomeric forms II or III, and the position of the equilibrium is strongly solvent dependent. Hydroxamates have been recognized to exist mainly as II or its resonance structure III in solvents such as DMSO, dioxane, and aqueous methyl cellosolve methanol but essentially as I in H_2O.[15−17]

II and III would be considered to be less nucleophilic than I toward the carbonyl carbon of PNPA due to the steric factor of II and the non-α-effect nucleophile structure of III. This argument can be supported from the fact that the O-acylated product ($C_6H_5CONHOCOMe$) can be easily prepared quantitatively from the reaction of benzohydroxamic acid with acylating agents such as acetic anhydride or acetyl chloride. Furthermore, the product analysis performed with a HPLC method has revealed that only the O-acylated product is produced in 100% yield from the reaction of PNPA with BHA^- in the present kinetic conditions for all the solvent compositions, supporting that II and III are less reactive than I. Therefore, one can consider that the position of the equilibrium shifts toward less nucleophilic II or III with increasing mol % MeCN and such an equilibrium shift is responsible for the unusual rate trend obtained from the reaction of PNPA with BHA^- in the MeCN-rich region due to reductions in the concentration of the more reactive species I.

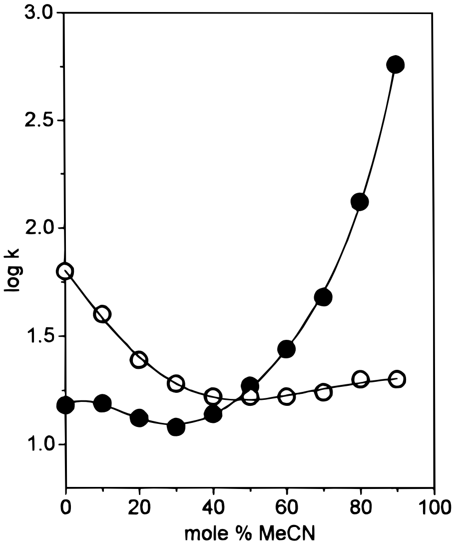


Figure 2. Plots showing dependence of log *k* on solvent composition for the reactions of PNPA with $MBHA^-$ (○) and M_2BHA^- (●) in MeCN−H_2O mixtures of varying compositions at 25.0 ± 0.1 °C.

In order to obtain further evidence for such an equilibrium, we have chosen $MBHA^-$ and M_2BHA^- as a new set of nucleophiles. The former can have its isomeric structures II and III, while the latter cannot form such structures. Therefore, one might expect that $MBHA^-$ would show a similar reactivity trend with BHA^-, but M_2BHA^- would exhibit a quite different one upon the addition of MeCN into the reaction medium if the preceding argument is correct. In fact, as shown in Figure 2, the reactivity of M_2BHA^- is significantly different from that of $MBHA^-$. The logarithmic second-order rate constant for the reaction of PNPA with M_2BHA^- shows a small rate decrease up to near 30 mol % MeCN, except for 10 mol % MeCN, and is followed by significant rate enhancements beyond 40 mol % MeCN. Such a rate behavior is indeed similar to those obtained from OH^- and $ClPhO^-$ systems. On the other hand, the reactivity of $MBHA^-$ decreases significantly upon the addition of MeCN up to near 30−40 mol % MeCN and remains nearly unchanged upon further additions of MeCN. Such a rate trend shown by $MBHA^-$ is almost identical with the one shown by BHA^-. Therefore, our present results strongly support that BHA^- and $MBHA^-$ exist as their isomeric structures upon additions of MeCN, and the equilibrium shift to the less reactive species (II or III) is responsible for the unusual rate trend

