13 ($[\alpha]_D^{25}$ = +139°, c = 1.30) and **14** ($[\alpha]_D^{25}$ = +42°, c = 1.16) in 70% yield. The major epimer **13** was reacted with benzoyl peroxide to yield a 1:1 mixture of **15** and **16**, which was converted to the olefin **17** ($[\alpha]_D^{27}$ = +196°, c = 0.59) upon treatment with DBU in THF (r.t., 0.5 h). The 5R stereochemistry was self-evident when optical rotation value of **17** was compared with that of **10**.

Having achieved the synthesis of the basic skeleton, attention was next turned to the synthesis of **1** with biologically viable phenoxyacetamide side chain. Deprotection of N-benzyloxycarbonyl group in **13** (31% HBr in HOAc, r.t., 1 h) and reprotection of the reaction product with phenoxyacetyl chloride (CH_2Cl_2-Et_3N, r.t., 27 h) resulted in the formation of V-protected bicyclic δ-lactam **18** in 56% yield. It was hydrolyzed in 91% yield (LiOH, THF-H_2O; 3:1, r.t., 0.5 h) and the corresponding PNB ester **19** ($[\alpha]_D^{28}$ = +124°, c = 2.28) was synthesized (PNBBr, $NaHCO_3$, DMF, r.t., 15 h) in 60% yield. Benzoyloxylation and elimination reactions were performed in the usual ways to produce the olefin **20** ($[\alpha]_D^{26}$ = +135°, c = 1.03) in 35% yield. The PNB group in **20** was readily cleaved off by hydrogenolysis (10% Pd/C, 38 psi, THF-pH 7 phosphate buffer 4 h) in excellent yield to give the carboxylate **1**.

Antibacterial test (MIC, 20 different strains) revealed **1** to be totally inactive.[6]

Acknowledgement. We wish to thank Korea Science and Engineering Foundation for a generous grant. Spectroscopic assistance of Dr. Y. Naya and Mr. H. Naoki of Suntory Institute of Bioorganic Research is gratefully acknowledged. We also thank Dr. E. K. Park of Korea Research Institute of Chemical Technology for performing bioassay.

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Absence of Polarizability Effect on the α-Effect in Aminolyses of *p*-Nitrophenyl Acetate and S-*p*-Nitrophenyl Thioacetate

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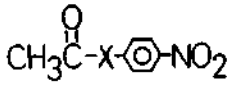
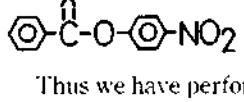
Basicity has most commonly been used as a measure of nucleophilicity.[1] However a group of nucleophiles often show abnormally higher reactivity toward various types of electrophiles than would be predicted from their respective basicity.[2] The enhanced nucleophilicity has been termed the α-effect and many theories have been suggested to explain the cause of the abnormal reactivity. These have focused mainly on ground-state destabilization of the α-nucleophile, transition-state stabilization, solvent effect and polarizability effect.[3]

Since the concept of Hard and Soft Acids and Bases (HSAB) principle[4] was introduced, the α-effect exhibited by a certain group of nucleophiles has been attributed to the high polarizability of them.[2] Although Pearson's concept of the HSAB principle is limited to a qualitative manner, it has often been applied successfully to many types of chemical reactions.



I: X = O, p-nitrophenyl acetate
II: X = S, S-p-nitrophenyl thioacetate



III: X = O, p-nitrophenyl benzoate
IV: X = S, O-p-nitrophenyl thiobenzoate

Thus we have performed a systematic investigation to examine the effect of polarizability on the α-effect. Firstly, we have recently demonstrated that the effect of polarizability on reactivity is significant for reactions of various anionic nucleophiles having different degree of polarizability with the esters of I, II, III and IV in H_2O.[5] We have now performed reactions of I and II with various primary amines including the so-called α-nucleophiles in H_2O. The experimental condition and method employed in the present study sre similar to the one used by Jencks *et al.*[10b] and Buncel *et al.*[12] The replacement of the ether-like oxygen in carboxylic ester by a sulfur atom has been reported to cause a significant increase in polarizability of the reaction center without changing the structure.[6] It has also been believed that amines are softer nucleophiles than oxygen centered nucleophiles, but the α-effect amines are much softer than the corresponding normal amines. Therefore the present system would be considered to be proper for a systematic study of polarizability effect on the α-effect as well as on reactivity. Futhermore, the amines employed in the present system are primary ones, and therefore any steric hindrance problems possibly caused for the reactions with secondary amines[8] would be excluded.

