Hydrolysis of Esters and Amides in Strongly Basic Solution. Evidence for the Intermediacy of Carbanions

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Received July 24, 1980

Kinetic studies of the decomposition of the carbanions derived from a number of esters and amides of *p*-nitrophenylacetic acid in strongly basic solution have been carried out. Kinetic solvent isotope effects and the large Hammett ρ value for substituents on the aromatic ring of substituted phenyl esters of *p*-nitrophenylacetic acid suggest decomposition occurs by an E1cB mechanism. Furthermore, it appears that the carbanion can decompose by either an ionic or a free-radical mechanism, depending on the nucleofugality of the leaving group. An intermediate predicted to be 4-nitrophenyl ketone has been detected spectroscopically in a number of cases.

The intermediacy of carbanions in the hydrolysis of esters (Scheme I) has been reported in a number of cases.[1-4]

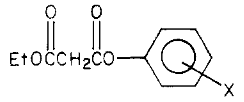
Scheme I

$$RCH_2C(O)OR' + OH^- \rightarrow R^-CHC(O)OR' + H_2O \quad \text{(i)}$$

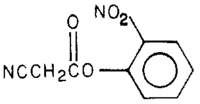
$$R^-CHC(O)OR' \rightarrow RCH{=}C{=}O + R'O^- \quad \text{(ii)}$$

$$RCH{=}C{=}O + H_2O \rightarrow RCH_2COOH \quad \text{(iii)}$$

This has generally been interpreted as evidence of ester hydrolysis by an E1cB mechanism, with the carbanion decomposing to a reactive ketene (reaction ii) which subsequently adds water (eq iii). Bruice has reported such a mechanism for the basic hydrolysis of substituted phenyl esters of type **1**,[1] the *o*-nitrophenyl ester of cyanoacetic acid (**2**),[2] the *o*-nitrophenyl ester of *S*,*S*-dimethylsulfoniumacetic acid (**3**),[2] and substituted phenyl esters of acetoacetic acid (**4**),[3] in aqueous solution. Trapping of the intermediate ketene with added aniline has been reported by Bruice[3] for compound **4g**. All of the above esters could be considered activated to such a process because of the presence of good electron-withdrawing groups (e.g., CN, COOEt, $COCH_3$, etc.).



1, X = 2-NO_2 or 4-NO_2



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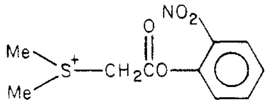

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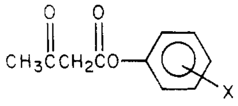
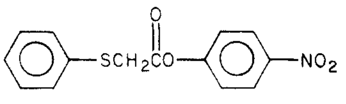


4a, X = H
b, X = 4-Cl
c, X = 3-Cl
d, X = 4-CO_2Me
e, X = 4-COMe
f, X = 3-NO_2
g, X = 4-NO_2

Tagaki[4] has reported that the hydrolysis of esters **5** and **6a** occurs by an E1cB mechanism in the presence of micelles of cetyltrimethylammonium bromide (ctab) but by the normal addition–elimination ($B_{Ac}2$) mechanism in water. The occurrence of the E1cB mechanism for esters **5** and **6a** in micelles of ctab is explained by the stabilization of the carbanion in the micellar phase of a cationic surfactant.[4] We have shown[5] that the hydrolysis of the corresponding amides **7** and **8** does not occur by the E1cB mechanism in micelles of ctab, presumably because ionization is not complete in ctab and because the amine leaving group is poor, compared to *p*-nitrophenoxide ion. Thus the competing $B_{Ac}2$ reaction of the unionized amide is the dominant reaction.



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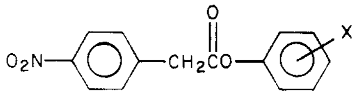
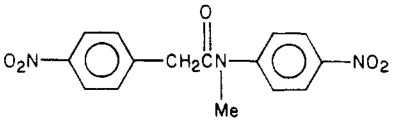


6a, X = 4-NO_2
b, X = 4-CN
c, X = 3-NO_2
d, X = 4-CF_3
e, X = 3-CF_3
f, X = 3-Cl
g, X = 4-Cl
h, X = H
i, X = 4-Me
j, X = 4-OMe
k, X = 4-NMe_2



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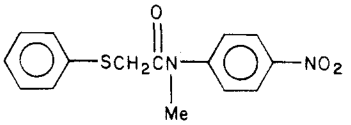

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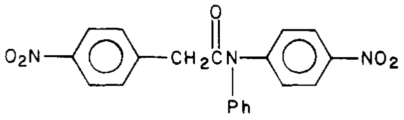
In an attempt to provide conditions that may favor reaction by an E1cB mechanism, we have now looked at the basic hydrolysis of esters **6a–k** and amides **7** and **9** in 80% (v/v) dimethyl sulfoxide (Me_2SO)–water. It was hoped that the far greater basicity of hydroxide ions in 80% Me_2SO–water (6 pK units)[6] than in water would re-



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[2] Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 3003.
[3] Pratt, R. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 5956.
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[5] Broxton, T. J.; Duddy, N. W. *Aust. J. Chem.* **1980**, *33*, 1771.

