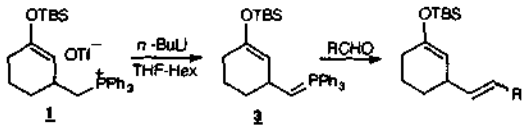

(3)

0.77 mmol) in dichloromethane (3 m*l*) were added bicyclo[4.1.0]-2-heptanone[5] (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, dichlormethane was removed under a reduced pressure and tetrahydrofuran (3 m*l*) was added. The reaction mixture was cooled to −78℃ and *n*-butyllithium (0.62 m*l*, 0.77 mmol) was added dropwise to give a black-colored solution. The reaction mixture was stirred for 1 h at −78℃ and benzaldehyde (93.4 mg, 0.88 mmol) was added to the ylide solution. After being stirred at −78℃ 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 sily enol ether[6] (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-bromohexanal[7] 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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6. R_f 0.70 (EtOAc/Hexane=1/20). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.35-7.19 (m, 5H), 6.39 (d, J=11.48 Hz, 0.37H), 6.36 (d, J=11.50 Hz, 0.63H), 5.56 (dd, J=11.55, 10.23 Hz, 0.37H), 5.49 (dd, J=11.32, 10.48 Hz, 0.63H), 4.88 (br s, 0.37H), 4.77 (br s, 0.63H), 3.41-3.39 (m, 0.63H), 2.88-2.98(m, 0.37H), 2.09-1.24 (m, 6H), 0.91 (s, 9H), 0.13 (s, 3.8H), 0.12 (s, 2.2H).
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Solvent Effect on the α-Effect in Nucleophilic Substitution Reaction of 4-Nitrophenyl Acetate in MeCN-H_2O Mixtures

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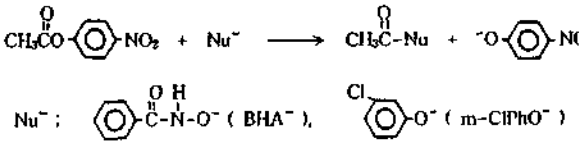
Abnormally enhanced nucleophilicity has often been observed in reactions of nucleophiles containing an atom with one or more nonbonding electron pairs adjacent to the reaction center (the α-position). Thus, the term α-effect was given to the enhanced nucleophilicity shown by this type of nucleophiles.[1] 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-H_2O 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 H_2O 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-

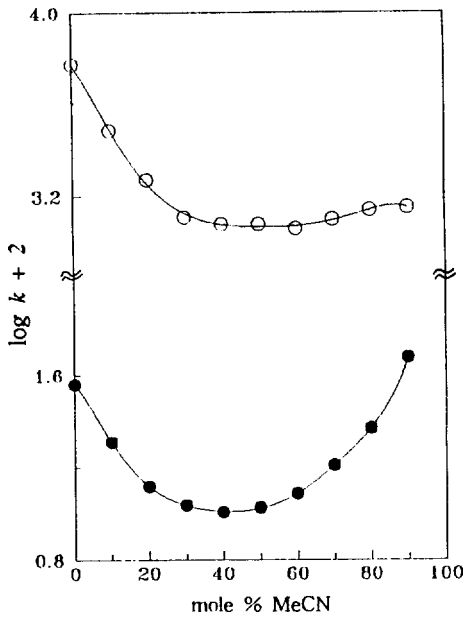


Figure 1. Plots showing dependence of log k_2 on the solvent composition for the reaction of PNPA with *m*-ClPhO$^-$ (●) and BHA$^-$ (○).

