Tertiary Amine-Catalyzed Acyl Group-Exchange Reactions of *N,O*-Diacyl-*o*-aminophenols

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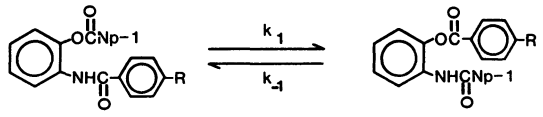
Synopsis. A kinetic study on the base-catalyzed acyl group-exchange reactions of *N,O*-diacyl-*o*-aminophenols was undertaken to show that the formation of the amidate ion should be the rate-determining step in these intramolecular acyl-exchange reactions, and that the electron-withdrawing power of acyl group becomes an important factor to control the relative stabilities of a pair of *N,O*-diacyl-*o*-aminophenols.

The acyl group-exchange reactions of *N,O*-diacyl derivatives of *o*-aminophenol have been extensively studied in the past because these exchange reactions have attracted attention of both theoretical and synthetic organic chemists.[1] The use of HPLC made it possible to separate and analyze quantitatively labile acyl-exchanged products and thus allowed Smith and Elrod to propose the hypothesis that the inductive effects of acyl groups attached to nitrogen or oxygen in the molecule determine the relative stabilities of a pair of *N,O*-diacyl-*o*-aminophenols.[1,2] The failure of this hypothesis to explain the relative stabilities of a pair of *N,O*-acyl-alkoxycarbonyl-*o*-aminophenols[3] prompted us to study the acyl-migration reactions whose mechanism still remains obscure.

We chose *N,O*-(*p*-substituted benzoyl)-(1-naphthoyl) derivatives of *o*-aminophenol as a new system and investigated the solvent, base (tertiary amine), and substituent effects on the rate and equilibrium constants for acyl-exchange reactions, hoping to shed light on the mechanism of these reactions.

The tertiary amine-catalyzed acyl-exchange reactions shown in Scheme 1 follow first-order kinetics in **1** ($2.5—3.3\times10^{-3}$ M, 1 M=1 mol dm^{-3}) at the amine concentration $8.6\times10^{-4}—1.2$ M at 30 °C (correlation coefficient r=0.990—0.999). In addition, the pseudo-first-order rate constants (k), observed typically for **1a—2a** pair, increase linearly in proportion to the amine concentration (r=0.996), suggesting that the reaction is first-order in both **1** and the amine. The acyl exchange was not observed in benzene and 1,2-dichloroethane without the amines, whereas the reaction proceeded to a minor extent in acetonitrile containing no amines. However, such a solvent(acetonitrile)-catalyzed reaction ($k\approx3\times10^{-5}$ min^{-1}) was shown to have a negligible effect on the observed rate constants, e.g., k=0.40 min^{-1} for the triethylamine(1.65×10^{-3} M)-catalyzed reaction of **1a** in acetonitrile. On the other hand, no HPLC peaks attributable to the conceivable intermediates could be detected during the course of the reaction under any conditions. The equilibrium constants (K) were estimated from the concentration ratios [**2**]/[**1**] at equilibrium state and the second-order rate constants (k_1) were obtained by dividing the k values by the amine concentration used. The rate and equilibrium constants thus evaluated are collected in Table 1.

First we discuss the solvent, base, and substituent effects on the rate of the acyl-migration reaction. The increased solvent polarity was found to greatly accelerate the reaction. In addition, the reaction rates have a tendency to increase with increasing the basicity of the amines and the electron-withdrawing power of the



1a: R=Me
1b: R=Cl
1c: R=NO_2

2a: R=Me
2b: R=Cl
2c: R=NO_2

1-Np = 1-naphthyl

Scheme 1.

