Catalysis of Anilide Ethanolysis by Barium– and Strontium–Ethoxide Pairs and Their Complexes with 18-Crown-6
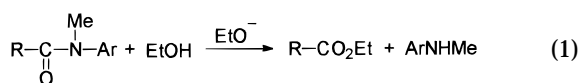
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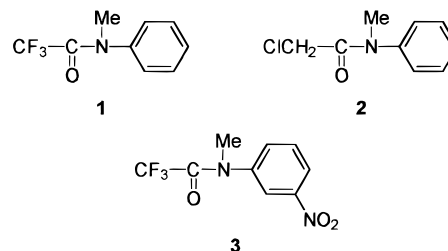
The metal-bound ethoxide species that are quantitatively formed upon mixing equimolar amounts of Me$_4$NOEt and alkaline-earth (Ba, Sr) metal salt in ethanol solution are more reactive than free ethoxide in the cleavage of simple activated amides (e.g. *N*-methyl-2,2,2-trifluoroacetanilide) lacking any donor group for binding to the metal ion. It is suggested that a metal-coordinated solvent molecule acts as a general acid catalyst for expulsion of the aniline leaving group in the rate-determining step. The position of the proton in the transition state is strongly dependent upon structural variations in the aniline portion, as suggested by the magnitude of kinetic solvent isotope effects. Enhanced catalysis is observed upon addition of equimolar amounts of 18-crown-6, which is tentatively interpreted on the basis of the notion that ion pairing is weakened upon cation binding to a crown ether. Important differences concerning metal ion effects in amide vs ester cleavage are pointed out and discussed on the basis of results obtained upon structural modifications of the substrates.

Our studies of the influence of alkaline-earth metal ions on rates of basic ethanolysis of esters[1,2] have shown that the metal-bound ethoxide species that are quantitatively formed in situ from 1:1 mixtures of Me$_4$NOEt and alkaline-earth (Ba, Sr) metal salt are significantly more reactive than free ethoxide in the cleavage of esters and that even larger rate enhancements are obtained upon addition of 1 molar equiv of 18-crown-6 (18C6).[2] Here the reacting species is an ethoxide–metal ion–crown ether ternary complex. We have now discovered that the same metal-bound ethoxide species, including the ternary complexes formed with 18C6, are more efficient catalysts than free ethoxide in the ethanolysis of *N*-methyl-2,2,2-trifluoroacetanilide **1** (eq 1).

$$\text{R}-\underset{\underset{\text{O}}{\|}}{\text{C}}-\underset{\overset{\text{Me}}{|}}{\text{N}}-\text{Ar} + \text{EtOH} \xrightarrow{\text{EtO}^-} \text{R}-\text{CO}_2\text{Et} + \text{ArNHMe} \qquad (1)$$

Since the structural requirements of a catalyst for cleaving amides are clearly different from those for cleaving esters, and since there is a wide interest in the mechanism of metal ion catalysis of amide hydrolysis (solvolysis),[3] we have carried out a kinetic investigation of the catalyzed ethanolysis of **1** with the aim of clarifying the nature of the catalytic phenomenon. Kinetic solvent isotope effects were also measured in a selected number of cases in order to gain a deeper insight into transition-state structure. For comparison purposes, *N*-methyl-1-chloroacetanilide (**2**) and *m*-nitro-*N*-methyl-2,2,2-triflu-

oroacetanilide (**3**) were also included in the kinetic study as representative substrates with modified acyl and aniline portions, respectively. The investigated substrates **1**–**3**, unlike the great majority of substrates used

in mechanistic studies of metal ion catalysis of ester and amide hydrolysis,[3] lack donor groups for binding to the metal catalyst.

Results

The spectrophotometrically monitored[4] basic ethanolysis of **1** takes place quantitatively according to a clean first-order time dependence. First-order rate constants (k_{obs}, s^{-1}) obtained at 25 °C over a 10-fold variation of Me$_4$NOEt concentration (Figure 1) are strictly proportional to base concentration throughout the entire range. The second-order rate constant $k_2 = 0.051$ M^{-1} s^{-1} is comparable in magnitude to the value of 0.104 M^{-1} s^{-1}