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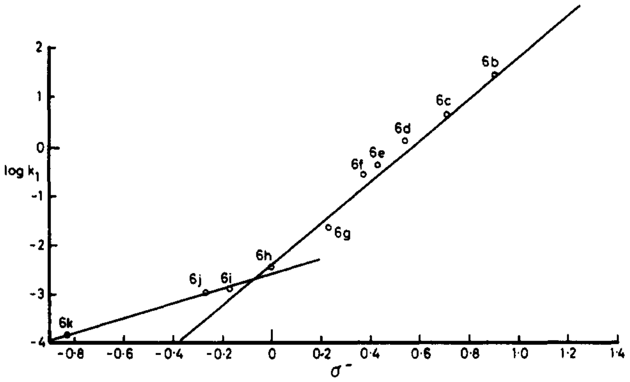


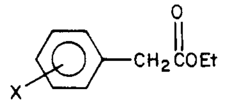
Figure 1. Hammett plot for the rate of loss of a carbanion from esters **6b–k** at 30.0 °C in 80% Me_2SO–water.

sult in complete ionization of the methylene groups in 80% Me_2SO–water. Thus the competing $B_{Ac}2$ mechanism of the unionized substrate would be effectively inhibited, allowing the carbanion pathway to dominate.

Discussion

(a) Carbanion Formation. Addition of an aqueous solution of barium hydroxide to a Me_2SO solution of compounds **6b–k**, **7**, or **9** resulted in the very rapid production of an intense purple color (λ_{max} = 550 nm) for esters **6b–k** and an intense blue color (λ_{max} = 590 nm) for amides **7** and **9**. This coloration was attributed to the carbanion as shown in eq i. No purple color was detected, however, for the *p*-nitro-substituted ester, **6a**. For compound **6f**, the half-life for the production of this species was about 4 ms as measured by stopped-flow kinetics. This leads to a rate constant for the production of this species (k_1) of 173 s^{-1}.

Colorations have previously been observed[7] in the basic hydrolysis of ethyl arylacetates **10**, and the intensity de-



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creased during hydrolysis, resulting in a colorless solution. In a basic ethanolic solution, the intensity of the color did not decrease significantly with time, thus allowing the position of maximum absorbance to be determined. Maximum absorbances were observed at 440 nm (**10**, X = 4-$COCH_3$), 535 nm (**10**, X = 4-CN), 540 nm (**10**, X = 4-NO_2), and 600 nm (**10**, X = 2-NO_2). The red color of an alkaline solution of 4-nitrobenzyl cyanide is attributed to an anion of similar type.[8] For the 4-nitro ester (**10**, X = 4-NO_2) the intensity of the coloration was low and the proportion of ester ionized was estimated to be only 1.5% and 0.5%, respectively, in 56% (by weight of organic solvent in an aqueous–organic mixture) acetone and in 85.4% ethanol.

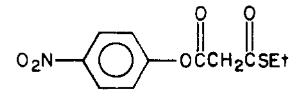
Previous studies[5] on compound **7** in the presence of micelles of ctab indicated that the proportion of amide ionized was approximately 22% if we assume first that ionization is complete in 80% Me_2SO–water and, second, that the extinction coefficient of the carbanion is not greatly solvent dependent.[7] In the presence of 80% Me_2SO–water the coloration is intense, and the intensity is not increased by increasing the concentration of hydroxide ions. This suggests that the ionization is complete in 80% Me_2SO–water solvent mixture.

Table I. Rate Constants (k_2) for Carbanion Loss (λ = 550 nm) from Esters 6b-k and Amides 7 and 9 in 80% Me_2SO-Water[a]

compd	X	10^3k_2, s^{-1}		
		air	N_2	O_2
6a	4-NO_2	*b*		
6b	4-CN	26200[c]		
6c	3-NO_2	4390[c]		
6d	4-CF_3	1296[c]		
6e	3-CF_3	420[c] (370)[d]		
6f	3-Cl	270[c] (260)[d]		
6g	4-Cl	22[e]		21.5
6h	H	3.6		
6i	4-Me	*f*	1.17	1.88
6j	4-OMe	0.94	1.07	1.50
6k	4-NMe_2	0.22	0.14	0.41
7		0.9[g]		
9		0.46[g]		

[a] At 30.0 °C with [OH^-] = 0.0017 M as Ba^{2+} salt and [substrate] = 5 × 10^{-5} M. [b] No carbanion detected for this compound. [c] Reaction carried out by the stopped-flow technique. Carbanion loss was followed at 620 nm because of interference by an intermediate (λ = 495 nm) at 550 nm. [d] Rate constant for reaction in 80% Me_2SO–D_2O. [e] Rate constant for hydroxide concentrations within the range 0.0006–0.002 M. [f] Reaction in the presence of air gave a curved first-order rate plot. Linear kinetic plots were obtained under N_2 and O_2 atmospheres. [g] Carbanion loss at 590 nm.

