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Tertiary Amine-Catalyzed Acyl Group Exchange Reaction of *N,O*-Diacyl-*o*-aminophenols. Its Mechanism and Factors Determining the Relative Stability of Acyl Exchanged Isomer Pairs

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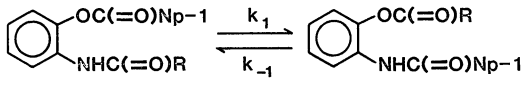
Acyl substituent effects on the equilibrium and rate constants for the acyl group exchange reactions of various *N,O*-diacyl-*o*-aminophenols have been investigated in solvents with different polarities. It was found that the relative stability of acyl exchanged isomer pairs is determined solely by the inductive effect of acyl groups, provided that the steric hindrance of acyl substituents bonded to amide nitrogen affects the stability to the same extent. The importance of steric hindrance exerted by a bulky acyl group in determining the relative stability was demonstrated by analyzing the correlation between the standard free energy change ($\Delta G°$) and pK_a, which were used as the measure of the relative stability of isomer pairs and of the electron-withdrawing ability of acyl groups, respectively. On the other hand, the logarithms of catalytic rate constants for the acyl migration reactions were correlated well to the pK_a values. In addition to this finding, a large negative value of activation entropy ($\Delta S^{\neq}=-160$ J K^{-1} mol^{-1}) and the Brønsted coefficient β of 0.65 for the reaction of *N,O*-(acetyl)-(1-naphthoyl) pair of *N,O*-diacyl-*o*-aminophenol provide a definitive evidence for the rate-determining proton transfer from this derivative to amine catalyst in the transition state.

In view of the theoretical and synthetic importance of acyl exchange reactions in *N,O*-diacyl-*o*-aminophenols, many workers have scrutinized the rearrangement taking place during the preparation of these diacyl derivatives.[1] However, their efforts have also revealed many conflicting results mainly because of great difficulty in separation and quantitative analysis of each labile acyl exchanged isomer. The first quantitative study by Smith and Elrod on the acyl migration in *N,O*-diacyl-*o*-aminophenols by high-performance liquid chromatography (HPLC) has shed some light on the uncertainty in this problem[2] and allowed them to confirm the theoretical prediction by LeRosen and Smith.[3]

In a previous paper[4] we have shown that the tertiary amine-catalyzed acyl exchange reactions of *N*-(*p*-substituted benzoyl)-*O*-(1-naphthoyl) and the corresponding *O,N*-derivatives of *o*-aminophenol proceed intramolecularly and that the electron-withdrawing ability of acyl group bonded to the nitrogen or oxygen atom in *o*-aminophenol is not the only facor to determine which isomer is more stable, although it plays a crucial role in controlling the relative stability of a pair of acyl exchanged isomers. Furthermore, the effects of solvent, substituent, and tertiary amine base on the rate of acyl exchange reactions suggested that the formation of an amidate ion is the rate-determining step in these reactions.

In order to elucidate factors determining the relative stability of a pair of acyl exchanged isomers and to clarify the mechanism of tertiary amine-catalyzed acyl exchange reactions in more detail, we will report on a systematic study concerning these reactions of various *N,O*-diacyl-*o*-aminophenols.



1a–g **2a–g**

1a,2a: R=$CH_2C_6H_4NO_2$-p
1b,2b: R=$CHPh_2$
1c,2c: R=CH_2Ph
1d,2d: R=Me
1e,2e: R=i-Pr
1f, 2f : R=Et
1g,2g: R=t-Bu

1-Np=1-naphthyl

Scheme 1.

Results and Discussion

Solvent and Substituent Effects on the Equilibrium Constants. As shown in Table 1, the equilibrium constants (K) for the triethylamine (TEA, 3.0×10^{-5}—7.1×10^{-2} M, 1 M=1 mol dm^{-3})-catalyzed acyl exchange reactions of our new system **1**–**2** (1.5—2.0×10^{-3} M, Scheme 1) show very little sensitivity to solvent polarity. In order to discuss the inductive effects of aliphatic acyl groups (RCO) on the relative stability of **1**–**2** pairs, we used pK_a of the corresponding carboxylic acids (RCOOH) in water as the measure of electron-withdrawing ability of these acyl groups.[5] In addition, the standard free energy change ($\Delta G°$) was calculated by the thermodynamic relation, $\Delta G°=-RT \ln K$[6] for the measure of the relative stability of our

Table 1. Rate and Equilibrium Constants for the Triethylamine-Catalyzed Acyl Exchange Reactions of *N,O*-Diacyl-*o*-aminophenols (**1a—g** and **2a—g**) at 30±0.1 °C