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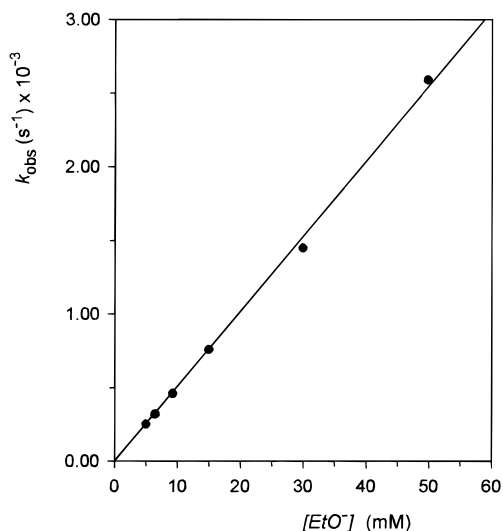
Figure 1. Basic ethanolysis of **1** at 25.0 °C. Observed first-order rate constants k_{obs} (s^{-1}) vs Me$_4$NOEt concentration. The slope of the regression line is 0.051 M^{-1} s^{-1}.

Table 1. Effect of Additives on the Reactions of Anilides 1−3 with Ethanol, Catalyzed by 10.0 mM Me$_4$NOEt

entry	substrate	T, °C	additive(s)[a]	k_{obs}, s^{-1} [b]	k_{rel}
1	**1**	25.0	none	5.10×10^{-4}	1.0
2	**1**	25.0	Ba(SCN)$_2$	7.63×10^{-3}	15
3	**1**	25.0	SrBr$_2$	9.70×10^{-3}	19
4	**1**	25.0	Ba(SCN)$_2$ + 18C6	2.82×10^{-2}	55
5	**1**	25.0	SrBr$_2$ + 18C6	7.82×10^{-2}	150
6	**1**	75.0	none	6.07×10^{-3}	1.0
7	**1**	75.0	Ba(SCN)$_2$	7.59×10^{-2}	12
8	**2**	75.0	none	1.5×10^{-5} [c]	1.0
9	**2**	75.0	Ba(SCN)$_2$	1.2×10^{-4} [c]	8.1
10	**3**	25.0	none	0.677	1.0
11	**3**	25.0	Ba(SCN)$_2$	0.313	0.46
12	**3**	25.0	Ba(SCN)$_2$ + 18C6	2.01	3.0

[a] The concentration of all additives was 10.0 mM. [b] From time course kinetics carried out spectrophotometrically on 0.050 mM substrate solutions, unless otherwise stated. Error limits on the order of ±3−5%. [c] Calculated from initial rates $v_o = \Delta[N$-methylaniline$]/\Delta t$. The *N*-methylaniline product was monitored by HPLC. Estimated errors in v_o on the order of ±10%. The initial concentration of **2** was 0.080 mM.

reported[5] for the methoxide-catalyzed methanolysis at the same temperature.

Ethanolysis of **1** is much faster upon addition of barium and strontium salts (Table 1, entries 2 and 3 compared with 1) and even more so in the presence of the metal complexes with the crown ether ligand (entries 4 and 5 compared with 2 and 3, respectively). Ethanolysis of **2** is inconveniently slow at room temperature. At 75 °C, **2** solvolyses about 400 times more slowly than **1** (entry 8 compared with 6), but the slower reaction does not exhibit the higher sensitivity to metal ions as would be expected on the basis of the reactivity−selectivity principle.[6] In fact, the rate-enhancing factor of the metal ion is lower with **2** than with **1** (entry 9 compared with 7). The *m*-nitro derivative **3** reacts more than 3 orders of magnitude more rapidly than **1** (entry 10 compared with 1). Interestingly, the effect of added Ba^{2+} is slightly rate

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Table 2. Solvent Isotope Effects (k_{ROH}/k_{ROD}) at 25.0 °C for Base-Catalyzed Alcoholysis Reactions of Anilides 1 and 3 and Phenyl Acetate

|	**1**	**3**	AcOPh
MeO$^-$ (MeOH/MeOD)	1.16[a]	0.71[a]	0.61[b]
EtO$^-$ (EtOH/EtOD)	1.16	0.55	0.54
(EtOBa)$^+$ (EtOH/EtOD)	0.66	0.64	0.66[c]
(EtOBa18C6)$^+$ (EtOH/EtOD)	0.57	0.62	0.54[c]

[a] From ref 5. [b] From ref 11. [c] $k_{EtOBa}/k_{EtO} = 34$ and $k_{EtOBa18C6}/k_{EtO} = 61$ in EtOH (data from ref 2).

retarding (entry 11), but the complex with 18C6 shows a 3-fold rate improvement over ethoxide alone (entry 12).