Norman[7] concluded that the hydrolysis of the ethyl esters **10** occurs by the normal $B_{Ac}2$ mechanism and that the small amount of ionization does not lead to a significant amount of E1cB reaction. Bruice,[1-3] on the other hand, suggests that esters **1–4** do indeed hydrolyze by an E1cB mechanism, and this is further substantiated by the trapping of the intermediate ketene with added aniline in the reaction of compound **4g**. The carbanion species from these esters were observed in the UV spectra at higher wavelength and greater intensity than the neutral esters. For compound **11**, the absorption maximum was at 268.5



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nm (log ε ~4.13) while for the corresponding carbanion, λ_{max} = 295 nm (log ε ~4.67).[3] Experimentally the maximum amount of carbanion observed during hydrolysis was 10% of the initial concentration of compound **11** 36 ms after mixing.[3] The observation of the maximum absorbance for the carbanions from esters **6b–k** and amides **7** and **9** at longer wavelength (590 nm) than the carbanion from compound **11** is presumably a result of the greater delocalization of the charge in the former cases.

Bruice[3] suggests that a generally applicable criterion for distinguishing between E1cB and $B_{Ac}2$ mechanisms (with an inert carbanion) is the deuterium solvent isotope effect. E1cB reactions are characterized by k_{H_2O}/k_{D_2O} ratios ≤1.3.[9] In this work we have found a solvent isotope effect on k_2, the k_{H_2O}/k_{D_2O} ratio (in the presence of 80% Me_2SO) being 1.14 for compound **6d** and 1.04 for compound **6f**.

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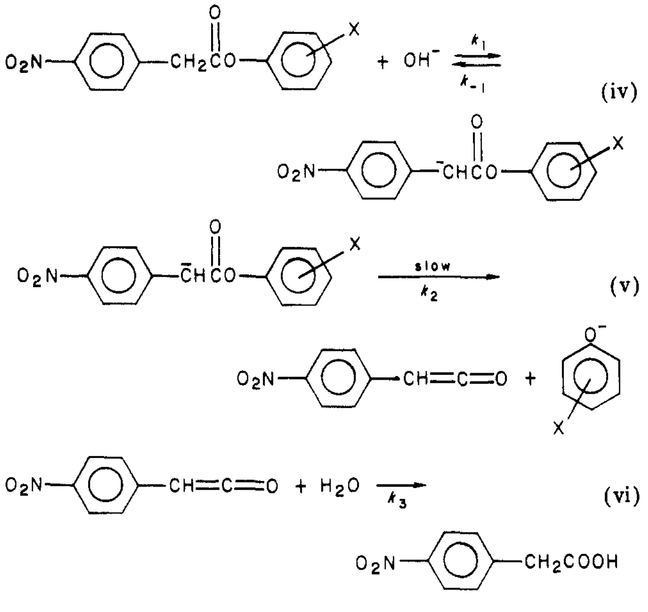
(6) Boyd, R. H. "Solute—Solvent Interactions"; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969; p 97.

(7) Norman, R. O. C.; Ralph, P. D. *J. Chem. Soc.* **1963**, 5431.

(8) Caldin, E. F.; Harbron, E. *J. Chem. Soc.* **1962**, 2314.

(9) More recent work has, however, criticized the use of the kinetic solvent isotope effect as a mechanistic probe for E1cB ester solvolyses. See: Kaiser, E. T.; Kezdy, F. J., Eds. "Progress in Bioorganic Chemistry"; Wiley: New York, 1976; Vol. 4, p 193.