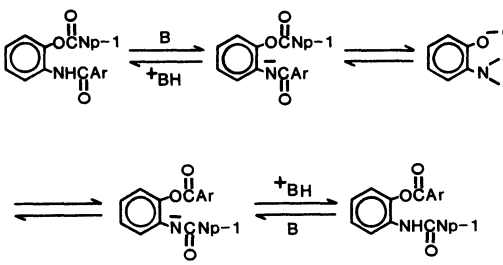
Table 1. Rate and Equilibrium Constants for the Base-Catalyzed Acyl Migration of *N,O*-Diacyl-*o*-aminophenols at 30 °C

1 M=1 mol dm^{-3}

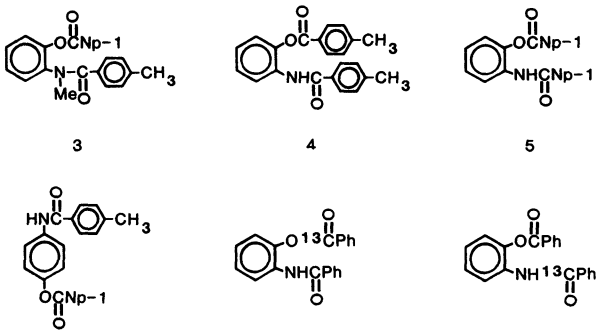
System	Solvent(ε)[a]	Base(pK_a)	$K=k_1/k_{-1}$	k_1/M^{-1} min^{-1}	k_{-1}[b]/M^{-1} min^{-1}
1a—2a	CH_2ClCH_2Cl (10.36)	Triethylamine (11.01[c], 10.75[d])	4.6	0.76	0.17
1b—2b	CH_2ClCH_2Cl	Triethylamine	3.4	2.9	0.85
1c—2c	CH_2ClCH_2Cl	Triethylamine	1.3	11	8.5
1a—2a	CH_2ClCH_2Cl	Tributylamine (10.89[e], 9.93[d])	4.9	0.54	0.11
1a—2a	CH_2ClCH_2Cl	*N*-Methylpiperidine (10.08)[c,d]	5.0	0.15	0.030
1a—2a	CH_2ClCH_2Cl	*N*-Methylmorpholine (7.38)[d]	5.3	0.0018	0.00034
1a—2a	CH_2ClCH_2Cl	Pyridine (5.25)[c,d]	4.6	1.2×10^{-5}	0.26×10^{-5}
1a—2a	CH_3CN (37.5)	Triethylamine	5.1	240	47
1a—2a	Benzene (2.275)	Triethylamine	3.9	0.019	0.0049
7—8	$CDCl_3$	Triethylamine	1.0	0.049	0.049

a) Dielectric constants which were taken from J. A. Riddick and W. B. Bunger, "Organic Solvents," 3rd ed, Wiley-Interscience, New York (1970). b) Determined by using the equation $k_{-1}=k_1/K$. c) "Handbook of Chemistry and Physics," 51st ed, CRC Press (1970). d) "Handbook of Tables for Organic Compound Identification," 3rd ed, CRC Press (1967). e) "Handbook of Biochemistry, Selected Data for Molecular Biology," 2nd ed, CRC Press (1970).

substituents R. All these observations can be nicely explained in terms of the rate-determining formation of the amidate ion. Thus we propose the mechanism shown in Scheme 2 to explain the observed acyl-exchange reactions of *N,O*-diacyl-*o*-aminophenol derivatives. Amundsen and Ambrosio[4] have previously proposed a similar mechanism but they have presented no kinetic evidence in support of their mechanism. The facts that both **1a** in acetic acid and the *N*-methyl derivative **3** in acetonitrile containing triethylamine do not undergo the acyl-exchange reaction to any extent support this mechanism. To ascertain the intra- or intermolecularity of this acyl-exchange reaction, an equimolar mixture of **1a** and **2a** was allowed to react with triethylamine in acetonitrile until the equilibrium is established. Careful HPLC analysis of the mixture indicates no formation of the crossover products **4** and **5**. In addition to the fact that the para-isomer **6** is not subject to the base-catalyzed exchange reaction in acetonitrile the result of this crossover experiment allows us to conclude that the observed acyl-migration is exclusively intramolecular reaction. Furthermore, definitive evidence for the occurrence of acyl-group migration comes from the observation of triethylamine-catalyzed exchange of ^{13}C-labeled benzoyl group between **7** and **8**. No migration of the benzoyl group was observed without the amine also in this case.



Scheme 2.



