

0.77 mmol) in dichloromethane (3 ml) were added bicyclo(4.1.0)-2-heptanone⁵ (80.3 mg, 0.73 mmol) and TBSOTf (192.9 mg, 0.73 mmol) under nitrogen. After being stirred at room temperature for 4 h, dichloromethane was removed under a reduced pressure and tetrahydrofuran (3 ml) was added. The reaction mixture was cooled to -78°C and *n*-butyllithium (0.62 ml, 0.77 mmol) was added dropwise to give a black-colored solution. The reaction mixture was stirred for 1 h at -78°C and benzaldehyde (93.4 mg, 0.88 mmol) was added to the ylide solution. After being stirred at -78°C for 1 h and warmed to room temperature over 30 min, saturated NaHCO_3 solution was added. The extractive work-up and chromatographic separation gave silyl enol ether⁶ (130.4 mg, 57%). Aliphatic (1° and 2°) as well as aromatic aldehydes can be used successfully in the Wittig condensation step. The reaction of ylide 3 with 6-bromohexanal⁷ and cyclohexanecarboxaldehyde gave the corresponding compounds in 54% and 51% yield, respectively. In case of bicyclo(3.1.0)-2-hexanone,⁸ 3-(2'-phenylethenyl)-1-cyclopentanone was produced in 23% yield after treatment of hydrogen fluoride.

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Solvent Effect on the α -Effect in Nucleophilic Substitution Reaction of 4-Nitrophenyl Acetate in MeCN-H₂O Mixtures

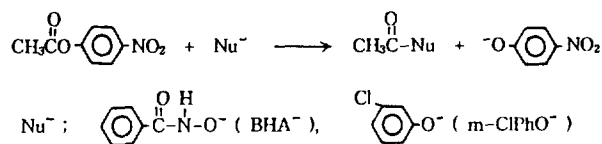
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Abnormally enhanced nucleophilicity has often been observed in reactions of nucleophiles containing an atom with one or more nonbonding electron pairs adjacent to the reaction center (the α -position). Thus, the term α -effect was given to the enhanced nucleophilicity shown by this type of nucleophiles.¹ Since then, numerous studies have been performed to investigate the cause of the α -effect.²⁻⁵ However, the origin of the α -effect has not been clearly understood. Particularly, the theory concerning solvent effect has been the subject controversy.⁶⁻⁸

In a recent study, we have demonstrated that the solvent effect on the α -effect is important for the nucleophilic substitution reaction of *p*-nitrophenyl acetate (PNPA) with butane-2,3-dione monoximate (Ox^-) and *p*-chlorophenoxide (*p*-Cl- PhO^-) in MeCN-H₂O mixtures of varying compositions.⁹ We have now chosen a different set of nucleophiles: benzohydroxamate (BHA^- , *pK*_a=8.88) and *m*-chlorophenoxide (*m*-Cl- PhO^- , *pK*_a=9.02) as an α -nucleophile and the corresponding normal one, respectively. Such a change in the nucleophile would allow us to examine whether the previous result was only a limited phenomenon in the Ox^- system.



The rate constants were measured spectrophotometrically by monitoring the appearance of *p*-nitrophenoxide ion at 400 nm. All the reactions obeyed pseudo-first-order kinetics up to over 90% of the total reaction. In Figure 1 are plotted the kinetic results, in which the logarithmic second-order rate constant for the *m*-ClPhO⁻ system decreases upon the initial addition of the MeCN into H₂O and is followed by a gradual increase of the rate constant upon further addition of MeCN, resulting in a rate minimum near 40 mole% MeCN. Such a rate minimum was also observed previously in the reac-

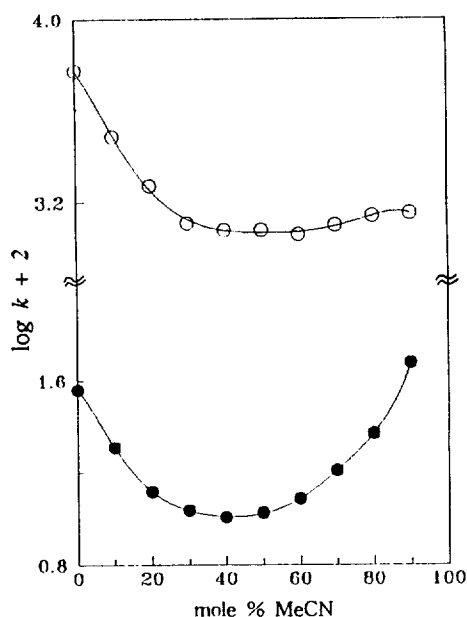


Figure 1. Plots showing dependence of $\log k_2$ on the solvent composition for the reaction of PNPA with $m\text{-ClPhO}^-$ (●) and BHA^- (○).

