Base-Catalyzed Acyl Exchange Reactions of *N*,*O*-Diacyl-*o*-aminophenols. Substituent and Temperature Effects on the Equilibrium Constants

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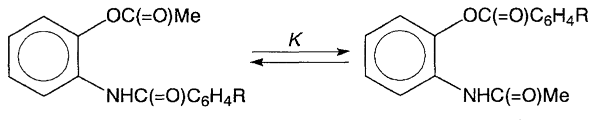
Substituent and temperature effects on the equilibrium constants for the triethylamine-catalyzed acyl exchange reactions of *N*-(substituted benzoyl)-*O*-acetyl-*o*-aminophenols have been investigated by ^{1}H NMR spectroscopy. It was found that the standard enthalpy change ΔH° in acyl exchange processes, estimated from temperature dependence of the equilibrium constant, correlates well with the standard free energy change ΔG° which was used as a measure of the relative stability of isomer pairs, while the standard entropy change ΔS° is approximately constant (-6 ± 2 J K^{-1} mol^{-1}) irrespective of the substituents in benzoyl introduced. The finding of enthalpy-controlled acyl exchange reactions confirms that the relative stability of a given isomer pair is determined by the difference in electrostatic force of attraction between the amide nitrogen with a partial positive charge and the ester carbonyl oxygen having a partial negative charge in both isomers.

Acyl groups in *N*,*O*-diacyl-*o*-aminophenols have been shown to be readily exchanged in the presence of a base.[1] But difficulty in the kinetic analysis of an interesting base-catalyzed acyl exchange reaction has prevented the elucidation of the mechanism of this exchange reaction.[2] The use of tertiary amine bases in organic solvents allowed detailed kinetic and thermodynamic analyses of the acyl-exchange equilibrium reactions.[3] In a previous study[3b] we have shown that both inductive and steric effects of acyl groups are important factors in determining the relative stability of acyl exchanged isomer pairs. The disadvantages of the model *N*,*O*-diacyl-*o*-aminophenols previously employed are that these model compounds possess a sterically bulky 1-naphthoyl group as a common acyl substituent and, additionally, aliphatic acyl groups in the model make it difficult to change systematically the electron-withdrawing ability of these acyl groups while maintaining the magnitude of steric bulkiness of acyl substituents constant. In order to remove these two disadvantages, we prepared *N*,*O*-(substituted benzoyl), acetyl derivatives of *o*-aminophenol (**1a**—**h** and **2a**—**h**, Scheme 1) as a new system and investigated substituent and temperature effects on the equilibrium constants for triethylamine (TEA)-catalyzed acyl exchange reactions, hoping to obtain insights into thermodynamic factors which determine the relative stability of acyl-exchanged isomer pairs.

Results and Discussion

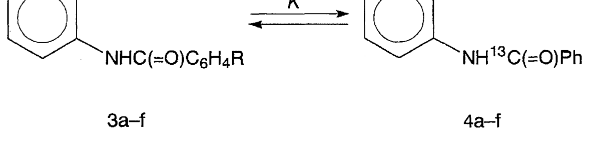
Substituent Effects on the Equilibrium Constants. Although it was impossible to separate and quantify the isomer pair **1**–**2** by high performance liquid chromatography under any conditions, the appearance of *O*-acetyl (**1**) and *N*-acetyl (**2**) proton signals at 2.3—2.4 and 2.0—2.1 ppm, respectively, made it possible to determine accurately the equilibrium constant *K* for a given acyl exchange reaction with the aid of ^{1}H NMR spectroscopy. In a previous study[3b] we demonstrated that the relative stability of ^{13}C-labeled isomer pairs **3**–**4** (Scheme 2) is determined solely by the electron-withdrawing ability of acyl groups, because steric hindrance exerted by both acyl substituents of the system **3**–**4** is of the same magnitude. Thus, the **3a**—**f**–**4a**—**f** pairs can be employed as a criterion for estimating the magnitude of steric effects of more bulky acyl group on the relative stability of



1a–h 2a–h

1a, 2a : R=*p*-OMe
1b, 2b : R=*p*-Me
1c, 2c : R=H
1d, 2d : R=*p*-F
1e, 2e : R=*p*-Cl
1f, 2f : R=*m*-Cl
1g, 2g : R=*p*-CN
1h, 2h : R=*p*-NO$_2$

Scheme 1.