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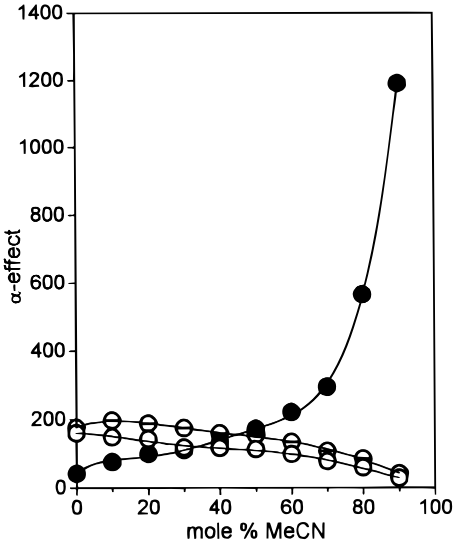

Figure 3. Plots showing dependence of the α-effect for the reactions of PNPA with ClPhO⁻, BHA⁻, MBHA⁻, and M_2BHA^- in MeCN−H_2O mixtures of varying compositions at 25.0 ± 0.1 °C: k^{BHA^-}/k^{ClPhO^-} (○), k^{MBHA^-}/k^{ClPhO^-} (⊖), and $k^{M_2BHA^-}/k^{ClPhO^-}$ (●).

obtained for the BHA⁻ and MBHA⁻ systems in the MeCN-rich region.

Solvent Effect on the α-Effect. As shown in Table 1, BHA⁻ is much more reactive than ClPhO⁻ in all the solvent compositions. Interestingly, BHA⁻ is even more reactive than highly basic OH⁻ up to 60 mol % MeCN. For example, BHA⁻ is about 5 times more reactive than OH⁻, although the former is known to be about 6.8 pK_a units less basic than the latter in H_2O. Therefore, it is evident that BHA⁻ exerts the α-effect in the present system. However, as shown in Figure 3, the magnitude of the α-effect (k^{BHA^-}/k^{ClPhO^-}) decreases as the mol % MeCN increases, *i.e.*, the magnitudes of the α-effect are 161, 113, and 29 in H_2O and 50 and 90 mol % MeCN, respectively. Similarly, the α-effect obtained from the MBHA⁻ system also decreases upon the addition of MeCN into the reaction medium. Extrapolation of the α-effect trend in Figure 3 to pure MeCN would result in absence of the α-effect for both BHA⁻ and MBHA⁻ systems, indicating that solvent effect on the α-effect is significant.

Wolfe *et al.* have calculated that the α-effect nucleophiles such as FO⁻ and HOO⁻ ions cannot exhibit the α-effect in the gas phase,[7a] in which solvent effect is absent. Similarly, DePuy and his co-workers did not observe an α-effect in the gas phase reaction of methyl formate with OH⁻ and HOO⁻ ions.[7b] Therefore, the decreasing α-effect trend upon the addition of MeCN might be consistent with the proposal that the α-effect should be absent or negligible in a solvent other than water, since α-effect nucleophiles are generally believed to be less solvated than the normal nucleophiles in H_2O.[7] In fact, HOO⁻ ion has been reported to be 12 kcal/mol less solvated than OH⁻ ion in H_2O.[18]

However, on the contrary, hydroxamates have been reported to be more strongly solvated than ClPhO⁻ in H_2O.[19a] In our previous study, BHA⁻ and MBHA⁻ were found to exhibit much smaller binding constants than ClPhO⁻ toward aqueous micelles of cetyltrimethylammonium bromide (CTAB).[19a] This result is consistent with the report that the hydroxamic acid moiety (−CONHOH) is about 3-fold more hydrophilic than the alcoholic OH group.[19b] On this basis, one might expect an increasing α-effect trend in the present system, since BHA⁻ would be more destabilized than ClPhO⁻ upon the addition of MeCN into the aqueous medium. Since the present decreasing α-effect trend shown by BHA⁻ and MBHA⁻ is contrary to the expectation, one can suggest that the ground state solvation effect is not an important factor in the present system, but the equilibrium shift to the less nucleophilic species II or III is responsible for the decreasing α-effect trend as mentioned in the preceding section. However, more quantitative analysis of the magnitude of the α-effect is not possible, since the equilibrium constant is not available at present.