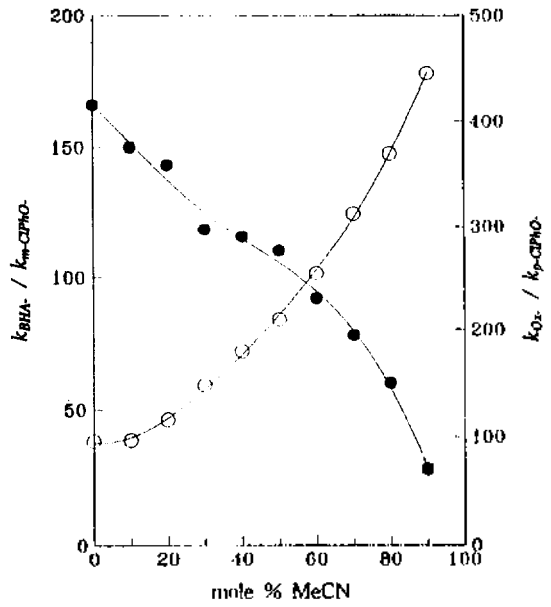


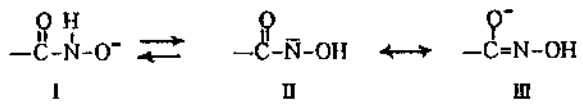
Figure 2. Plots showing dependence of the α-effect on the solvent composition for the reaction of PNPA with BHA$^-$/*m*-ClPhO$^-$ (●) and the Ox$^-$/*p*-ClPhO$^-$ (○) at 25.0℃. The data for Ox$^-$/*p*-ClPhO$^-$ were taken from reference 9.

tions of PNPA with Ox$^-$, *p*-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 manner.[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 ($k_{BHA^-}/k_{m\text{-}ClPhO^-}$) 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*-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*-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*-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*-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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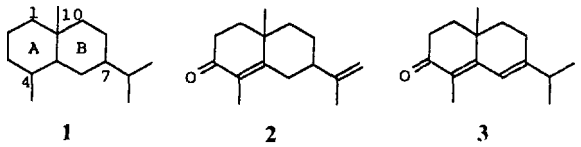
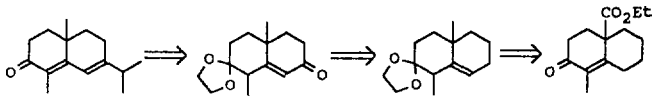
The eudasmain sesquiterpenoid is a group family of natural products that shares a carbobicyclic hydronaphtalene skeletons.[1] α-Cyperone[2] **2**, and β-cyperone[2] **3**, isolated from the tubers of *Cyperous rotundus*,[2] were members of this group and shown in Figure 1. Since β-cyperone **3** contained a dienone and an angular methyl group in an octalone skeleton, it is expected to serve as a useful starting meterial 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 synthesis[3] and biological activity of it has not been reported well in the literature.

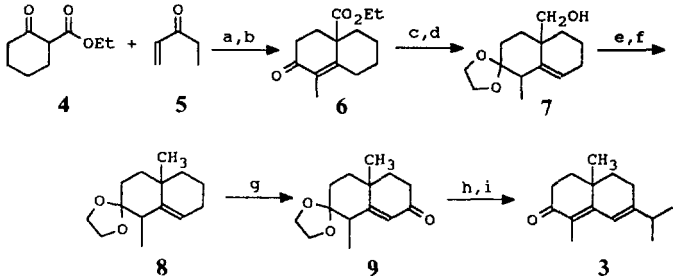


1 **2** **3**

Figure 1.



Scheme 1.



Reagents and Conditions: (a) 0.03 eq EtONa/EtOH, (b) 1.30 eq EtONa/EtOH, 0℃ →RT, (c) Ethylene glycol, TCA, Benzene, Reflux, (d) LAH, Ether, (e) *p*-TsCl, Pyridine, 0℃, (f) LAH, THF, (g) CrO_3, DMP, CH_2Cl_2, −23℃ →0℃, (h) $(CH_3)_2CHMgCl$, THF, (i) *p*-TsOH, Benzene.

Scheme 2.

Our continuing efforts to develop efficient synthetic routes for complex natural products utilizing an octalone[4] 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 annulation[5] 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 delicated 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℃. 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 condition[6]