System (pK_a)[a]	Solvent	$K=k_1/k_{-1}$	k_1[b]/M^{-1} min^{-1}	k_{-1}[c]/M^{-1} min^{-1}
1a—2a (3.85, 3.70[d])	DMSO	0.35	120	350
	CH_3CN	0.40	110	270
	CH_2ClCH_2Cl	0.38	1.2	3.2
1b—2b (3.94)	DMSO	0.30	39	130
	CH_3CN	0.35	33	95
	CH_2ClCH_2Cl	0.40	0.088	0.22
1c—2c (4.31)	DMSO	0.57	26	46
	CH_3CN	0.61	25	41
	CH_2ClCH_2Cl	0.49	0.16	0.32
1d—2d (4.76)	DMSO	1.2	7.9	6.6
	CH_3CN	1.4	5.3	3.8
	CH_2ClCH_2Cl	1.6	0.17	0.11
	Dioxane	1.9	0.0080	0.0042
1e—2e (4.86)	DMSO	1.9	3.9	2.1
	CH_3CN	2.1	3.2	1.5
	CH_2ClCH_2Cl	2.8	0.072	0.026
1f—2f (4.87)	DMSO	1.4	5.0	3.6
	CH_3CN	1.4	2.2	1.6
	CH_2ClCH_2Cl	1.6	0.084	0.053
1g—2g[e] (5.05)	DMSO	6.4	1.2	0.19

a) pK_a values of the corresponding carboxylic acids (RCO_2H) in water at 25 °C (see Ref. 5). b) Determined by using the equation $k_1=k_{-1}K$ for the systems **1a—2a**, **1b—2b**, and **1c—2c**. c) Determined by using the equation $k_{-1}=k_1/K$ for the systems **1d—2d**, **1e—2e**, **1f—2f**, and **1g—2g**. d) pK_a value of 1-naphthoic acid in water at 25 °C (see Ref. 5). e) K and k_1 values of this system in acetonitrile and 1,2-dichloroethane could not be determined accurately because side reactions compete with the acyl exchange reaction in these solvents.

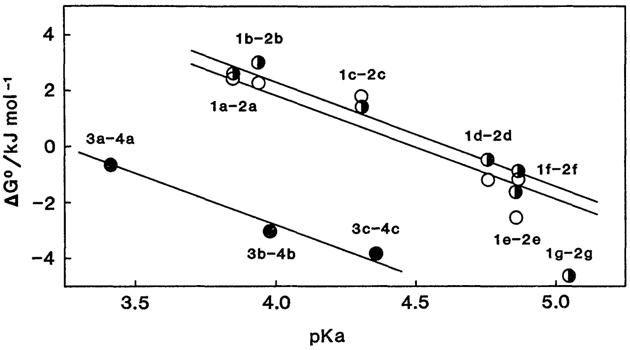
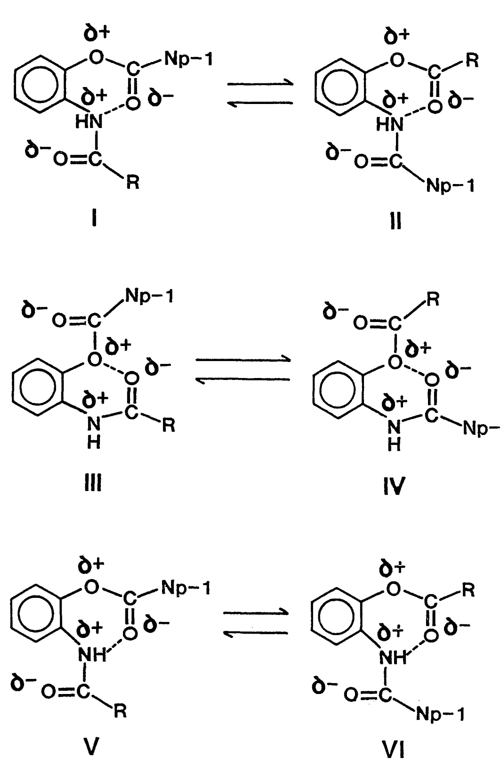


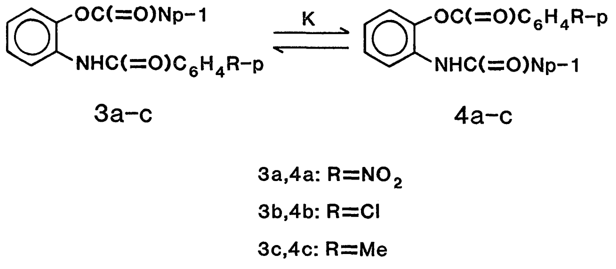
Fig. 1. Standard free energy change (ΔG°) for the acyl exchange reactions of the systems **1a—g–2a—g** in dimethyl sulfoxide (◑), **1a—f–2a—f** in 1,2-dichloroethane (○), and **3a—c–4a—c** in 1,2-dichloroethane (●) at 30±0.1 °C as a function of pK_a of the carboxylic acids (◑, ○: RCO_2H; ●: *p*-$RC_6H_4CO_2H$).

systems. Figure 1 shows that the ΔG° values in dimethyl sulfoxide (DMSO) correlate reasonably well to the pK_a except the case that R=*t*-butyl (*t*-Bu) (correlation coefficient, $\gamma=0.981$). This good correlation reveals that the electron-withdrawing ability of acyl group is one of the important factors to determine the relative stability of **1**–**2** pairs. Almost the same correlation was observed also in acetonitrile ($\gamma=0.974$) and 1,2-dichloroethane ($\gamma=0.946$). The finding that the system **1g**–**2g** with *t*-Bu group shows a negative deviation from the correlation suggests that steric hindrance due to bulky *t*-Bu group decreases the relative stability of **1** to shift the equilibrium to the direction of opposite isomer **2**.