Scheme II



Rate constants for carbanion loss from compounds **6b–k**, **7**, and **9** in basic 80% Me_2SO–water are in Table I. A Hammett plot for the rate of loss of carbanion from compounds **6b–k** is in Figure 1. Correlation with σ^- for electron-withdrawing para substituents (i.e., *p*-cyano) is much better (correlation coefficient $r = 0.991$) than with σ ($r = 0.968$). The σ^- fit and the large ρ value (4.4) for compounds **6b–h** are consistent with an E1cB reaction although little previous work has been done on the effects of substituents on E1cB reactions in only slightly aqueous media. Correlation with σ^- was also noted in the Hammett plot for the rate of hydrolysis of substituted phenyl acetoacetates **4a–g** in water.[3] However, a major difference between these two Hammett plots is that for esters **6b–k** the points lie on two different lines whereas for esters **4a–g** all points fall on a single line (ρ 2.8). Esters **4a–g** include compounds substituted with groups from hydrogen to *p*-nitro. For esters **6b–h** (i.e., 4-CN to H), $\rho = 4.4$ ($r = 0.991$) whereas for esters **6h–k** (H to 4-NMe_2), $\rho = 1.6$ ($r = 0.988$). Furthermore, it was noticed that the rate of loss of carbanions from compounds **6i–k**, **7**, and **9** was dependent on the atmosphere. The reaction was catalyzed by oxygen and to a lesser extent by air. The rates used in the Hammett plot for these compounds were those obtained under a nitrogen atmosphere. The rate of loss of carbanions obtained from compounds **6b–h** was not dependent on the atmosphere. On the basis of the Hammett plot it was concluded that the decomposition of the carbanion can occur by more than one mechanism. On the basis of the varied dependence of the rate of decomposition of carbanions on the atmosphere it was concluded that the two mechanisms were ionic (large ρ value and no effect of the atmosphere; compounds **6b–h**) and free radical (smaller ρ value and dependence on the atmosphere; compounds **6i–k**, **7**, and **9**).

(b) Ionic Decomposition of the Carbanion. Decomposition of the carbanions containing good leaving groups most likely occurs by the loss of the substituted phenoxide ion and production of ketene (Scheme II). This mechanism is similar to that proposed by Bruice[1-3] for esters **1–4**. Correlation of the rates of decomposition with σ^- in the Hammett plot is expected in both cases (compounds **4a–g** and **6b–k**) since both reactions involve loss of substituted phenoxide ions and since the σ^- scale was originally established to correlate the ionization of substituted phenols.[10] The magnitude of ρ for reaction of compounds **6b–h** in 80% (v/v) Me_2SO–water (4.4) is greater than for reaction of compounds **4a–g** in water (2.8). This is probably a result of the solvent differences. Because of the reduced solvation of anions in dipolar aprotic solvents, e.g., Me_2SO,[6] the demand for substituent stabilization is greater in these solvents[11] than in protic solvents, e.g., H_2O. This, of course, is reflected in the magnitude of ρ. For example, in the basic methanolysis of amides,[11] the effect of substituents in the amine ring on the rate of reaction via the solvent-assisted bond breaking mechanism is greater in 80% Me_2SO–water ($\rho = 5.4$) than in methanol ($\rho = 2.8$). For compound **6a** (X = 4-NO_2) no carbanion intermediate is observed by stopped flow spectrophotometry. Extrapolation of the Hammett plot to $\sigma^- = 1.27$ (a reasonable value for σ^- of the 4-nitro group in this reaction)[12] yields a prediced rate of loss of carbanion ($k_2 = 1120$ s^{-1}). We predict that for this compound carbanion formation is rate determining and that the carbanion does not accumulate (i.e., irreversible E1cB).[13a]

Table II. Rate Constants (k_3) for Decomposition of Intermediate Detected (λ_{max} = 495 nm) during the Reaction of Esters **6b–f** in 80% Me_2SO-Water[a]

compd	X	k_3,[b] s^{-1}
6b	4-CN	0.5
6c	3-NO_2	0.5
6d	4-CF_3	0.5
6e	3-CF_3	0.28 (0.012)
6f	3-Cl	0.20 (0.024)

[a] At 30.0 °C with $[OH^-] = 0.0017$ M as Ba^{2+} salt and [substrate] = 5×10^{-5} M. [b] Values in parentheses are for reaction in 80% Me_2SO-D_2O.

The rate of formation of carbanion (k_1) should not greatly depend on the nature of substituent X. For compound **6f** (X = 3-Cl) $k_1 = 173$ s^{-1}. Thus, provided that k_1 is indeed not greatly dependent on the substituent X, $k_1 < k_2$ for compound **6a**, leading to the irreversible E1cB mechanism, whereas for compound **6b** and for all others $k_1 > k_2$ ($k_2 = 26$ for compound **6b** and is less than that for compounds **6c–k**), leading to the Type 11, E1cB mechanism which is also called the E1 anion mechanism[13a] and involves the non-steady-state production of carbanion.[14,15] Type 11 E1cB reactions have previously been reported by Rapoport, and the necessary criteria for its occurrence are a highly acidic proton (e.g., the CH_2 group in compounds **6b–k**, **7**, and **9**) and a poor leaving group (e.g., the substituted phenoxide ions except the *p*-nitro compound). Further evidence for the occurrence of the Type 11 E1cB mechanism in this case is that the rate of loss of carbanion is not dependent on the [hydroxide] (Table I).[13a] This also excludes the E2 mechanism as an explanation, at least for the 4-chloro compound, **6g**.

Decomposition of the ketene (k_3) is expected to be fast, but it is possible that if the rate of decomposition of carbanion (k_2), i.e., ketene production, is faster, then the ketene should accumulate in solution, and its subsequent decomposition (k_3) should be measurable. For compounds with very good leaving groups (**6b–f**) an intermediate has been detected by stopped-flow measurement (λ_{max} 495 nm).