Table 1. Second-Order Rate Constants for the Reactions of I and II with Primary Amines at 25.0 °C

	Nucleophile	*pKa*[a]	k, $M^{-1}s^{-1}$ I	II
1	Methoxylamine[b]	4.6	0.00298	0.166
2	Aniline	4.85	0.00021	0.0136
3	Trifluoroethylamine	5.7	0.00134	0.0286
4	Hydroxylamine[b]	5.97	1.63	12.2
5	Glycine ethyl ester	7.75	0.0631	1.54
6	Hydrazine[b]	8.1	7.62	93.1
7	Glycylglycine	8.25	0.146	2.47
8	Ethanolamine	9.5	2.28	13.8
9	Glycine	9.76	2.61	20.6
10	Ethylamine	10.63	13.5	31.8

[a] *pKa* values are obtained from W. P. Jencks, F. Regenstein in Handbook of Biochemistry. Selected data for Molecular Biology; H. A. Sober Ed. The Chemical Rubber Co., Cleveland, OH, 1968. [b] the α-effect nucleophiles.

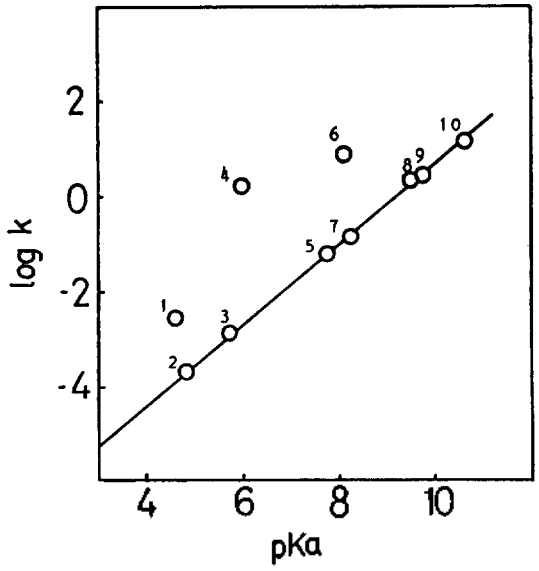


Figure 1. Bronsted plot for the reaction of *p*-nitrophenyl acetate (I) with various amines. The numbers refer to amines of Table 1.

In Table 1 are summarized the results of the present study. As expected, the thiol ester is more reactive than the corresponding oxygen ester toward all the amines employed, indicating that the HSAB principle is applicable to the present system.[7] The Bronsted plots (log k *vs.* *pKa*) have been made to correlate nucleophilicity with basicity in Figure 1 and 2 for reactions of I and II, respectively. It is clearly demonstrated that the α-nucleophiles exhibit significantly enhanced nucleophilicity compared to the respective basicity. However a good linearity between nucleophilicity and basicity can be seen for both ester systems, if the α-effect amines are excluded, in the *pKa* range of 4–10. The negative deviation of ethylamine (*pKa* 10.6) in Figure 2 is considered due to a change of rate determining step for the thiol ester system. Such a curvature in Bronsted type plot has often been observed for the reaction of thiol ester with secondary

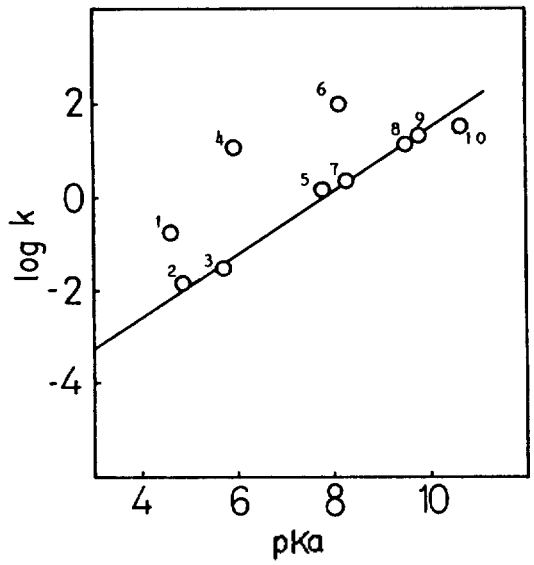


Figure 2. Bronsted plot for the reaction of S-p-nitrophenyl thioacetate (II) with various amines. The numbers refer to amines of Table 2.