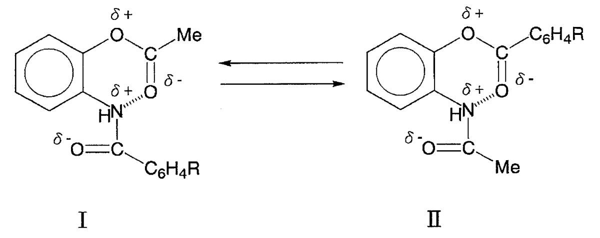
3a–f 4a–f

3a, 4a : R=*p*-OMe
3b, 4b : R=*p*-Me
3c, 4c : R=H
3d, 4d : R=*p*-Cl
3e, 4e : R=*m*-Cl
3f, 4f : R=*p*-NO$_2$

Scheme 2.

isomer pair with different sizes of acyl groups. In order to discuss the inductive effects of aromatic acyl groups (ArCO) on the relative stability of **1**–**2** pairs, we used pK_a of the corresponding carboxylic acids (ArCOOH) in water as a measure of electron-withdrawing ability of these acyl groups.[4] In addition, the standard free energy change ΔG° was calculated by the thermodynamic relation, $\Delta G^\circ = -RT \ln K$,[5] where K is the equilibrium constant for the new system **1**–**2** in [$^2H_6$]-dimethyl sulfoxide (DMSO-d_6), for a measure of the relative stability of **1**–**2** pair. In Fig. 1 is shown a correlation between pK_a and ΔG° for the system **1**–**2**. The ΔG°–pK_a correlation for the ^{13}C-labeled system **3**–**4** studied in the same solvent is also indicated in Fig. 1, for comparison. In both systems there are good linear correlations between ΔG° and pK_a, except the case that R = *p*-OMe. As previously suggested,[3b)] the negative deviation of the system with *p*-OMe substituent from the ΔG°–pK_a correlation, though it is small, may be due to the weaker electron-withdrawing ability of *p*-anisoyl group in DMSO than that predicted from pK_a of *p*-anisic acid in water. If so, this acyl group in nonaqueous solvents is considered to have an electron-attracting ability comparable to the pK_a value of about 4.7.

The finding that the slope of the correlation line for the **3**–**4** system (correlation coefficient, $\gamma = 0.997$) is consistent with that for the new **1**–**2** system ($\gamma = 0.993$) within the experimental error reveals that, if one acyl group bonded to the amino nitrogen or the hydroxy oxygen in *o*-aminophenol is a common acyl substituent of a given system, the relative stability of its system is determined solely by the inductive effect of another acyl group. This acyl substituent effect on the relative stability of acyl-exchanged isomer pair was previously explained in terms of the electrostatic models I and II (Scheme 3) in which the amide and ester groups should be in nearly the same plane as the benzene ring,[6)] since the relative stability is subject to solvent polarity effects to only a very small extent.[3)] If the difference in electrostatic force of attraction for I and II between the amide nitrogen and the ester carbonyl oxygen is the major factor to control the relative stability of the isomer pair I–II, the introduction of a stronger electron-withdrawing acyl group into the nitrogen atom in *o*-aminophenol increases the stability of I to a greater extent accompanied by more decreased stability of II. As a result, the relative stability (ΔG°) of I increases with increased electron-withdrawing ability of the ArCO group bonded to the nitrogen, as manifested in Fig. 1, making the assumption mentioned above reasonable. In the models I and II, the influence of the substituent R on the extent of resonance itself of carbonylamino and carbonyloxy groups might play some role in determining the relative stability of the I–II pair. As previously shown,[3b)] acyl substituent effects on the strength of intramolecular hydrogen bonds between the amide hydrogen and the ester carbonyl oxygen may also explain the observed ΔG°–pK_a correlation, but this possibility was ruled out by an IR spectral analysis.



Scheme 3.