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[10] Jaffe, H. H. *Chem. Rev.* **1953**, *53*, 191.

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Rate constants for the decomposition of this intermediate are given in Table II. For compounds in which the production of the intermediate is complete before its decomposition is monitored (i.e., **6b,c,d**; $k_2 > 0.5\ s^{-1}$), a constant rate of decomposition of the intermediate ($k_3 = 0.5\ s^{-1}$) was observed.

This suggests a common intermediate is formed from compounds **6b,c,d**, and the most likely candidate for that is 4-nitrophenyl ketene; i.e., the observed rate of loss of the intermediate is k_3 ($0.5\ s^{-1}$). For compounds **6e** and **6f** the rate of ketene production (k_2) is slightly less [$0.42\ s^{-1}$ (**6e**) and $0.27\ s^{-1}$ (**6f**)] than its rate of decomposition; so although it can be seen to accumulate in solution, its apparent rate of decomposition is less than for compounds **6b,c,d**.

The maximum absorbance detected at 495 nm was 2.7 for compound **6d** but only 2.5 for **6e** and 1.9 for **6f**. This is consistent with the above discussion.

Interestingly, no evidence for the production of this intermediate could be detected for compound **6a**. We would initially have expected to see the intermediate for this compound since we predict that carbanion formation (k_1) is rate determining and that decomposition (i.e., ketene production $-k_2$) is fast. However, the detection of the intermediate ketene ($\lambda_{max} = 495$) is made difficult since the *p*-nitrophenoxide ion formed has an intense yellow color ($\lambda_{max} = 400$ nm), and this may effectively mask the presence of any ketene in the solution.

The observed rate of decomposition of the intermediate (ketene) from compounds **6e** and **6f** was considerably faster (rate 8–23) in 80% Me_2SO-H_2O than in 80% Me_2SO-D_2O. Whether this result constitutes a valid solvent isotope effect or not is the subject of further study. Solvent isotope effects[16] are usually within the range $k_H/k_D = 1-5$, and so the above result may not be solely the result of the solvent isotope effect.

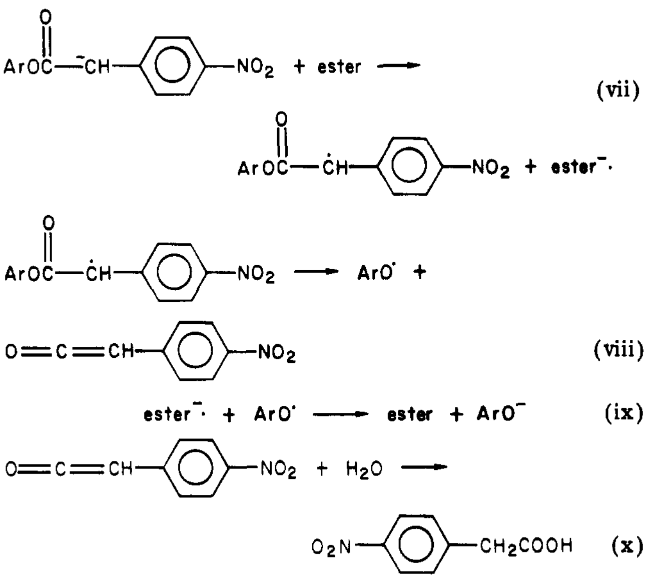
(c) Free-Radical Decomposition of Carbanion. For compounds with poor leaving groups (e.g., esters **6i–k**) it appears that a free-radical mechanism of decomposition is operational. This change of mechanism from an ionic one is indicated by the change in slope of the Hammett plot and the dependence of the rate of carbanion loss on the atmosphere.

ESR studies at −196 °C, in a solid glass, have confirmed the presence of free radicals for compound **6i**. Free radicals could not be detected in solution at room temperature. Unfortunately the ESR spectrum of the radical obtained in a solid phase at −196 °C had poor resolution, and no information about the structure of the radical intermediate could be obtained from this spectrum. Attempts to obtain a spectrum in dimethylformamide solution at 20 °C were unsuccessful.

An ESR scan with the empty tube in the cavity of the spectrophotometer excluded the possibility of paramagnetic impurities in the ESR tube leading either to the ESR signal for compound **6i** or to its poor resolution.

The rate of decomposition of the carbanion from compound **6k** ($X = 4\text{-}NMe_2$) was increased by atmospheric oxygen (Table I), by the addition of *p*-dinitrobenzene (1.5×10^{-4} M; $10^3k_2 = 0.41\ s^{-1}$; cf. $10^3k_2 = 0.14\ s^{-1}$ for reaction under nitrogen), by the addition of ferric phenanthroline complex, and by the addition of ferricyanide ions. This suggests that the carbanion decomposes by electron transfer. As a possible mechanism for the radical decomposition of the carbanions from esters **6i–k** we propose Scheme III.