The equilibrium constants obtained for **1—2** pairs were found to decrease as the electron-withdrawing ability of the substituents R is increased. Smith and Elrod[2] have suggested that the more stable isomer should be the one with the stronger electron-withdrawing acyl group bonded to nitrogen. Because the electron-withdrawing ability of acyl groups in our system should have the following order on the basis of the p*K*a values of the corresponding carboxylic acids: *p*-$NO_2C_6H_4CO$ > 1-naphthoyl > *p*-ClC_6H_4CO > *p*-CH_3-C_6H_4CO, only the relative stabilities of **1c—2c** pair do not conform to their proposal. We felt that the solvent polarity also plays a role in determining the relative stabilities of **1** and its isomer **2**. For this purpose **1a—2a** pair was chosen and the solvent effects on the magnitude of *K* were examined. Although there is a tendency that the increased solvent polarity shifts the equilibrium slightly to the direction of **2**, the equilibrium is not much affected by a change in solvent polarity. On the other hand, the magnitude of *K* is neither very sensitive to a change in the amine bases nor correlate with the basicity of tertiary amines used.

Although in *N,O*-acetyl-chloroacetyl-,[5] *N,O*-(1-naphthoyl)-(*p*-toluoyl)-, and *N,O*-(1-naphthoyl)-(*p*-chlorobenzoyl)-*o*-aminophenols the more stable isomer is the one with the stronger electron-withdrawing acyl group attached to nitrogen as proposed by Smith and Elrod, their hypothesis cannot predict the more stable isomer in acetyl-aroyl,[2] acetyl-alkoxycarbonyl,[3] and 1-naphthoyl-(*p*-nitrobenzoyl) derivatives of *o*-aminophenol, indicating that the inductive effects of acyl groups are not the only factor to determine which isomer is more stable. As mentioned above, however, the results of substituent effects on the magnitude of *K* demonstrate that the electron-withdrawing ability of acyl group plays a crucial role in controlling the relative stabilities of **1—2** pairs.

We expect that the equilibrium constant for the reaction of *N,O*-diacyl-*o*-aminophenol wherein the two acyl groups are the same becomes practically unity. As expected, it was estimated to be unity for **7—8** pair within the limits of experimental accuracy.

Experimental

Materials. *N*-(*p*-Substituted benzoyl)-*o*-aminophenol and *N*-(1-naphthoyl)-*o*-aminophenol were prepared by *N*-aroylation of two equiv of *o*-aminophenol with *p*-substituted benzoyl and 1-naphthoyl chlorides in dichloromethane, respectively. Recrystallization of the crude products from aqueous ethanol gave pure samples whose physical properties are the followings. *N*-Benzoyl-*o*-aminophenol, mp 167.5—168.5 °C; IR (KBr) 3400, 3000 (broad), 1640 cm^{-1}. *N*-(*p*-Toluoyl)-*o*-aminophenol, mp 157.5—158.5 °C; IR (KBr) 3410, 3080 (broad), 1640 cm^{-1}. *N*-(*p*-Chlorobenzoyl)-*o*-aminophenol, mp 180.5—181.5 °C; IR (KBr) 3200 (broad), 1630 cm^{-1}. *N*-(*p*-Nitrobenzoyl)-*o*-aminophenol, mp 206—207 °C; IR (KBr) 3280, 3120 (broad), 1650, 1520, 1350 cm^{-1}. *N*-(1-Naphthoyl)-*o*-aminophenol, mp 194.5—195.5 °C; IR (KBr) 3400, 3100 (broad), 1640 cm^{-1}.

N-Methyl-*N*-(*p*-toluoyl)-*o*-aminophenol was prepared according to the following reaction steps. The crude product obtained was recrystallized from aqueous ethanol and then from benzene-hexane affording colorless crystals, mp 140—141 °C; IR (KBr) 3100 (broad), 1620 cm^{-1}.