Comparison of rates of the EtO$^-$-, (EtOBa)$^+$-, and (EtOBa18C6)$^+$-catalyzed ethanolyses of **1** and **3** in EtOH and EtOD yielded the kinetic solvent isotope effects listed in Table 2. For comparison purposes, the corresponding data for the ethanolysis reactions of phenyl acetate were also measured. Table 2 shows that isotope effects are quite inverse in most cases. The only exception is the EtO$^-$-catalyzed ethanolysis of **1**, for which a normal isotope effect was found.

Discussion

Mechanism and Metal Ion Effects. The mechanism of the methoxide-catalyzed methanolysis of trifluoroacetanilides is well-established. Schowen et al.[5] showed that rate-limiting decomposition of the tetrahedral intermediate takes place via a transition state in which proton transfer to the leaving nitrogen from a general acid catalyst facilitates C−N bond breaking, as schematically depicted in **I**. The influence of substituents in the
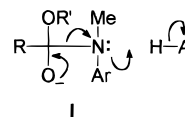
aniline portion and the solvent isotope effect indicate that decomposition of the tetrahedral intermediate occurs by parallel pathways involving either predominant proton transfer with little C−N bond breaking or predominant C−N bond breaking with little proton transfer (solvation catalysis). These two mechanisms are conveniently illustrated in the More O'Ferrall diagram of Figure 2 by pathways a and b, respectively. The asterisks denote positions of valence isomeric transition states. The former mechanism dominates with electron donors (including hydrogen) and the latter with electron acceptors. But independent of the degree of advancement of bond-making and bond-breaking processes, there is no doubt that in the transition state there is a substantial dispersal of the negative charge that in the reactant state is concentrated on the alkoxide oxygen. If one makes the reasonable assumption that ethanolysis takes place according to the same mechanism as methanolysis, the conclusion is drawn that in the absence of further effects ethanolysis should be inhibited, not accelerated, by metal ions, on account of a stronger interaction with the more localized negative charge in the reactant state than with the more dispersed negative charge in the transition state. We see in Table 1 that this is not the general case.

The simplest mechanism that could account for the enhanced catalysis observed in the presence of metal ions is shown in **II**, where a metal coordinated ethanol molecule serves as general acid catalyst for C−N bond
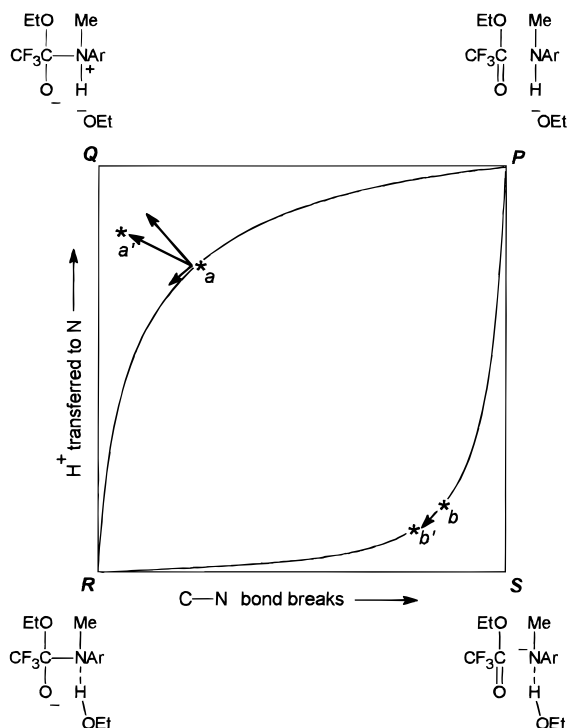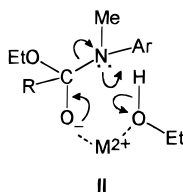
Figure 2. More O'Ferrall diagram for the decomposition of the tetrahedral intermediate in base-catalyzed alcoholysis reactions of anilides. The two competing pathways are indicated as a and b and the asterisks denote the positions of valence isomeric transition states. The central portion of the diagram is a high-energy region.

cleavage. Whenever proton transfer from a general acid to the leaving nitrogen is significant, i.e., with amides **1** and **2**, the interaction of the metal ion incorporated in the transition state complex with the fractional negative charge developing at the oxygen atom of the coordinated ethanol molecule is an important stabilizing factor. In other words, the transition state behaves as a bidentate chelating ligand whose ligating ability outweighs that of the monodentate ethoxide ligand. But with the *m*-nitro derivative **3**, for which the importance of general acid catalysis is low, the metal ion complexing ability of the transition state decreases to such an extent that inhibition instead of catalysis is observed upon addition of barium ion.