Scheme III



Decomposition of carbanions by electron transfer to aromatic nitro compounds has previously been reported.[17]

The electron acceptor in step vii is suggested to be a trace of unionized ester which, being an aromatic nitro compound, should readily accept an electron from the carbanion.[18] Step viii involves decomposition of the radical by a β scission which is a standard mechanism for the unimolecular breakdown of free radicals.[13b] In step ix electron transfer is postulated from the radical anion of the ester to the substituted phenoxy radical. This is reasonable since it is known that radicals are readily reduced (e.g., alkoxy radicals by ferrous ions)[19] and that radical anions are good reducing agents (good electron-transfer agents).[20,21] Step x involves the reaction of the transient ketene with water, producing the acid product.

Steps vii–ix constitute a chain by which the carbanion may be consumed by a small quantity of unionized ester, and the substituted phenoxy radicals are reduced to substituted phenoxide ions.

Oxygen gas, *p*-dinitrobenzene, ferric phenanthroline complex, and ferricyanide ions may all accelerate this reaction by assuming the role of the ester in Scheme III.

Bruice obtained no evidence of free radical intermediates in the E1cB reactions that he studied.[1-3] The Hammett plot for the substituent effects on decomposition of the acetoacetate esters **4** was linear, but it is of interest that only substituents from hydrogen to 4-nitro were studied. The Hammett plot for the hydrolysis of esters of *p*-nitrophenylacetic acid (**6**) is linear within this range of substituents. It would be interesting to extend Bruice's series to esters containing poorer leaving groups to see if evidence of a radical reaction could be obtained in that series as well. The choice of solvent, water for compound **4** and 80% Me_2SO–water for compound **6**, may also be an important factor in determining the mechanism. The dipolar aprotic solvent would hinder an ionic breakdown of the carbanion relative to water, and, in addition, the radical process may be more favorable in this solvent than in water.[22]

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(d) Fate of the Carbanion from Amides 7 and 9. The carbanions from amides 7 and 9 would most likely decompose by a free-radical electron-transfer route analogous to Scheme III. This would be expected since the amine anions are poorer leaving groups than the phenoxide ions.[5] The rate of decomposition of the carbanions from the amides 7 and 9 (Table I) reflects the poor nucleofugality of the amine anions, and the rates for these compounds fall within the range of the rates of decomposition of esters **6i–k**. Furthermore, the rate of decomposition of the carbanions from compounds 7 and 9 is sensitive to the atmosphere and is accelerated by added *p*-dinitrobenzene (10^3k_2 = 0.7 for compound 7 in the presence of 0.004 M *p*-dinitrobenzene).

The less than quantitative yields of amine from these amides (e.g., approximately 50% from compound 9) may reflect the difficulty of electron transfer to an Ar–N–Ph radical (analogous to step ix in Scheme III) compared to the situation in the ester reactions. Certainly the Ar–N–Ph anion is much less stable than the phenoxide ions produced in step ix for the esters.

(e) Product Studies. Product studies for compounds **6a–k** were carried out by NMR spectroscopy in 80% $Me_2SO-d_6-D_2O$ solution under conditions of both excess base and excess ester. In all cases the detected products were the substituted phenol and *p*-nitrophenylacetic acid in greater than 80% yield (relative to an internal NMR standard). For amides 7 and 9 the yields (~50%) of *p*-nitro-*N*-methylaniline and (*p*-nitrophenyl)phenylamine, respectively, were determined from the UV–vis spectrum of the reaction products. *p*-Nitrophenylacetic acid was detected in high yield by the NMR analysis of the reaction mixture.

Experimental Section

Materials. AR grade barium hydroxide was used without further purification. Distilled water was further purified by using a Millipore system. Dry Me_2SO was prepared by distillation from calcium hydride under reduced pressure and was stored in a brown bottle over molecular seives. Me_2SO-d_6 was used without further purification.