Smith and Elrod proposed the hypothesis that the more stable isomer should be the one with stronger electron-withdrawing acyl group bonded to the nitrogen atom in *o*-aminophenol.[2] However, their hypothesis cannot predict which isomer is more stable in the acetyl-aroyl and 1-naphthoyl-*p*-nitrobenzoyl systems. In addition, the relative stability of **1a**–**2a**, **1b**–**2b**, and **1c**–**2c** pairs also do not conform to their proposal that these pairs should have K values greater than unity. An important question is the origin of good correlation between ΔG° and pK_a shown in Fig. 1. It is well known that amide (RCONHR′) and ester (RCOOR′) have resonance forms, $R\text{–}C(=O)NH\text{–}R' \leftrightarrow R\text{–}C(\text{–}O^-)=\overset{+}{N}H\text{–}R'$ and $R\text{–}C(=O)O\text{–}R' \leftrightarrow R\text{–}C(\text{–}O^-)=\overset{+}{O}\text{–}R'$, so that the amide nitrogen and ester carbonyl oxygen possess partially positive and negative charges, respectively.[7,8] Molecular model indicates that in addition to the phenolic oxygen and amide carbonyl oxygen atoms, the amide nitrogen and ester cabonyl oxygen atoms may also be located closely to each other as shown in Scheme 2. A favorable coulombic interaction between the nitrogen and oxygen atoms in **I** and **II** or between the two oxygen atoms in **III** and **IV** should stabilize both the isomers to some extent. On the basis of these intramolecular resonance structures we predict that the stronger electron-withdrawing acyl



Scheme 2.

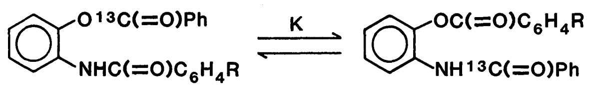


Scheme 3.

group bonded to the nitrogen increases the relative stability of **I** to more extent, whereas the relative stability of **III** decreases with increased electron-withdrawing ability of acyl group attached to the nitrogen. Because the equilibrium between **III** and **IV** is expected to give the $\Delta G°$–pK_a correlation with a positive slope, the results obtained (Fig. 1) cannot be explained in terms of this equilibrium. Thus the contribution of these two resonance forms to the relative stability of our system **1**–**2** should be minor. Although the equilibrium between **I** and **II** provides a good explanation for the observed linear $\Delta G°$–pK_a correlation with a negative slope, intramolecular hydrogen bonds between the amide hydrogen and ester carbonyl oxygen atoms (**V** and **VI**) also can explain our results, because the relative stability of **V** increases with increasing electron-withdrawing ability of acyl group attached to the nitrogen. To examine the possibility of this hydrogen bond, we measured IR spectra of *N*-(*p*-toluoyl)-*O*-(1-naphthoyl)-*o*-aminophenol (**3c**, 1.5×10^{-2} M, 1 M=1 mol dm^{-3}) and *N*-methyl-*N*-(*p*-toluoyl)-*O*-(1-naphthoyl)-*o*-aminophenol (*N*-methyl derivative of **3c**, 1.5×10^{-2} M) in carbon tetrachloride at room temperature. The IR absorption band of the ester carbonyl group in **3c** and its *N*-methyl derivative appeared at 1741 and 1738 cm^{-1}, respectively, demonstrating that the formation of hydrogen bond between the ester carbonyl oxygen and amide hydrogen is negligible. Thus we have to abandon this attractive candidate. From considering the intramolecular resonance structures we propose the equilibrium between **I** and **II** to account for the $\Delta G°$–pK_a correlation observed (Fig. 1). In resonance forms **I** and **II**, the influence of the substituent R on the extent of resonance itself of carbonylimino and carbonyloxy groups may also play a some role in determining the relative stability of **I**–**II** pair.

Next we turn to the steric effects of acyl groups on the relative stability of **1**–**2** pairs. An inspection of molecular models for **I** and **II** suggests that the attractive interaction between the ester carbonyl oxygen and the amide nitrogen should be weakened owing to steric bulkiness of the acyl group bonded to nitrogen rather than that attached to the phenolic oxygen. If so, the increased steric hindrance of substituent R in **I** will decrease the relative stability of the isomer to move the equilibrium to the direction of **II**, because the magnitude of steric effect of the 1-naphthyl group in **II** on the stability remains constant in our systems. The result obtained with **1g** having a bulky *t*-Bu substituent is consistent with our expectation. In addition, the finding of good correlation between $\Delta G°$ and pK_a values for **1**–**2** pairs, except **1g**–**2g**, indicates that there is not much difference in the magnitude of steric hindrance among aliphatic acyl groups in **1a**—**f**. Therefore, by analyzing the $\Delta G°$–pK_a correlation we find that both the inductive and steric effects of acyl groups are important factors to determine the relative stability of a pair of *N*,*O*-diacyl-*o*-aminophenols. On the other hand, the relative stability of each *N*,*O*-(*p*-substituted benzoyl)-(1-naphthoyl) pair of *o*-aminophenol derivatives (Scheme 3), which was previously studied,[4] correlates nicely with the pK_a's of *p*-substituted benzoic acids but has a different correlation from that of the **1a**—**f**–**2a**—**f** system in the same solvent (Fig. 1). This result can be explained in terms of the difference in the magnitude of steric hindrance between aliphatic and aromatic acyl groups, because both **1**–**2** and **3**–**4** pairs have 1-naphthoyl group as a common acyl substituent. The latter group may be regarded as a more bulky substituent compared to the former group and, hence, aromatic acyl groups in **3** exert the steric effect to a larger extent to give smaller $\Delta G°$ value than that for **1**–**2** pairs by comparing system **3**–**4** with system **1**–**2** bearing acyl group of the same electron-withdrawing ability.