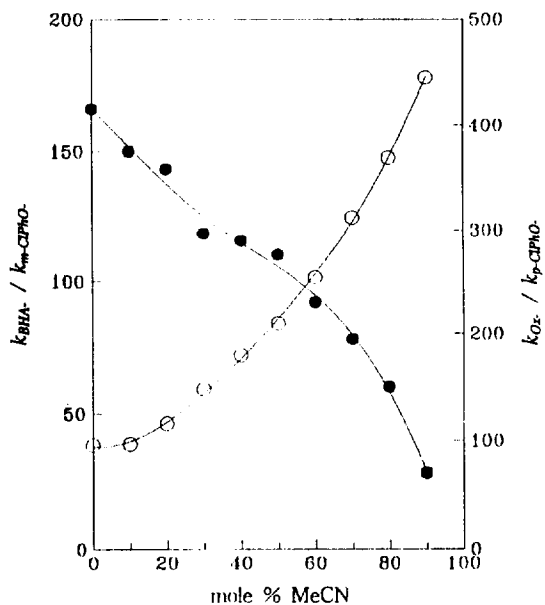


Figure 2. Plots showing dependence of the α -effect on the solvent composition for the reaction of PNPA with $\text{BHA}^-/m\text{-ClPhO}^-$ (●) and the $\text{Ox}^-/p\text{-ClPhO}^-$ (○) at 25.0°C . The data for $\text{Ox}^-/p\text{-ClPhO}^-$ were taken from reference 9.

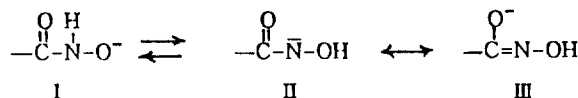
tions of PNPA with Ox^- , $p\text{-ClPhO}^-$ and HO^- ions and was attributed to the change of the solvent structure upon the addition of MeCN into H_2O .¹⁰ The BHA^- system also exhibits such an initial rate decrease. However, the rate trend beyond 40 mole% MeCN is significantly different from the one in the other system, *i.e.*, the rate enhancement beyond 40 mole% MeCN is nearly negligible. Such a solvent effect on the rate is quite an unexpected result based on the Hughes and Ingold rules of solvent effect in a qualitative man-

ner.¹¹

The present solvent effect on the rate has produced an interesting result, as shown in Figure 2. The magnitude of the α -effect in the present system ($k_{\text{BHA}^-}/k_{m\text{-ClPhO}^-}$) decreases as the MeCN concentration increases. Moreover, extrapolation of the α -effect trend would yield the absence of the α -effect in pure MeCN. This result is opposite from the previous one for the Ox^- and $p\text{-ClPhO}^-$ system (See Figure 2).

Recently Wolfe and his coworkers have calculated that the α -effect nucleophiles such as HOO^- and FO^- ions cannot exhibit the α -effect in the gas phase, in which solvent effect is absent.^{6a} Similarly, DePuy *et al.* have also observed no α -effect in the gas phase reaction of methyl formate with HOO^- and HO^- .^{6b} Therefore, the absence of the α -effect in pure MeCN might be consistent with the proposal that the α -effect should be absent or negligible in a solvent other than water, since α -nucleophiles are generally believed to be less solvated than the normal ones in H_2O . However, on the contrary, BHA^- has been considered to be more strongly solvated than $m\text{-ClPhO}^-$ in H_2O based on the study of the binding constant toward aqueous micelles of cetyltrimethylammonium bromide,¹² and the lipophilicity constant.¹³ On this basis, one would have expected to see an increasing α -effect trend, since BHA^- would experience more desolvation than $m\text{-ClPhO}^-$ upon the addition of MeCN into H_2O . The decreasing α -effect trend is, therefore, contrary to what would have been expected if the ground-state solvation were an important factor. Therefore, it appears that the differential solvation between the two nucleophiles is not solely responsible for the α -effect. It is further evident from the fact that the α -effect in pure water is significantly large, although BHA^- is more strongly solvated than $m\text{-ClPhO}^-$ in H_2O .