Esters. Esters **6a–k** were prepared by heating to reflux either toluene or xylene solutions of 4-nitrophenylacetyl chloride and the substituted phenol for 2–48 h, depending on the nucleophilicity of the phenol. The solvent was then removed by distillation under reduced pressure and the residue recrystallized until pure by thin-layer chromatography (silica/CH_2Cl_2). Data for these compounds are as follows. **6a**: mp 108–110 °C (benzene–petroleum ether); mol wt calcd for $C_{14}H_{10}N_2O_6$ requires ($M^{+\cdot}$) 302.0539, found 302.0539. **6b**: mp 103–104 °C (ethanol); mol wt calcd for $C_{15}H_{10}N_2O_4$ ($M^{+\cdot}$) 282.0640, found 282.0639. **6c**, mp 101–103 °C (benzene–petroleum ether). Anal. Calcd for $C_{14}H_{10}N_2O_6$: C, 55.6; H, 3.3; N, 9.3. Found: C, 55.4; H, 3.5; N, 9.1. **6d**: mp 111–113 °C (aqueous ethanol); mol wt calcd for $C_{15}H_{10}F_3NO_4$ requires 325.0562, found 325.0562. **6e**, mp 57–59 °C (aqueous ethanol). Anal. Calcd for $C_{15}H_{10}F_3NO_4$: C, 55.4; H, 3.1; F, 17.5; N, 4.3. Found: C, 55.3; H, 3.2; F, 17.5; N, 4.3. **6f**, mp 73–75 °C (aqueous methanol). Anal. Calcd for $C_{14}H_{10}ClNO_4$: C, 57.6; H, 3.4; Cl, 12.2; N, 14.8. Found: C, 57.3; H, 3.6; Cl, 12.1; N, 4.8. **6g**, mp 101–104 °C (benzene–petroleum ether). Anal. Calcd for $C_{14}H_{10}ClNO_4$: C, 57.6; H, 3.4; Cl, 12.2; N, 4.8. Found: C, 57.3; H, 3.5; Cl, 11.9; N, 5.0. **6h**, mp 79–82 °C (benzene–petroleum ether). Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.4; H, 4.3; N, 5.5; mol wt 257.0688 ($M^{+\cdot}$). Found: C, 65.2; H, 4.5; N, 5.2; mol wt 257.0706 ($M^{+\cdot}$). **6i**, mp 78–80 °C (benzene–petroleum ether). Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.4; H, 4.8; N, 5.2. Found: C, 66.3; H, 4.8; N, 5.1. **6j**, mp 84–86 °C (benzene–petroleum ether). Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.7; H, 4.5; N, 4.9. Found: C, 62.5; H, 4.6; N, 4.8. **6k**: mp 165–167 °C (aqueous methanol); mol wt calcd for $C_{16}H_{16}N_2O_4$ ($M^{+\cdot}$) 300.1110, found 300.1110 ($M^{+\cdot}$).

Amides. The preparation of amides 7 and 9 has previously been reported.[5]

Kinetics. Stock solutions of esters **6a–k** or amides 7 and 9 (10^{-2} M) were prepared in purified Me_2SO. These solutions were diluted to 2.5×10^{-4} M for kinetic use. A barium hydroxide stock solution (0.0058 M in hydroxide) was prepared in purified water. Substrate solution (5 mL) and hydroxide solution (5 mL) were pipetted into a 25-mL volumetric flask and the mixture diluted to the mark with purified Me_2SO. The solution was thoroughly shaken and then added to the cuvette which had previously been equilibrated to 30.0 °C in the UV–vis spectrophotometer. The rate of loss of carbanion was followed at 590 nm (amides) or at 550 nm (esters **6g–k**).

The rate of carbanion loss for esters **6b–f** was measured by a stopped-flow technique using an instrument constructed in the Department of Inorganic and Analytical Chemistry, La Trobe University.[23] Solutions of ester (1×10^{-4} M) in Me_2SO and barium hydroxide (2.34×10^{-3} M hydroxide) in 60% Me_2SO–water were thermostatically equilibrated in the drive syringes of the stopped-flow apparatus. The reaction was then initiated by mixing equal volumes of each solution, and the rate of carbanion loss was followed at 550 nm for compound **6f** and at 620 nm for compounds **6b,c,e**. In addition, an intermediate was observed to accumulate for compounds **6b–e** (λ_{max} = 495 nm). The wavelength of maximum absorbance for this intermediate was determined by repeated stopped-flow experiments in which the wavelength was increased by 5 nm between each measurement. The maximum absorbance was found to be at 495 nm. The rate of loss of this intermediate was followed at 495 nm. Reactions carried out under a nitrogen or an oxygen atmosphere were bubbled with the appropriate gas for 1–2 min before addition of the solution to the cuvette.

Product Studies. The identities and yields of the products of the basic hydrolysis of esters **6a–k** were determined by the NMR analysis of the reaction solution. A solution of ester (0.4 mL, 0.15 M) in Me_2SO-d_6 was placed into an NMR tube. A sealed capillary tube containing methylene chloride was added to the NMR tube to act as an external NMR standard. A spectrum of the reactant was then scanned, and the integral relative to the methylene chloride was obtained.

A solution of sodium deuteroxide (from dissolving sodium metal in D_2O; 0.1 mL, 0.5 M) was then added to the NMR tube. The NMR tube was vigorously agitated and left at 30 °C for sufficient time to allow complete reaction. The NMR spectrum of the products was then scanned, and from the integral relative to methylene chloride (after allowing for dilution) the yields of the various products were calculated. The spectra of the products were identical in all cases with the spectra of a mixture of the appropriate substituted phenol and *p*-nitrophenylacetic acid. The yields of individual products were greater than 80% in all cases, e.g., from compound **6i**, 90% *p*-nitrophenylacetic acid and 92% *p*-cresol. Analyses of solutions containing excess sodium deuteroxide were also carried out, and the same products in slightly lower yields were obtained. It was noticed that it is essential to carry out the reactions for product analysis at 30 °C rather than for a shorter time at 100 °C because *p*-nitrophenylacetic acid is unstable at 100 °C in the presence of excess base.