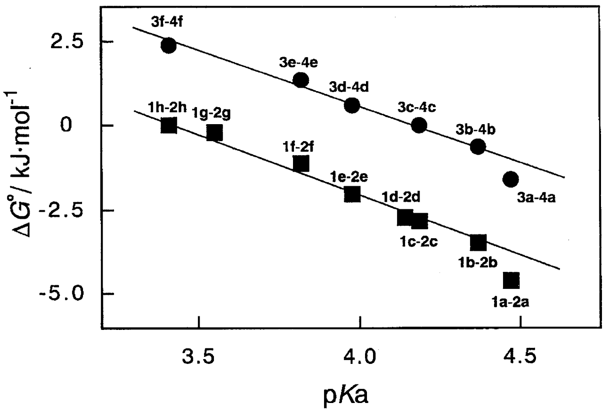
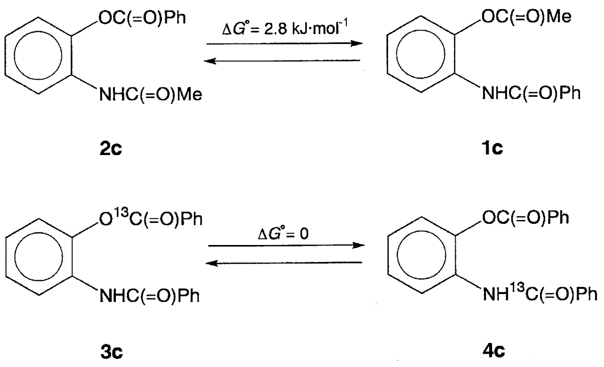


Fig. 1. Standard free energy change (ΔG°) for the TEA-catalyzed acyl exchange reactions of the systems **1**–**2** (■) and **3**–**4** (●) in DMSO-d_6 at 30±0.3 °C as a function of pK_a of the carboxylic acids (RC_6H_4COOH).

An inspection of Fig. 1 shows that **1a**—**h**-**2a**—**h** pairs give a ΔG°–pK_a correlation with almost the same slope as, but a different intercept from that for **3a**—**f**-**4a**—**f** pairs. Taking into account that the benzoyl group is a more bulky acyl substituent than the acetyl one, this observation can be explained in terms of the hypothesis proposed in a previous paper that in *N*,*O*-diacyl derivatives of *o*-aminophenol the more stable isomer is the one with the sterically less hindered acyl group bonded to the nitrogen, provided that both acyl groups possess the same electron-withdrawing ability.[3b)] Is it possible to estimate quantitatively the magnitude of steric hindrance of the more bulky benzoyl group on the relative stability ? First, we compare equilibrium reactions shown in Scheme 4 to correct for the difference in electron-attracting ability of acetyl and benzoyl groups. We predict based on the slope of the ΔG°–pK_a correlation line (Fig. 1) that the replacement of *N*-benzoyl group in **3c** by acetyl one (**2c**), corresponding to an increase in pK_a of 0.57 [ΔpK_a = pK_a(MeCOOH,



Scheme 4.

Table 1. Equilibrium Constants and Thermodynamic Parameters for the TEA-Catalyzed Acyl Exchange Reactions of **1**–**2** Pairs in DMSO-d_6

System ($\mathrm{p}K_\mathrm{a}$)[a)]	Temp	K	ΔG°	ΔH°	ΔS°
	°C		kJ mol^{-1}	kJ mol^{-1}	J K^{-1} mol^{-1}
1a–**2a** (4.47)	30	6.23	−4.61	−7.1	−8.3
	40	5.81			
	50	5.34			
	60	4.90			
	70	4.48			
1b–**2b** (4.37)	30	3.97	−3.47	−4.8	−4.4
	40	3.93			
	50	3.50			
	60	3.38			
	70	3.24			
1c–**2c** (4.19)	30	3.07	−2.83	−4.6	−5.9
	40	2.91			
	50	2.62			
	60	2.54			
	70	2.52			
1d–**2d** (4.14)	30	2.97	−2.74	−3.9	−3.8
	40	2.80			
	50	2.62			
	60	2.55			
	70	2.48			
1e–**2e** (3.98)	30	2.23	−2.02	−4.0	−6.6
	40	2.14			
	50	2.08			
	60	1.99			
	70	1.83			
1f–**2f** (3.82)	30	1.54	−1.09	−2.5	−4.7
	40	1.50			
	50	1.47			
	60	1.42			
	70	1.37			
1g–**2g** (3.55)	30	1.09	−0.22	−1.7	−5.0
	40	1.05			
	50	1.03			
	60	1.03			
	70	0.99			
1h–**2h** (3.41)	30	0.99	+0.025	−2.4	−8.0
	40	0.96			
	50	0.95			
	60	0.90			
	70	0.89			

a) $\mathrm{p}K_\mathrm{a}$ values of the corresponding aromatic carboxylic acids (ArCOOH) in water at 25 °C.