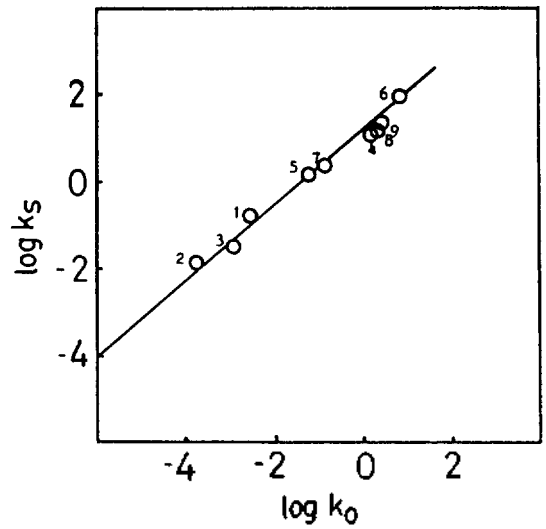


Figure 3. Plot of logarithmic second-order rate constants for the reaction of II with amines (log k_s) *vs.* logarithmic second-order rate constants for the reaction of I with the same nucleophiles (log k_o). The numbers refer to amines of Table 1.

amines[8] and aryloxides[9], and been attributed to a change of mechanism. Therefore the two esters are considered to have the same mechanism, *i.e.* rate determining break-down of the tetrahedral intermediate for the amines having *pKa* less than 10 in the present system.

In Figure 3 the logarithmic rate constant for thiol ester has been plotted against that of the corresponding oxygen ester to examine the effect of polarizability on the α-effect. The good linearity demonstrated in Figure 3 indicates that the effect of polarizability on the α-effect is absent, since one would expect significant positive deviations for the α-effect amines from the line if polarizability effect is responsible for the cause of the α-effect. This is because the α-effect amines

have been considered to be more polarizable than the corresponding normal amines having similar basicity, consequently they are expected to exhibit extra α-effect for the more polarizable thiol ester. Thus the result showing absence of polarizability effect on the α-effect in the present system is quite opposite to the generally known theory.

An explanation for the absent of polarizability effect on the α-effect is considered to be related with the rate determining step of the present reaction system. Since the formation of the tetrahedral intermediate is believed to be readily achieved for this mechanism[10], the nature of α-nucleophiles (*e.g.* low degree of solvation, ground-state destabilization, high polarizability) would not influence significantly the rate of intermediate formation. On the contrary, the presence of the nonbonding electrons adjacent to the reaction center for the α-effect amines is expected to stabilize the intermediate, while such a stabilization is absent for the normal amine system due to the absence of the nonbonding electrons. Since the stabilization of intermediate would also be considered to stabilize the transition-state for the α-amine system[11], the α-effect observed in the present reaction system is considered to originate from the stabilization of transition state. Thus the effect of polarizability is not considered to be important as the cause of the α-effect for the present system.

However more systematic studies would be required for a complete understanding of the present results. The kinetic study for IV and related esters are underway.

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Selective Transport of Amino Acids Derivatives through Calix[6]arene-Based Liquid Membrane

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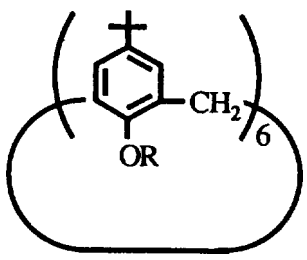
The understanding of selective recognition and transport of amino acids is one of the fundamental interests, in part from the point of view of mimicking the natural biological system.[1] Calixarene derivatives containing ester,[2] amide,[3] or ketone[4] groups have been reported to exhibit unique and selective ionophoric properties toward alkali and alkaline earth metal cations. In this study, the ionophoric property of calix[6]arene-based carrier was utilized for the separation of amino acids in carboxylate form, a common form of amino acids and proteins in physiological fluids.

Ethyl ester derivative of calix[6]arene was prepared by the reported procedure.[2] Transport experiment of N-benzoyl(Bz) derivative of amino acids was performed by using a U-tube (*i.d.* = 1.8 cm) through the chloroform liquid membrane containing a carrier, ethyl ester of calix[6]arene, at 25 °C. As summarized in Table 1, the liquid membrane containing the carrier exhibited the pronounced transport rate as well as selectivity toward amino acids, whereas no detectable amount of amino acid was transported without the carrier under the identical experimental conditions. It has been known that the transport efficiency strongly depends upon both the physicochemical nature of amino acids and the size of metal ions employed.[1] As can be seen from the Table 1, the transport rate for a given cation increased with increasing hydrophobicity of amino acids as follows; Bz-Gly<Bz-Ala< Bz-Val ≅ Bz-Trp<Bz-Phe. This trend is consistent with other results for the transport of amino acids and simple peptides.[5,6]



R = CH_2CO_2Et