The use of the benzoyl-(substituted benzoyl) systems makes it possible to examine exactly the inductive effects of acyl group on the relative stability of isomer pairs by maintaining the magnitude of steric hindrance of this group constant. For this purpose we prepared *N*-(substituted benzoyl)-*O*-(benzoyl-*carbonyl*-^{13}C)-*o*-aminophenols (**5a**—**f**, Scheme 4) and determined the equilibrium constant (K) in dimethyl-d_6 sulfoxide by means of ^{13}C NMR spectroscopy: K=0.39 (**5a**–**6a**), 0.59 (**5b**–**6b**), 0.78 (**5c**–**6c**), 1.0 (**5d**–**6d**), 1.3 (**5e**–**6e**), and 1.9 (**5f**–**6f**) at 30±0.1 °C. From Fig. 2 it was revealed that except **5f**–**6f** pair with a *p*-MeO group there is a good correlation (γ=0.999) between $\Delta G°$ and pK_a of the corresponding carboxylic acids ($RC_6H_4CO_2H$; pK_a=3.41 (R=*p*-NO$_2$), 3.82 (*m*-Cl), 3.98 (*p*-Cl), 4.19 (H), 4.39 (*p*-Me), and 4.47 (*p*-MeO) in water at 25 °C).[5] Interestingly the relative stability of **5**–**6** pairs precisely conforms to the hypothesis proposed by Smith and Elrod.[2] Therefore we conclude that the relative stability of acyl exchanged isomer pairs is determined solely by the electron-withdrawing ability of acyl groups, if the magnitude of steric hindrance exerted by acyl substituents bonded to amide nitrogen is the same in both isomers. From the plausible conclusion that both the inductive and steric effects of acyl groups seem the major factors to determine the relative stability of our systems, we can explain why the Smith–Elrod hypothesis failed to predict more stable isomer in acetyl-aroyl derivative pairs of *o*-aminophenol in addition to the systems **1a**—**c**-**2a**—**c** and **3a**-**4a**. This kind of consideration allows us to revise their qualitative hypothesis in a more quantitative fashion. (1) In *N,O*-diacyl derivatives of *o*-aminophenol the more stable isomer is the one with stronger electron-withdrawing acyl group bonded to nitrogen provided that the magnitude of steric hindrance of both acyl groups is the same in isomer pairs. (2) In *N,O*-diacyl derivatives of *o*-aminophenol the more stable isomer is the one with the sterically less hindered acyl group bonded to nitrogen provided that both acyl groups possess the same electron-withdrawing ability.



5a–f 6a–f

5a,6a: R=p-NO$_2$
5b,6b: R=m-Cl
5c,6c: R=p-Cl
5d,6d: R=H
5e,6e: R=p-Me
5f, 6f: R=p-OMe

Scheme 4.

On the other hand, the small but perceivable negative deviation of the benzoyl-(*p*-anisoyl) system (**5f**–**6f**) from the $\Delta G°$-pK_a correlation implies that the *p*-anisoyl substituent possesses somewhat weaker electron-withdrawing ability in non-aqueous solvents than that predicted from pK_a of *p*-anisic acid in water.

Solvent and Substituent Effects on the Rate Constants. The TEA-catalyzed acyl exchange reaction of **1** or **2** proceeds according to the first-order kinetics in **1** or **2** (γ=0.996—0.999, Scheme 1). Also in this system the pseudo-first-order rate constant (k) for the forward reaction (**1**→**2**) varied with the TEA concentration according to the equation $k=k_1[\mathrm{TEA}]$, derived from the relationship $K=k_1/k_{-1}=(k/[\mathrm{TEA}])/(k'/[\mathrm{TEA}])$, where k' is the pseudo-first-order rate constant for the reverse reaction (**2**→**1**), as illustrated typically for **1d**–**2d** pair in Fig. 3. Thus the rate constant (k_1) is the overall second-order, i.e., the first-order in each of substrate and TEA. No reaction occurred without TEA in either DMSO, 1,2-dichloroethane, or dioxane, whereas acetonitrile catalyzed the reaction to some extent. But the contribution from this solvent-catalyzed reaction to the overall rate was found to be negligible, e.g., $k \approx 5\times10^{-6}\,\mathrm{min}^{-1}$ for **1c**–**2c** pair in acetonitrile at 30±0.1 °C.

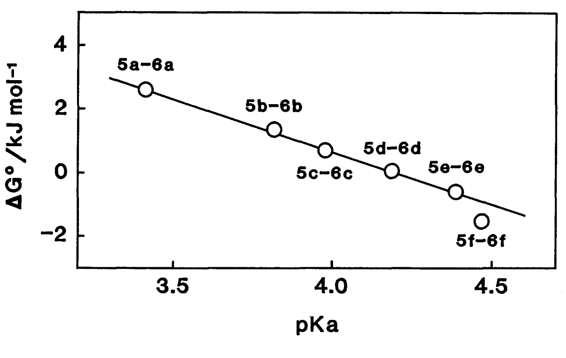


Fig. 2. Standard free energy change ($\Delta G°$) for the ^{13}C-labeled system **5a**—**f**-**6a**—**f** in dimethyl-d_6 sulfoxide at 30±0.1 °C as a function of pK_a of the carboxylic acids ($RC_6H_4CO_2H$).