An important point is whether efficient general acid catalysis of C−N cleavage by the acidic metal ion complexed solvent molecule may result in switching the rate-determining step to formation of the tetrahedral intermediate.[3a] This possibility is definitely ruled out by the finding that metal ion catalysis is less efficient with the less reactive **2** than with the more reactive **1**. In ester ethanolysis, where addition to the carbonyl group is rate-limiting, we found that $k_{\text{EtOBa}}/k_{\text{EtO}}$ is 34 with phenyl acetate,[2] but drops to 7.0 with the more reactive *p*-nitrophenyl acetate.[1a] It is worth noting that application

of Thornton's reacting bond rules[7] to the decomposition of transition state **I** indicates that replacement of CF$_3$ with CH$_2$Cl reduces the extent of proton transfer to nitrogen. Hence, a lower sensitivity to metal ions is expected for the ethanolysis reaction of **2**, which is consistent with experimental findings.

Enhanced catalysis is observed upon addition of 1 mol equiv of 18C6. With **1**, accelerations as high as 55- and 150-fold are brought about by the barium and strontium complexes, respectively. Interestingly, in the barium reaction of **3**, a switch is observed from inhibition to catalysis. Although our data do not allow a dissection of rate data into reactant state and transition state effects, a basis for discussion of the observed effects is provided as before[2] by the argument that ion pairing is generally weakened by cation binding to a crown ether.[8] Consequently, the 18C6-enhanced metal ion catalysis would imply that complexation of the metal ion to 18C6 destabilizes the metal ion−ethoxide pair more strongly than the metal ion−transition state pair, with the net result that the activation free energy is decreased.

Isotope Effects. According to Schowen,[9] kinetic solvent isotope effects can be regarded as containing both secondary (sec) contributions, from hydrogens not undergoing transfer, and primary (pri) contributions, from

$$(k_\text{H}/k_\text{D}) = (k_\text{H}/k_\text{D})_\text{sec}(k_\text{H}/k_\text{D})_\text{pri} \qquad (2)$$

any hydrogen that is undergoing transfer, as shown in eq 2. The secondary contribution in the basic methanolysis of trifluoroacetanilides was estimated by Schowen et al.[5] as $(0.72)^3 = 0.37$ from More O'Ferrall's fractionation factor $\varphi = 0.72$ for the methoxide ion,[10] assuming triple solvation. Thus, $(k_{\text{CH}_3\text{OH}}/k_{\text{CH}_3\text{OD}})_\text{pri}$ is calculated to be about 3.1 for **1**, and 1.9 for **3**.[5] The value of 1.9 is assigned to hydrogen bonding from the spectator solvent molecule to the leaving nitrogen in mechanism b, while the value of 3.1 is easily ascribed to a primary isotope effect in mechanism a, where proton transfer to nitrogen dominates.[5] A primary isotope effect of about 3 is clearly consistent with a rather late transition state in which the proton is more than 50% transferred to the aniline nitrogen, as shown in Figure 2 for the transition state of pathway a.

Extension of the above discussion to the ethanolysis reactions involves a consideration of the $(k_{\text{EtOH}}/k_{\text{EtOD}})_\text{sec}$ quantity. The required fractionation factor φ of the ethoxide ion is not available, but the close similarity of the magnitudes of the isotope effects for the basic solvolysis reactions of **1** and **3** in methanol and ethanol (Table 2) suggests secondary contributions to be of comparable magnitudes in the two solvents. This hypothesis is corroborated by the very similar isotope effects obtained for the mechanistically simple alcoholysis reactions of phenyl acetate, for which rate-limiting formation of the tetrahedral intermediate is well-established.[11] We

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conclude therefore that cleavage of anilides **1** and **3** not only occurs in ethanol solution according to the same mechanism proposed by Schowen et al.[5] for the methanolysis reaction, but also that the positions of the proton in the two valence isomeric transition states are very similar in the two solvents.