4.76) − $\mathrm{p}K_\mathrm{a}$(PhCOOH, 4.19)],[4] stabilizes **1c** by 2 kJ mol^{-1} relative to **2c** to give the ΔG° value of −2 kJ mol^{-1} for **2c**–**1c** pair, which is much less than the observed value of 2.8 kJ mol^{-1}. Since this difference in the expected and observed ΔG° values must be attributed to the difference in steric bulkiness between acetyl and benzoyl substituents, we conclude that the introduction of benzoyl group instead of acetyl one into the nitrogen destabilizes **1c** by $2.8+2=4.8$ kJ mol^{-1} relative to **2c**. As inferred from this molecular model, the attractive interaction between the amide nitrogen and the ester carbonyl oxygen should be weakened, owing to the steric bulkiness of the benzoyl group bonded to the nitrogen (**1c**) rather than that of the one attached to the phenolic oxygen (**2c**).

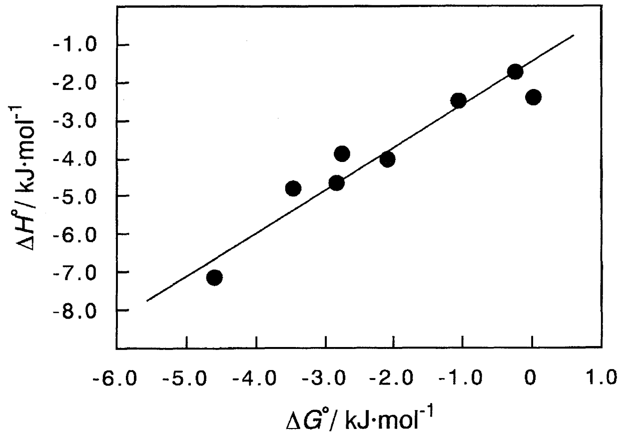


Fig. 2. Relationship between standard enthalpy (ΔH°) and free energy (ΔG°) changes for the TEA-catalyzed acyl exchange reactions of the system **1**–**2** at 30 °C.

Temperature Effects on the Equilibrium Constants. If the strength of electrostatic bonding between the amide nitrogen and the ester carbonyl oxygen is a predominant factor to determine the relative stability of a given isomer pair (I–II pair), we are allowed to anticipate that the difference in this strength between I and II is reflected in the standard enthalpy change ΔH°, but not in the standard entropy change ΔS° for the formation of II. From the slope for the linear van't Hoff plots of $\log K$ against the reciprocal of absolute temperature ($1/T$) ($\gamma=0.960$—0.997), we can evaluate the ΔH° value. In addition, the ΔS° at 30 °C was determined with the ΔH° and ΔG° values. The thermodynamic parameters thus estimated are collected in Table 1, along with the ΔG° and K values for each isomer pair.

Two interesting tendencies can be found from an analysis of Table 1. One is that ΔS° in the formation of **2** is small (−8.3— −3.8 J K^{-1} mol^{-1}) and has no correlation with the electron-attracting ability of acyl groups. The small temperature dependence of the K value necessarily results in a relatively large error of the slope (ΔH°) for the van't Hoff plots and thus of the ΔS°. This allows us to regard the ΔS° obtained as being approximately constant (−6±2 J K^{-1} mol^{-1}). The other is that the ΔH° for **1**–**2** pair has a tendency to increase with increased electron-withdrawing ability of acyl substituents. As Fig. 2 demonstrates, the ΔH° correlates well with the ΔG° ($\gamma=0.956$), establishing that the relative stability of acyl-exchanged isomer pair **1**–**2** is governed exclusively by the difference in enthalpy between **1** and **2**, but the entropy difference between these isomers contributes to controlling the stability to a negligible extent. Thus, the finding of enthalpy-controlled acyl exchange reactions provides a strong piece of evidence for the isomer structures I and II being stabilized by the Coulombic attraction between the amide nitrogen and the ester carbonyl oxygen in both isomers.