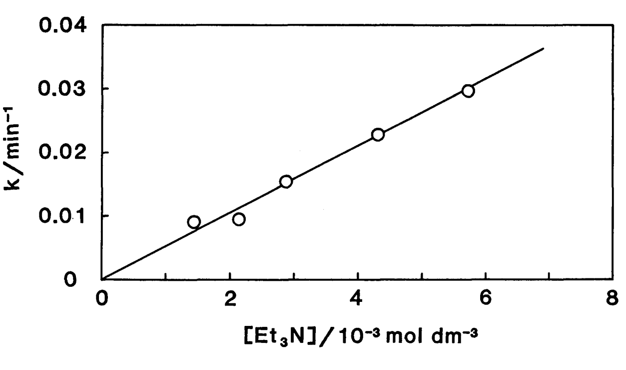


Fig. 3. Dependence on triethylamine concentration of the pseudo-first-order rate constant (k) for the system **1d**–**2d** in acetonitrile at 30±0.1 °C.

It has previously been found that both the increased solvent polarity and the increased electron-withdrawing ability of the acyl group greatly accelerate the acyl exchange reaction of the system **3**–**4**.[4] A similar result was obtained for the present system **1**–**2** (Table 1). The observation of a linear correlation between log k_1 and pK_a in DMSO (γ=0.971, Fig. 4) is consistent with the rate-determining proton transfer from **1** to TEA in the transition state. A similar correlation was observed also in acetonitrile (γ=0.971) and 1,2-dichloroethane (γ=0.839). As already mentioned in the preceding section, the introduction of a bulky *t*-Bu substituent into **1** destabilizes the ground state to reduce the relative stability of **1g** to a larger extent, compared with other sterically less hindered aliphatic acyl groups. This ground-state destabilization effect is expected to accelerate the forward reaction and, thus, to result in a positive deviation from the correlation indicated in Fig. 4. The result obtained was not consistent with this expectation. It is very likely that the steric bulkiness of *t*-Bu substituent also destabilizes the transition state so as to compensate for the rate enhancement by the ground-state destabilization.

In order to obtain additional evidence supporting the rate-determining proton transfer in the transition state, we chose **1d**–**2d** pair and investigated the temperature and base strength effects on the rate of base (tertiary amine)-catalyzed acyl exchange reaction of this pair (Table 2). From the Arrhenius plot shown in Fig. 5 thermodynamic activation parameters for the forward reaction were determined at 30 °C: E_a=33 kJ

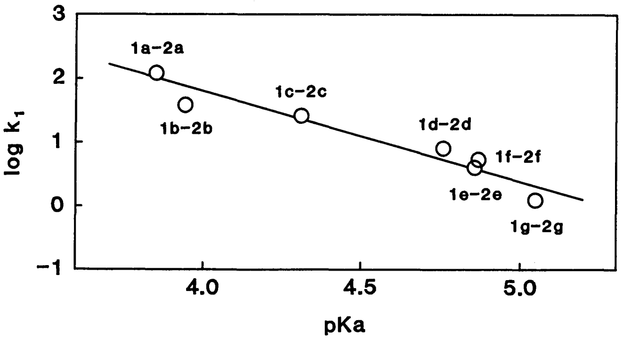


Fig. 4. Logarithm of the second-order rate constant (k_1) for the system **1a**—**g**–**2a**—**g** in dimethyl sulfoxide at 30±0.1 °C plotted against pK_a of the carboxylic acids (RCO_2H).

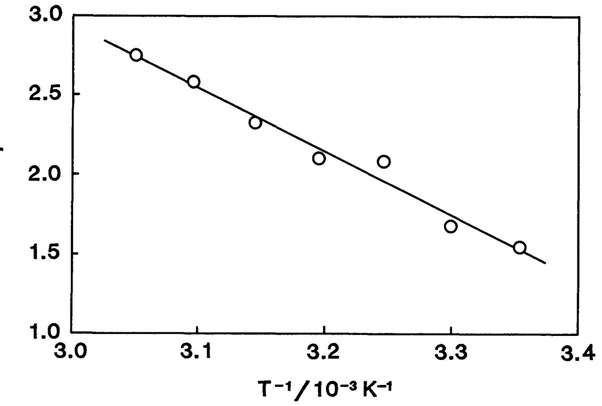


Fig. 5. Arrhenius plot for the triethylamine-catalyzed acyl exchange reaction of the system **1d**–**2d** in acetonitrile.