Interpretation of metal ion influences on solvent isotope effects in terms of variations in transition state structure requires at least a rough knowledge of metal ion induced variations in the secondary contributions. We note (Table 2) that the isotope effect in the ethanolysis of phenyl acetate, that is devoid of primary contributions, is remarkably insensitive to the presence of either the barium ion or its complex with 18C6. This finding provides a strong indication that the magnitude of secondary contributions is hardly affected by the metal ion.[12] By this hypothesis the primary contribution to the solvent isotope effect in the ethanolysis of **1** is significantly reduced by both the barium ion and its crown complex to a value of ca. 2 or even less, whereas it is left substantially unchanged in the ethanolysis of **3**.

Application of Thornton's reacting bond rules with the aid of the diagram of Figure 2 provides a rationale for the above conclusions. Addition of barium ion (or its crown complex) stabilizes corner P relative to R because the metal ion binds more strongly to the ethoxide than to the tetrahedral intermediate on account of the more basic character of the former. Furthermore, the metal ion strongly stabilizes corner Q because it can favorably interact with the two oxide ions, but has a minor influence on the energy of corner S. Thus, addition of the metal ion should move the transition state for mechanism a from *a along the reaction coordinate toward R and, to a much larger extent, perpendicular to the reaction coordinate toward Q. The net result expected is a new transition state structure at *a′. Compared to *a, the new structure has a greater degree of proton transfer to nitrogen which, in line with observations, causes a decrease in the primary contribution to the solvent isotope effect. When a similar reasoning is applied to transition state *b, a relatively minor change along the reaction coordinate toward R and little or no change perpendicular to the reaction coordinate are predicted. The degree of proton transfer to nitrogen in the new position *b′ is so close to that in *b that any variation in the primary contribution to the solvent isotope effect should be hardly noticeable, which is again in line with experimental findings.

Concluding Remarks

The possible involvement of a metal-coordinated solvent (water) molecule as general acid catalyst in the expulsion of the amine leaving group had been considered in papers by earlier workers,[13,3a] but it was not until 1992 that Suh et al.[14] reported convincing evidence of the general acid role of a Cu(II)-bound water molecule in amide hydrolysis. The results reported in this paper add to the above evidence and point to general acid catalysis by a metal-bound solvent molecule in the expulsion of the amine leaving group as a fundamental mode of catalysis by metal ions in amide cleavage reactions. Furthermore, they widen considerably the scope of s-block metal ions as efficient catalysts of acyl transfer processes.[15] Finally, the very finding that a barium or strontium ion is still catalytically active after complexation to a crown ether proved to be useful in the construction of more elaborate catalysts with esterase and amidase activity capable of substrate recognition in which the catalytic site was provided by a crown ether complexed alkaline-earth metal ion. The results of this investigation will be reported in due time.

Experimental Section

Amides **1**[4] (mp 27.6−28.1 °C; lit.[4] mp 26−28 °C), **2**[16] (mp 68−69 °C; lit.[16] mp 68−69 °C), and **3**[4] (mp 73.5−74 °C; lit.[4] mp 70.5−72.5 °C) were prepared according to standard literature procedures. Spectrophotometric rate measurements were carried out in the thermostated cell compartment of a diode array spectrometer. Reactions in EtOH and EtOD were determined successively within a short time interval for each compound. Each measurement was carried out in duplicate. Errors in the (k_{EtOH}/k_{EtOD}) quantities are on the order of 0.01−0.02. HPLC rate measurements were carried out on a liquid chromatograph fitted with a UV−vis detector operating at 230 nm. Samples of the reaction mixture were withdrawn at time intervals, quenched with dilute hydrobromic acid, and subjected to HPLC analysis after addition of a known amount of the internal standard (4-methylanisole). Analyses were carried out on a Supelcosil LC-18-DB column (25 cm × 4.6 mm i.d.; particle size 5 μm) with 55:45 (v/v) MeOH (30 mM sodium 1-heptanesulfonate)−H_2O (30 mM sodium 1-heptanesulfonate and 8.0 mM H_3PO_4/50 mM NaH_2PO_4 buffer, pH = 3) as mobile phase, at a flow rate of 0.65 mL/min. The mobile phase was prepared daily and stored at 4 °C when not used. Other materials, apparatus, and techniques were as reported previously.[1,2]

(12) This is understandable if the metal−ethoxide pair has the structure of a solvent-separated ion pair, where at least the first solvation sphere of the ethoxide is substantially unchanged compared with the free ion. Tight pairing of the barium cation to the ethoxide would presumably result in a reduction of the number of ethanol molecules hydrogen bonded to the latter and, consequently, in a substantial increase in the (k_{EtOH}/k_{EtOD})$_{sec}$ quantity.

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