Unlike BHA⁻ and MBHA⁻, M_2BHA^- results in an increasing α-effect trend as shown in Figure 3 *i.e.*, the magnitudes of the α-effect ($k^{M_2BHA^-}/k^{ClPhO^-}$) for the M_2BHA^-/ClPhO⁻ system are calculated to be 42, 173, and 1190 in H_2O and 50 and 90 mol % MeCN, respectively. A similar result was obtained in our previous study for the reaction of PNPA with 2,3-butanedione monoximate (Ox⁻) as an α-effect nucleophile and *p*-chlorophenoxide (*p*-ClPhO⁻) as a corresponding normal nucleophile in various MeCN−H_2O mixtures.[9] The α-effect for the Ox⁻/*p*-ClPhO⁻ system has been demonstrated to increase with increasing mol % MeCN, *i.e.*, the magnitudes of the α-effect are 96, 210, and 445 in H_2O and 50 and 90 mol % MeCN, respectively.[9]

One can expect such an increasing α-effect trend for a system in which the ground state solvation is an important factor that influences the magnitude of the α-effect. In fact, Terrier *et al.* found that some basic α-effect nucleophiles exhibit no α-effect in the reaction of PNPA in H_2O.[20] The absence of the α-effect was attributed to strong solvation of basic α-effect nucleophiles in H_2O.[20] A similar result was observed in our recent study for the reaction of *p*-nitrophenyl benzoate with a series of substituted acetophenone oximates ($X-C_6H_4C(Me)=NO^-$).[21] The reactivity of these oximates was found to decrease with increasing base-strengthening ability of the substituent X in H_2O containing 20 mol % DMSO but to increase in DMSO containing 10 mol % H_2O, indicating that solvent effect on reactivity is significant and the oximate having a stronger base-strengthening substituent is more strongly solvated in H_2O.[21] Accordingly, the α-effect was observed to be larger in the solvent containing more DMSO.[21] Therefore, it is proposed that the effect of solvent on the α-effect is significant in the present reaction system. However, ground state contribution is not considered to be solely responsible for the α-effect, since the present benzohydroxamates exhibit large α-effects even in H_2O.

Solvent Effect on Basicity. Solvent transfer from H_2O to MeCN−H_2O mixtures would influence not only the reactivity but also the basicity of the present nucleophiles. Carboxylic acids and phenols have been suggested to be weaker acids in dipolar aprotic solvents than

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Table 2. Summary of the Relative Basicity of the Nucleophiles (ΔpK_a = pK_a of the Conjugate Acid of the Nucleophiles − pK_a of the Conjugate Acid of the Reference Base, NO_2PhO^-) in $MeCN-H_2O$ Mixtures of Varying Compositions at 25.0 ± 0.1 °C[a]

mol % MeCN	ΔpK_a			
	$ClPhO^-$	BHA^-	$MBHA^-$	M_2BHA^-
0	0.60 (0.64)[b]	0.65 (0.50)[c]	0.66 (0.52)[c]	0.30 (0.12)[d]
10	0.61	0.47	0.62	0.49
20	0.66	0.45	0.63	0.59
30	0.68	0.30	0.55	0.67
40	0.69	0.16	0.47	0.75
50	0.70	0.10	0.46	0.81
60	0.71	0.02	0.43	0.85
70	0.75	−0.05	0.41	1.02
80	0.77	−0.12	0.37	1.19
90	0.89	−0.31	0.32	1.40
100	1.20[b]			

[a] The error in ΔpK_a values is estimated to be less than ±0.1 pK_a unit. [b−d] Data from refs 22, 15d, and 19b, respectively.