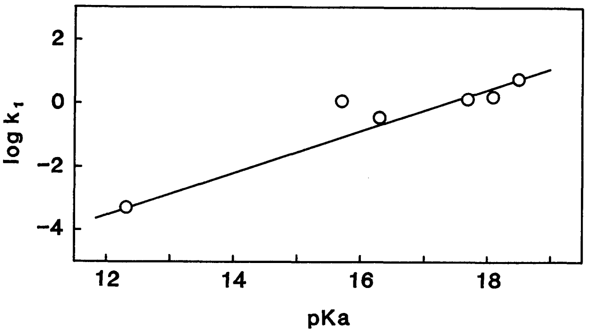
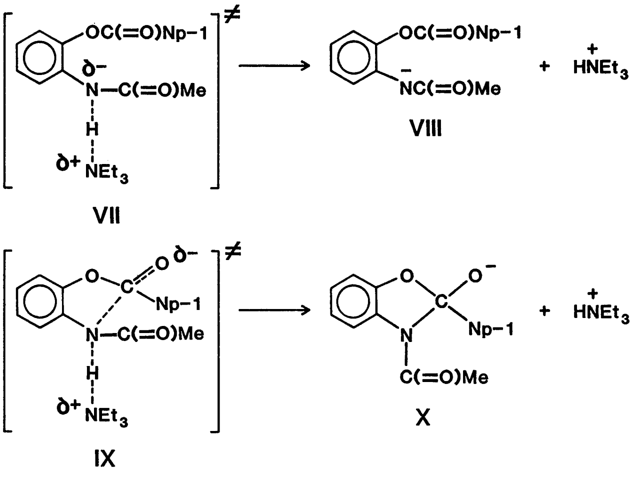


Fig. 6. Brønsted plot for the tertiary amine-catalyzed acyl exchange reaction of the system **1d**–**2d** in acetonitrile at 30±0.1 °C.

Table 2. Temperature and Base Strength Effects on the Equilibrium and Rate Constants for the Base-Catalyzed Acyl Exchange Reactions of **1d**—**2d** Pair in Acetonitrile

Base (pK_a)[a]	Temperature/°C	$K=k_1/k_{-1}$	k_1/M^{-1} min^{-1}	k_{-1}[b]/M^{-1} min^{-1}
Et_3N (18.5)	25	1.3	4.7	3.6
	30	1.4	5.3	3.8
	35	1.4	8.1	5.8
	40	1.3	8.2	6.3
	45	1.3	10	7.7
	50	1.4	13	9.3
	55	1.4	16	11
n-Bu_3N (18.1)	30	1.3	1.5	1.2
$Et_2NCH_2CH_2OH$ (17.7)	30	1.3	1.3	1.0
$EtN(CH_2CH_2OH)_2$ (16.3)	30	1.3	0.34	0.26
$N(CH_2CH_2OH)_3$ (15.7)	30	1.3	1.1	0.84
Pyridine (12.3)	30	1.3	0.00047	0.00036

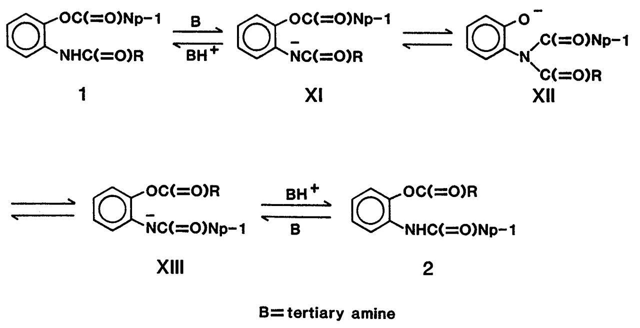
a) pK_a values of the conjugate acids determined in acetonitrile at room temperature (see Ref. 9). b) Determined by using the equation $k_{-1}=k_1/K$.



Scheme 5.

mol^{-1}, $\Delta H^{\neq}$=30 kJ mol^{-1}, $\Delta S^{\neq}$=−160 J K^{-1} mol^{-1}, and $\Delta G^{\neq}$=80 kJ mol^{-1}. The Brønsted plot of the catalytic rate constants (k_1) for the reaction has a slope (β) of 0.65 (Fig. 6). The magnitude of this Brønsted coefficient together with large negative value of activation entropy confirms that the rate-limiting proton transfer occurs at the transition state **VII** or **IX** (Scheme 5). The reaction that proceeds through **VII** should give the amidate ion intermediate **VIII**, whereas the reaction that proceeds through **IX** should form the tetrahedral intermediate **X**. The difference between these two transition-state structures is that **VII** bears partial negative charge on amide nitrogen but **IX** possesses, if any, much less negative charge than **VII**. The result that the linear correlation between log k_1 and pK_a has a slope of −1.4 requires that partial negative charge must develop on amide nitrogen in the transition state, and hence the transition-state structure **IX** seems less likely.

On the other hand, the equilibrium constant exhibits very small temperature dependence and the extent of change in K value in the temperature range investigated is within the limit of experimental accuracy (Table 2). The positive deviation of triethanolamine (Fig. 6) may be due to much stronger hydrogen bond formation between amide nitrogen with partial negative charge and hydroxyl group of this amine in the transition state, compared with other two ethanolamines. The evidence for this explanation comes from an examination of IR spectra of **1d** (1.5×10^{-2} M) in 1,2-dichloroethane containing ethanolamines (5.0×10^{-2} M), which reveals the negligible formation of hydrogen bond between amide or ester carbonyl group of **1d** and hydroxyl group of the catalysts in the ground state. Owing to strong IR absorption bands of hydroxyl groups in ethanolamines, we could not inspect the possibility of hydrogen bond between amide hydrogen and these amines.



Scheme 6.