Table 2. Physical Properties of **1a**—**h** and **2a**—**h**

Compound	Mp θ_m	IR (KBr)/cm^{-1}		Anal/%, Found (Calcd)		
	°C	N–H	C=O	C	H	N
1a	116—117	3424	1746, 1665	67.70 (67.36)	5.43 (5.30)	4.98 (4.91)
1b	107.5—108.5	3388	1749, 1674	71.84 (71.36)	5.73 (5.61)	5.30 (5.20)
1c	111—112	3232	1761, 1653	71.03 (70.58)	5.24 (5.13)	5.57 (5.49)
1d	105—107	3244	1779, 1653	66.34 (65.93)	4.59 (4.43)	5.27 (5.13)
1e	112—113	3370	1743, 1683	62.31 (62.19)	4.41 (4.18)	4.91 (4.83)
1f	97—98	3298	1770, 1656	62.60 (62.19)	4.43 (4.18)	4.82 (4.83)
1g	137.5—138.5	3352	1740, 1677	69.03 (68.56)	4.58 (4.32)	10.09 (9.99)
1h	123—124	3356	1746, 1682	60.27 (60.00)	4.28 (4.03)	9.26 (9.33)
2a	141.5—142.5	3360	1720, 1694	67.55 (67.36)	5.62 (5.30)	4.73 (4.91)
2b	124.5—125.5	3368	1720, 1694	71.40 (71.36)	5.91 (5.61)	5.05 (5.20)
2c	128.5—129.5	3360	1718, 1690	70.29 (70.58)	5.36 (5.13)	5.62 (5.49)
2d	123.5—124.5	3352	1719, 1686	66.09 (65.93)	4.52 (4.43)	5.19 (5.13)
2e	138.5—139.5	3352	1722, 1686	62.62 (62.19)	4.49 (4.18)	4.69 (4.83)
2f	115.5—116.5	3376	1725, 1689	62.61 (62.19)	4.48 (4.18)	4.87 (4.83)
2g	147—148	3280	1743, 1659	68.81 (68.56)	4.56 (4.32)	9.91 (9.99)
2h	142.5—143.5	3256	1746, 1665	60.44 (60.00)	4.34 (4.03)	9.27 (9.33)

Experimental

General Methods. The ^{1}H NMR spectra were recorded on a JEOL Model FX-200 spectrometer. Tetramethylsilane was used as an internal standard. A JEOL temperature-control unit (Model NM-PVTS2) with the thermocouple external to the sample was employed to monitor the probe temperature. The IR spectra were taken by a Hitachi Model 270-30 infrared spectrometer. Attempts to separate acyl-exchanged isomer pairs by high-performance liquid chromatography were performed on a Shimadzu Model LC-6A HPLC apparatus equipped with a 4.6×250-mm ODS(Zorbax) column and a Shimadzu Model SPD-2A UV detector.

Materials and Solvents. *N*-(Substituted benzoyl)-*O*-acetyl-*o*-aminophenols (**1a**—**h**) and *N*-acetyl-*O*-(substituted benzoyl)-*o*-aminophenols (**2a**—**h**) were prepared according to the previously described procedures.[3] The crude products containing small amounts of the starting material, *N*-acetyl-*o*-aminophenol or *N*-(substituted benzoyl)-*o*-aminophenol, were purified by column chromatography over silica gel (70—230 mesh, Merck) using chloroform as the eluent followed by recrystallization from ethyl acetate–hexane or ethyl acetate. IR and ^{1}H NMR spectral analyses of these *N*,*O*-diacyl-*o*-aminophenols, physical properties of which are listed in Table 2, showed them to be pure samples free from the opposite isomers. [^{2}H$_6$]Dimethyl sulfoxide (DMSO-d_6, 99.9 atom%, Aldrich) was used as supplied. Triethylamine (TEA) was fractionally distilled from sodium hydroxide.

Equilibrium Constants. The acyl exchange reactions were initiated by the addition of appropriate amounts of TEA ([TEA] = 1.4—2.9×10^{-2} mol dm^{-3}) to 1 ml of a solution of **1** ([**1**] = 0.15—0.28 mol dm^{-3}) in DMSO-d_6. At regular time intervals, ^{1}H NMR spectra of the reaction mixture placed in a sealed NMR tube cell, whose temperature was maintained at 30±0.3 °C, were recorded. The concentration of **2** was estimated from the area ratio of the *N*-acetyl proton signal (2.0—2.1 ppm) to the *O*-acetyl proton signal (2.3—2.4 ppm). This area ratio at the equilibrium gives the equilibrium constant *K* for a given system. Temperature dependence of the *K* value for each system in DMSO-d_6 was accomplished on a JEOL temperature-control unit. A minimum of 10 min was allowed for the sample solution to equilibrate when the temperature was changed. The same *K* value was obtained also by following the exchange reaction using **2** as the starting material.

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