It has often been suggested that hydroxamates form an equilibrium of I with their isomeric forms II or III, and the position of the equilibrium is strongly medium dependent.^{14,15} Recently, the gas phase acidity measurement has led to a conclusion that hydroxamic acids behave as NH acids in the gas phase.^{14a} Similarly, hydroxamates have been recognized to exist mostly as II or its resonance structure III in dipolar



aprotic solvents such as DMSO, DMF and MeCN, but essentially as I in hydroxylic solvents.¹⁵ Therefore, as the concentration of MeCN increases in the reaction medium, the above equilibrium would shift toward II or III, which are considered to be less nucleophilic than I due to the steric factor of II and the non- α -nucleophile structure of III. Instead, such an equilibrium causes a significant reduction in the concentration of the reactive species (I), which results in a significant rate retardation. Therefore, the unusual rate trend obtained for the reaction of BHA^- would be attributed to the equilibrium of I with II (or III) upon the medium change, which, in consequence, would be considered to be responsible for the decreasing α -effect trend.

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Synthetic Application of Octalone Systems (I): Synthesis of β -Cyperone

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The eudasmain sesquiterpenoid is a group family of nat-

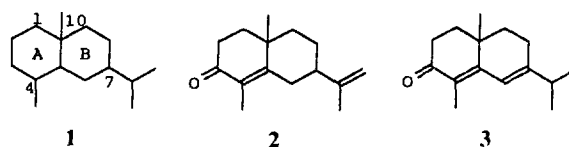
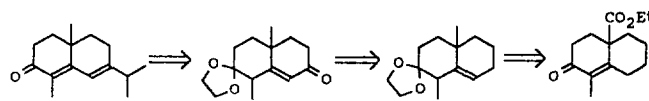
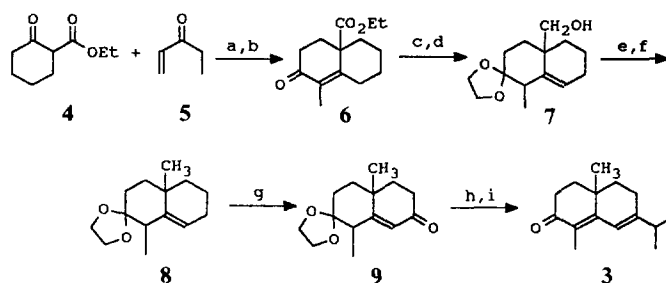


Figure 1.



Scheme 1.



Reagents and Conditions: (a) 0.03 eq EtONa/EtOH, (b) 1.30 eq EtONa/EtOH, $0^{\circ}\text{C} \rightarrow \text{RT}$, (c) Ethylene glycol, TCA, Benzene, Reflux, (d) LAH, Ether, (e) *p*-TsCl, Pyridine, 0°C , (f) LAH, THF, (g) CrO_3 , DMP, CH_2Cl_2 , $-23^{\circ}\text{C} \rightarrow 0^{\circ}\text{C}$, (h) $(\text{CH}_3)_2\text{CHMgCl}$, THF, (i) *p*-TsOH, Benzene.

Scheme 2.

ural products that shares a carbobicyclic hydronaphtalene skeletons.¹ α -Cyperone² **2**, and β -cyperone² **3**, isolated from the tubers of *Cyperous rotundus*,² were members of this group and shown in Figure 1. Since β -cyperone **3** contained a dienone and an angular methyl group in an octalone skeleton, it is expected to serve as a useful starting material for synthesis of natural products. In addition, it is feasible to have a biological activity owing to its structure. In spite of a simple and well-known structure, total synthesis³ and biological activity of it has not been reported well in the literature.

Our continuing efforts to develop efficient synthetic routes for complex natural products utilizing an octalone⁴ system, a general and flexible synthetic route for β -cyperone was investigated. Our retrosynthetic analysis is outlined in Scheme 1. Necessary functional groups are introduced in sequence to provide structure variations. Basic carbon skeleton was constructed by Robinson annulation⁵ which was exclusively employed in our laboratory.

The strategy for the target compound was realized in Scheme 2. Robinson annulation of ethyl 2-cyclohexanonecarboxylate **4** and ethyl vinyl ketone **5** was conducted in two step sequences under the delicate condition. At first, Michael addition of keto ester **4** to enone **5** was facilitated by addition of a catalytic amount of sodium ethoxide at 0°C . Treatment of the resulting reaction mixture with stoichiometric amount of sodium ethoxide gave rise to an octalone **6** in 72% yield. Ketalization of compound **6** would enable us to protect a carbonyl group and to functionalize B ring by migration of a double bond. Under the standard condition⁶