Since the neighboring amidate ion is a powerful intramolecular nucleophile,[10] the attack of this ion on the ester carbonyl carbon in **XI** should give *N*,*N*-diacyl-*o*-aminophenolate ion **XII** as indicated in Scheme 6. Acyl migration from amide nitrogen to phenolic oxygen in this intermediate yields amidate ion **XIII** of acyl exchanged isomer **2**, which then forms **2** by protonation. The fact that no HPLC peaks corresponding to these intermediates were detected in any system indicates that the conversion of **XI** into **2** or of **XIII** into **1** must be very fast compared to the rate-limiting formation of **XI** and **XIII**.

Experimental

General Methods. The HPLC analysis of acyl group exchange reactions was performed on a Shimadzu Model LC-6A high-performance liquid chromatography apparatus equipped with a 4.6×250-mm ODS (Zorbax) column and a Shimadzu Model SPD-2A UV detector. The IR spectra were taken by a Hitachi Model 270-30 infrared spectrometer. The ^{13}C NMR spectra were recorded on a JEOL Model FX-200 spectrometer. Microanalyses were performed on a Perkin-Elmer Model 240C elemental analyzer.

Materials and Solvents. Diphenylacetyl and *p*-nitrophenylacetyl chlorides, which are not commercially available, were prepared by treating the corresponding carboxylic acids with thionyl chloride or phosphorus pentachloride. The syntheses of *N*-(aliphatic acyl)-*o*-aminophenols were accomplished by the reactions of two equiv of *o*-aminophenol with aliphatic acyl chlorides in dichloromethane at 0 °C. *N*-(Aromatic acyl)-*o*-aminophenols were synthesized similarly. Repeated recrystallization of crude *N*-acyl-*o*-aminophenols from aqueous ethanol or hexane–ethyl acetate gave pure samples, physical properties of which were collected in Table 3. The reactions between *N*-acyl-*o*-aminophenols (0.01 mol) and acyl chlorides (0.01 mol) in the presence of triethylamine (0.009 mol) in dichloromethane at 0 °C afforded crude *N*,*O*-diacyl-*o*-aminophenols (**1a**—**g** and **2a**—**g**), which were purified by column chromatography on silica gel (70—230 mesh, Merck) with chloroform eluent, followed by recrystallization from benzene–hexane or ethyl acetate. *N*-(Substituted benzoyl)-*O*-(benzoyl-*carbonyl*-^{13}*C*)-*o*-aminophenols (**5a**—**f**) were obtained from the reactions of *N*-(substituted benzoyl)-*o*-aminophenols with benzoyl-*carbonyl*-^{13}*C* chloride (99+ atom%, Aldrich). The same

Table 3. Physical Properties of *N*-Acyl-*o*-aminophenols *o*-RC(=O)NHC$_6$H$_4$OH

Substituent R	Mp θ_m/°C	IR (KBr)/cm^{-1}		
		N-H	O-H[a)]	C=O
p-$\mathrm{CH_2C_6H_4NO_2}$	175—177	3320[a)]		1640
$\mathrm{CHPh_2}$	155—156	3400	3200	1660
$\mathrm{CH_2Ph}$	156—157	3380	3120	1650
Me	208—210	3420	3100	1660
$\mathrm{CHMe_2}$	113—114	3420	3100	1670
Et	74—75	3420	3100	1650
$\mathrm{CMe_3}$	132—133	3450	3090	1650
1-Np[b),c)]	194.5—195.5	—	—	—
p-$\mathrm{C_6H_4NO_2}$[c)]	206—207	—	—	—
m-$\mathrm{C_6H_4Cl}$	171—172	3410	3200	1650
p-$\mathrm{C_6H_4Cl}$[c)]	180.5—181.5	—	—	—
$\mathrm{C_6H_5}$[c)]	167.5—168.5	—	—	—
p-$\mathrm{C_6H_4Me}$[c)]	157.5—158.5	—	—	—
p-$\mathrm{C_6H_4OMe}$	172—173	3260[a)]		1630

a) Broad band. b) 1-Naphthyl. c) The same sample as in the previous study (see Ref. 4).