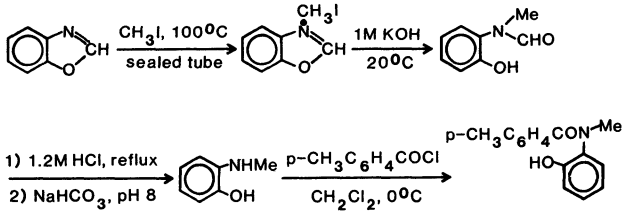


Table 2. Physical Properties of **1a—c**, **2a—c**, and **3—7**

Compd	Mp	IR(KBr)/cm^{-1}			Anal/%, Found(Calcd)		
	θ_m/°C	Ester C=O	Amido C=O	Amido NH	C	H	N
1a	137—138	1735	1675	3430	78.87(78.74),	4.92(4.99),	3.67(3.67)
1b	156—157	1710	1680	3340	71.92(71.73),	4.00(4.01),	3.42(3.49)
1c	177—178	1710	1675	3310	69.88(69.90),	3.85(3.91),	6.82(6.79)
2a	168—170	1730	1650	3180	79.02(78.74),	4.96(4.99),	3.65(3.67)
2b	177.5—179.5	1735	1655	3200	72.10(71.73),	3.95(4.01),	3.47(3.49)
2c	201—203	1735	1650	3200	69.65(69.90),	3.83(3.91),	6.74(6.79)
3	130.5—131.5	1730	1640	—	79.34(78.99),	5.31(5.32),	3.58(3.54)
4	108.5—109.5	1735	1640	3270	76.58(76.52),	5.53(5.51),	4.07(4.06)
5	177.5—178.5	1730	1640	3200	80.95(80.58),	4.54(4.56),	3.36(3.36)
6	235.5—236.5	1730	1650	3300	78.95(78.74),	4.98(4.99),	3.67(3.67)
7	181—182	1690	1655	3270	75.63(75.77),	4.71(4.75),	4.34(4.40)

N,O-Diacyl-*o*-aminophenols (**1a—c**, **2a—c**, **3—5**, and **7**) were derived from the reactions between *N*-acyl-*o*-aminophenols (1 mol) and the corresponding acyl chlorides (1 mol) in the presence of triethylamine (0.9 mol) in dichloromethane. The usual work-up gave the crude products which were purified by column chromatography on silica gel (70—230 mesh, Merck) with chloroform as eluent, followed by recrystallization from benzene-hexane yielding analytical samples whose physical properties are listed in Table 2. IR and HPLC analyses of these diacyl derivatives showed them to be pure samples containing negligible amounts of the opposite isomers. Benzoyl-*carbonyl*-^{13}C chloride (99+ atom% ^{13}C, Aldrich) was employed as acylating agent to synthesize **7**.

N-(*p*-Toluoyl)-*o*-(1-naphthoyl)-*p*-aminophenol (**6**) was prepared by treatment of *N*-(*p*-toluoyl)-*p*-aminophenol (mp 212.5—214 °C, 1 mol), which was obtained from the reaction of two equiv of *p*-aminophenol with *p*-toluoyl chloride, with 1-naphthoyl chloride (1.1 mol) in the presence of triethylamine (1.1 mol) in dichloromethane. Analytical sample, listed in Table 2, was obtained by recrystallizing the crude product from ethyl acetate.

Kinetic Methods. The rate of appearance of **2a—c** or disappearance of **1a—c** was followed with a JASCO twincle HPLC apparatus equipped with an UV detector (254 nm) and a 25 cm×4.6 mm (i.d.) ODS column at 30 °C. Carefully purified acetonitrile containing 35% (by volume) distilled water was used as the developing solvent in all cases. In this developing solvent the acyl-exchange reaction proceeds to a negligible extent. Each kinetic run was carried out by analyzing 2-μl aliquots of the solutions at suitable time intervals. The concentrations of **1** and **2** were determined by employing the linear calibration curves made for each compound under the same analytical conditions.

All the pseudo-first-order rate constants (k) were determined from the following rate equation and the extent of the reaction studied was more than two half-lives, allowing us to get reliable rate constants.

$$\ln\{[\mathbf{2}]_e/([\mathbf{2}]_e-[\mathbf{2}]_t)\} = [\mathbf{1}]_0 kt/[\mathbf{2}]_e$$

where $[\mathbf{1}]_0$, $[\mathbf{2}]_t$, and $[\mathbf{2}]_e$ refer to initial concentration of **1**, concentration of **2** at time t and at equilibrium state, respectively. The acyl-exchange rate of ^{13}C-labeled **7** was determined with a JEOL FX-200 spectrometer (200 MHz) in $CDCl_3$ at 30 °C. Tetramethylsilane was used as an internal standard. Increasing concentration of **8** or decreasing concentration of **7** was estimated from the area ratio of the two signals arising from the ester (164.5 ppm) and amido (165.3 ppm) carbonyl carbons. The migration reaction of ^{13}C-labeled benzoyl group also follows first-order kinetics (r=0.997). The experimental errors in the estimated rate and equilibrium constants are of the order of about 10%.

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