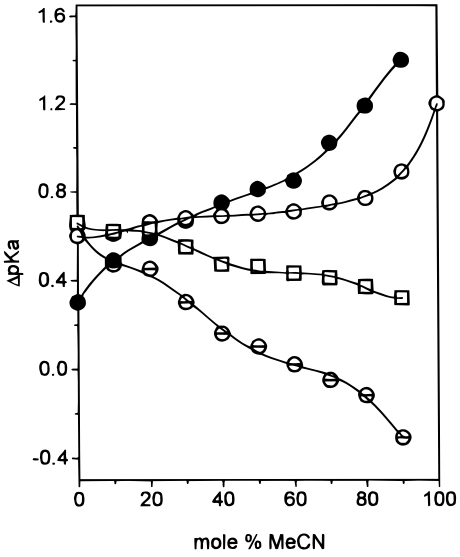

Figure 4. Plots showing solvent effect on the relative basicity (ΔpK_a) of the nucleophiles: (○) $ClPhO^-$, (⊖) BHA^-, (□) $MBHA^-$, and (●) M_2BHA^-.

in H_2O *i.e*, pK_a values of benzoic acid and phenol have been reported to be 20.7 and 27.2 in MeCN and 11.1 and 16.4 in DMSO, respectively.[22] Amines have been also reported to be weaker acids in MeCN, but the decrease in the acidity of amines is less significant than that of the oxygen acids.[23] The pK_a values of the conjugate acids of the present nucleophiles in $MeCN-H_2O$ mixtures are not available. Therefore, as a part of the present study, relative basicities of the nucleophiles ($\Delta pK_a = pK_a$ of the conjugate acid of the nucleophile − pK_a of the conjugate acid of the reference base, *m*-nitrophenoxide, NO_2PhO^-) have been measured in H_2O and $MeCN-H_2O$ mixtures. The results are summarized in Table 2 and demonstrated graphically in Figure 4.

One can notice that the ΔpK_a of $ClPhO^-$ increases as the mol % MeCN increases. Since $ClPhO^-$and NO_2PhO^- are in the same family, no drastic change in ΔpK_a is expected upon the additions of MeCN into the medium. In fact, $ClPhO^-$ has been reported to be about 0.6 and 1.2 pK_a units more basic than the reference base (NO_2PhO^-) in H_2O and pure MeCN, respectively.[22] Therefore, the increasing ΔpK_a value for $ClPhO^-$ is considered to be reliable. Besides, as shown in Table 2, the ΔpK_a values of BHA^- and $MBHA^-$ in H_2O are also nearly identical to the reported values, indicating that all the ΔpK_a values obtained in the present system are reliable. The ΔpK_a value of M_2BHA^- in H_2O appears to be about 0.2 pK_a unit higher than the reported value; however, this difference is considered to be negligible for purposes of the present discussion.

Interestingly, as shown in Table 2 and Figure 4, M_2BHA^- shows an increasing ΔpK_a trend, while BHA^- exhibits a decreasing ΔpK_a trend as the mol % MeCN increases. $MBHA^-$ also results in a decreasing ΔpK_a trend, but the degree is not as significant as with BHA^-. Consequently, M_2BHA^- appears to be about 1.1 pK_a units more basic in 90 mol % MeCN than in H_2O, while BHA^- and $MBHA^-$ become about 1.0 and 0.3 pK_a unit less basic in 90 mol % MeCN than in H_2O, respectively.

In dipolar solvents, hydroxamic acids which can act as NH acids have been reported to be about 3−4 pK_a units stronger acids than *N*-methylhydroxamic acids which can act only OH as acids.[17] Therefore, the decreasing ΔpK_a trends for BHA^- and $MBHA^-$ strongly suggest that the conjugate acids of these hydroxamates behave as NH acid in $MeCN-H_2O$ mixtures. This is consistent with the proposal made from the kinetic study mentioned in the preceding section. Therefore, one can suggest that the equilibrium shift from I to II or III is responsible for the unusual rate trends for the BHA^- and $MBHA^-$ systems in $MeCN-H_2O$ mixtures, and the decreasing α-effect trends for these hydroxamate systems are not simply due to the decrease in basicity of the hydroxamates upon the addition of MeCN into the reaction medium.