Table 4. Physical Properties of **1a—g**, **2a—g**, and **5a—f**

Compound	Mp θ_m/°C	IR (KBr)/cm^{-1}		Anal/%, Found (Calcd)		
		N-H	C=O	C	H	N
1a	198—199	3330	1690	70.84 (70.41)	4.45 (4.26)	6.60 (6.57)
1b	127—128	3290	1740, 1670	81.75 (81.37)	5.30 (5.08)	3.03 (3.06)
1c	144—145	3240	1740, 1670	78.78 (78.71)	5.20 (5.03)	3.66 (3.67)
1d	137.5—138.5	3340	1710, 1690	75.01 (74.73)	5.18 (4.96)	4.59 (4.59)
1e	120—122	3360	1720, 1700	76.02 (75.65)	5.96 (5.76)	4.21 (4.20)
1f	118—120	3290	1750, 1675	75.45 (75.21)	5.51 (5.38)	4.40 (4.39)
1g	109—110	3360	1745, 1660	76.22 (76.05)	6.24 (6.10)	4.02 (4.03)
2a	189—190	3220	1775, 1640	70.24 (70.41)	4.43 (4.26)	6.52 (6.57)
2b	102—104	3230	1770, 1655	81.61 (81.37)	5.27 (5.08)	3.01 (3.06)
2c	121—123	3330	1770, 1670	78.98 (78.71)	5.26 (5.03)	3.65 (3.67)
2d	128—130	3230	1765, 1645	74.96 (74.73)	5.15 (4.96)	4.55 (4.59)
2e	107—108	3270	1780, 1670	75.82 (75.65)	5.87 (5.76)	4.20 (4.20)
2f	134—135	3250	1785, 1665	75.60 (75.21)	5.54 (5.38)	4.40 (4.39)
2g	115—116	3230	1755, 1655	76.18 (76.05)	6.28 (6.10)	4.02 (4.03)
5a	183—185	3370	1710, 1685, 1660	66.41 (66.38)	4.08 (3.89)	7.61 (7.71)
5b	118—119	3360	1685, 1660	68.78 (68.37)	4.07 (4.01)	4.00 (3.97)
5c	156—157	3390	1690, 1650	68.50 (68.37)	4.15 (4.01)	3.95 (3.97)
5d[a)]	181—182	—	—	—	—	—
5e	122—123	3470	1710, 1690, 1660	76.04 (76.18)	5.27 (5.17)	4.19 (4.22)
5f	142—143.5	3300	1700, 1650	72.53 (72.68)	5.03 (4.93)	4.01 (4.02)

a) The same sample as in the previous study (see Ref. 4).

purification procedure as above was applied to crude **5a—f** whose physical properties were listed in Table 4 with those of **1a—g** and **2a—g**. *N*-(*p*-Toluoyl)-*O*-(1-naphthoyl)-*o*-aminophenol and *N*-methyl-*N*-(*p*-toluoyl)-*O*-(1-naphthoyl)-*o*-aminophenol were the same as those in the previous study.[4)]

Dioxane, 1,2-dichloroethane, and dimethyl sulfoxide were of spectroscopic grade and used as received. Acetonitrile and acetic acid were purified by the standard methods.[11)] Pyridine, tributylamine, and triethylamine were fractionally distilled from sodium hydroxide. 2-(Diethylamino)ethanol, *N*-ethyldiethanolamine, and triethanolamine were purified by fractional distillation at reduced pressure. Purification of acetonitrile and water employed for HPLC analysis was done by distillation.

Kinetic Procedure. The acyl exchange reactions were initiated by the addition of appropriate amounts of tertiary amine to 10 ml of a solution of **1** or **2** in a given solvent, when the temperature was maintained at 30±0.1 °C until the equilibrium was established. At suitable time intervals a 0.5 ml aliquot was pipetted off and immediately added to 0.5 ml of acetic acid to stop the reaction. A 5 μl aliquot of this mixture was then subjected to HPLC analysis (detection wavelength, 240 nm) using acetonitrile–water (65:35 v/v) as the developing solvent. Linear calibration curves (HPLC peak area vs. concentration), made for each compound under the same analytical conditions, were employed to determine the concentration of **1** or **2** at a given period of reaction time. The acyl exchange reactions were found to follow the first-order kinetics for at least 3 half-lives. Pseudo-first-order rate constants for the forward (k) and reverse (k') reactions were evaluated graphically by the use of Eqs. 1 and 2, respectively, and determined at least in triplicate for each reaction.

$$\ln\{[\mathbf{2}]_e/([\mathbf{2}]_e-[\mathbf{2}]_t)\} = (1+1/K)kt \tag{1}$$

and

$$\ln\{[\mathbf{1}]_e/([\mathbf{1}]_e-[\mathbf{1}]_t)\} = (1+K)k't, \tag{2}$$

where [**1** or **2**]$_t$ and [**1** or **2**]$_e$ are concentrations of **1** or **2** at reaction time t and at equilibrium, respectively. Equilibrium constants ($K=k_1/k_{-1}$) were estimated from the concentration ratio $[\mathbf{2}]_e/[\mathbf{1}]_e$ at the equilibrium. Second-order rate constants ($k_1=k/$[tertiary amine] or $k_{-1}=k'/$[tertiary amine]) were obtained by dividing pseudo-first-order rate constants (k or k') by the concentration of tertiary amine used. The same equilibrium ($K=1.4$) and rate ($k_1=k_{-1}K=5.0\ \mathrm{M^{-1}\ min^{-1}}$) constants were obtained also by following the exchange reaction in acetonitrile at 30 °C using **2d** as the starting material.

Equilibrium constants ($K=[\mathbf{6}]_e/[\mathbf{5}]_e$) for the triethylamine (5.0×10^{-2} M)-catalyzed ^{13}C-labeled benzoyl migration reactions of **5a**—**f** (0.25—0.30 M) in dimethyl-d_6 sulfoxide were determined from the area ratio at the equilibrium of two ^{13}C NMR signals arising from the ester (around 163.8 ppm) and amide (around 165.4 ppm) carbonyl carbons at 30±0.1 °C. Tetramethylsilane was used as an internal standard. The ^{13}C-labeled benzoyl migration reactions attained the equilibrium within 10 h under our conditions. Instrumental parameters for the integration of these two signals are as follows: frequency, 50.10 MHz; transform, 32.768 K; spectral width, 12500 Hz; pulse width, 7 μs; acquisition time, 58 s.

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