It has been generally known that weaker acids show larger ΔpK_a upon solvent transfer from H_2O to dipolar aprotic solvents. However, interestingly, the ΔpK_a of M_2BHA^- increases more significantly than that of $ClPhO^-$ upon the solvent transfer from H_2O to $MeCN-H_2O$ mixtures. Consequently, M_2BHA^- becomes more basic than $ClPhO^-$ beyond 40 mol % MeCN. Such ΔpK_a trends appear to explain the rate trends shown by these two nucleophiles *i.e*, as shown in Figures 1 and 2, M_2BHA^- shows less rate retardation up to 40 mol % MeCN and more rate enhancement beyond 40 mol % MeCN than $ClPhO^-$. Therefore, one might attribute the increasing α-effect trend shown by the $M_2BHA^-/ClPhO^-$ system to the difference in ΔpK_a trends of these nucleophiles. However, the reactivity of the present hydroxamates cannot be explained by ΔpK_a alone because BHA^- is less basic than $ClPhO^-$ but the former is more reactive than the latter in the whole solvent region. Besides, the reactivity of $ClPhO^-$ and M_2BHA^- decreases up to 30−40 mol % MeCN, although the basicity of these nucleophiles increases in this solvent region.

In order to see the effect of ΔpK_a on reactivity, novel Brønsted-type plots[24] have been constructed in Figure 5 for the reaction of PNPA with $ClPhO^-$ and M_2BHA^-. The data points that represent reactions in the H_2O-rich region (≤30 mol % MeCN) are excluded due to the abnormal reactivity mentioned above. As shown in Figure 5, the reactivity of these nucleophiles increases linearly with increasing ΔpK_a values. The slopes of the plots are calculated to be 3.55 and 2.40 for the $ClPhO^-$ and M_2BHA^- systems, respectively, indicating that the

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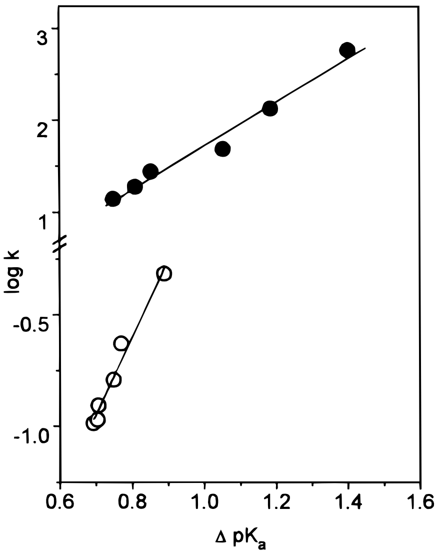

Figure 5. Novel Brønsted-type plots for the reactions of PNPA and $ClPhO^-$ (○) and M_2BHA^- (●) in $MeCN-H_2O$ mixtures at 25.0 ± 0.1 °C.

reactivity of $ClPhO^-$ is more sensitive than that of M_2BHA^- to ΔpK_a. Consequently, the gap between the two novel Brønsted-type plots at a given ΔpK_a value decreases with increasing ΔpK_a values, indicating that the α-effect actually decreases as the basicity of the α-effect nucleophile increases. This is somewhat consistent with the results obtained by Terrier[20] and Um[21] as mentioned in the preceding section. Therefore, it is proposed that basicity is also an important factor for the α-effect, but basicity alone cannot explain the unusually high reactivity shown by the present hydroxamates.

Conclusions

The results of the kinetic study for the reaction of PNPA with $ClPhO^-$, BHA^-, $MBHA^-$, and M_2BHA^- and relative basicity measurements of these nucleophiles in various $MeCN-H_2O$ mixtures have allowed us to draw the following conclusions. (1) Hydroxamic acids behave as NH acids in MeCN. Accordingly, hydroxamates (I) can equilibrate with their isomeric structures (II or III) in $MeCN-H_2O$ mixtures, and the equilibrium shifts toward II or III with increasing mol % MeCN. (2) The magnitude of the α-effect is significantly dependent on the solvent composition, indicating that solvent effect on the α-effect is an important factor. (3) The basicity of the hydroxamates appears to influence the magnitude of the α-effect. (4) The ground state solvation effect is not considered to be solely responsible for the α-effect observed in the present system. However, a dissection of the solvent effect into the ground state and transition state contributions is not clear at this moment.

Experimental Section

Materials. Benzohydroxamic acid (mp 124−125 °C; lit.[25a] mp 124−125 °C), *p*-methylbenzohydroxamic acid (mp 142−143 °C; lit.[25b] mp 141−143 °C), and *p*-methyl-*N*-methylbenzohydroxamic acid (mp 118−120 °C; lit.[19b] mp 117−120 °C) were prepared as reported in the literature. Acetyl benzohydroxamate ($C_6H_5CONHOCOCH_3$) (mp 125−126 °C; lit.[26] mp 126.5 °C) was easily prepared from the reaction of acetyl chloride with benzohydroxamic acid in dioxane. Other chemicals used were of the highest quality available (Aldrich) and generally recrystallized or distilled before use. MeCN was distilled over P_2O_5 under a nitrogen atmosphere. Doubly-glass-distilled water was further boiled and cooled under a nitrogen atmosphere just before use.

Product Analysis. One of the reaction products (acetyl benzohydroxamate) was analyzed by HPLC using a Shimadzu LC-10A liquid chromatograph equipped with an SPD-10A spectrophotometric detector, an 7125 Rheodyne injector, C-R6A Chromatopac integrator, and a column of Shiseido Supheriorex ODS (5 μm) (4.6 mm i.d. × 250 mm length). The flow rate was 1 mL/min at 40.0 °C, and the eluent was a mixture of 40% MeCN and 60% 0.05 M NaH_2PO_4 buffer solution (pH = 4.5). Quantitative analysis was performed by comparison of the HPLC peak area of the reaction mixture with that of the authentic sample ($C_6H_5CONHOCOMe$) at 230 nm.

Kinetics. Kinetic studies were performed with a Hitachi U-2000 UV−vis spectrophotometer for slow reactions ($t_{1/2} \geq 10$ s) or with an Applied Photophysics SX-17MV stopped-flow spectrofluorimeter for fast reactions ($t_{1/2} < 10$ s) equipped with a Neslab RTE-110 constant temperature circulating bath to keep the temperature in the reaction cell at 25.0 ± 0.1 °C. The reactions were followed by monitoring the appearance of the leaving *p*-nitrophenoxide at 400 nm. All the reactions were carried out under pseudo-first-order conditions in which the concentrations of nucleophiles were generally 20 times, but at least 10 times, greater than that of the substrate. Nucleophilic stock solutions of *ca.* 0.2 M were prepared in a 25.0 mL volumetric flask under a nitrogen atmosphere by adding 2 equiv of *m*-chlorophenol (or the appropriate benzohydroxamic acid) to 1 equiv of standardized NaOH solution (solvent composition with ≤40 mol % MeCN) or 1 equiv of $NMe_4OH \cdot 5H_2O$ (solvent composition with ≥50 mol % MeCN) in order to obtain a self-buffered solution. All the solutions were transferred by Hamilton gas-tight syringes. Other details of kinetic methods were reported previously.[9]

Relative Basicity Measurements. Relative basicities of $ClPhO^-$, BHA^-, $MBHA^-$, and M_2BHA^- were determined spectrophotometrically. *m*-Nitrophenoxide (NO_2PhO^-) was chosen as a reference base. Determinations of relative basicity were done by measuring the absorbance of NO_2PhO^- which is at equilibrium with the conjugate acid of the nucleophiles using the same UV−vis spectrophotometer used for the kinetic study. Standard 1.0 cm quartz cells (Helma) closed on top with a rubber septum were used. Hamilton gas-tight syringes were used to transfer solutions. All the solutions were prepared in 25.0 mL volumetric flasks closed on top with a rubber septum just before use under a nitrogen atmosphere. Other details of relative basicity measurements are similar to the one in the literature.[27]

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