The products from the basic hydrolysis of amide 7 were identified as above. A quantitative yield of *p*-nitrophenylacetic acid was detected, but the yield of *p*-nitro-*N*-methylaniline was only 8%. UV analysis of the kinetic solution (5×10^{-5} M amide) showed that approximately 50% amine was formed from both amides 7 and 9. Amide 9 was not soluble enough to allow the NMR analysis of the products. The differences in the yields of amine from amide 7 by both methods probably reflects the different concentrations of amide used in each analysis (NMR method, 0.1–0.15 M; kinetic method, i.e., UV, 5×10^{-5} M) and the difficulty in reducing the Ar–N–Me radicals. This results in a higher percentage yield of amine from the more dilute solution.

ESR Measurements. A solution of ester **6i** in Me_2SO (1.2 mL, 0.005 M) was placed in a quartz ESR tube. Barium hydroxide solution in water (0.3 mL, 0.43 M) was added carefully to minimize

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mixing. The tube was then stoppered, shaken vigorously, and plunged into a Dewar flask containing liquid nitrogen. After 1 min the tube was removed and placed in the ESR spectrometer in a liquid nitrogen bath. An ESR spectrum was then detected (gyromagnetic ratio 2.0025). The spectrum obtained in this way suffered from poor resolution, so no information about the structure of the radical was able to be obtained. Attempts to obtain a solution spectrum in dimethylformamide at room temperature were unsuccessful.

Solvent Isotope Effects. Kinetic studies in Me_2SO-D_2O (4:1 v/v) were carried out as described above except that NaOD in D_2O was substituted for $Ba(OH)_2$ in water.

Registry No. 6a, 35665-94-2; **6b**, 75993-59-8; **6c**, 21997-26-2; **6d**, 75993-60-1; **6e**, 75993-61-2; **6f**, 75993-62-3; **6g**, 53218-11-4; **6h**, 6335-82-6; **6i**, 53274-19-4; **6j**, 53218-13-6; **6k**, 75993-63-4; **7**, 75990-87-3; **9**, 75993-64-5; 4-nitrophenylacetyl chloride, 50434-36-1; *p*-nitrophenol, 100-02-7; *p*-cyanophenol, 767-00-0; *m*-nitrophenol, 554-84-7; *p*-(trifluoromethyl)phenol, 402-45-9; *m*-(trifluoromethyl)phenol, 98-17-9; *m*-chlorophenol, 108-43-0; *p*-chlorophenol, 106-48-9; phenol, 108-95-2; *p*-cresol, 106-44-5; *p*-methoxyphenol, 150-76-5; *p*-(dimethylamino)phenol, 619-60-3.

Aromatization of Arene 1,2-Oxides. 1,2-Oxides of Methyl Phenylacetate and Methyl *trans*-Cinnamate

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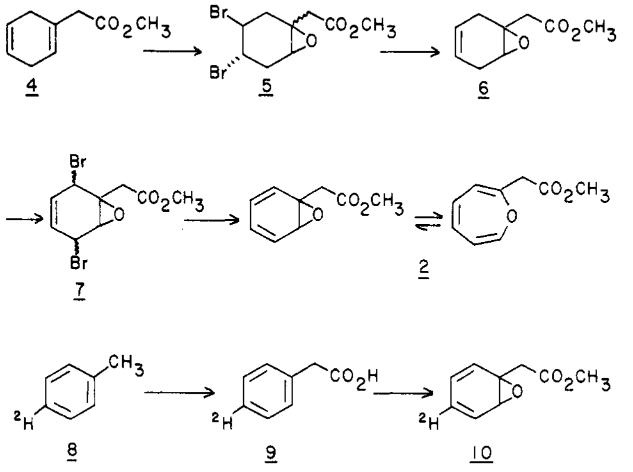
Received July 30, 1980

Substituent migration is observed only to a minor extent during aromatization of the 1,2-oxide of methyl phenylacetate to methyl (*o*-hydroxyphenyl)acetate; the major aromatization pathway does not involve substituent migration. Substituent migration is not observed during aromatization of the 1,2-oxide of methyl *trans*-cinnamate to methyl *o*-coumarate.

Our previous studies of the aromatization of arene 1,2-oxides have established the extent to which reaction occurs by C_1–O cleavage as opposed to C_2–O cleavage of the oxirane ring when the substituent is CH_3,[1] CH_2OH,[2] CHO[2], CO_2H,[2,3] CO_2CH_3,[2,3] and $Si(CH_3)_3$.[4] Whether the reaction proceeds by substituent migration or by substituent loss when C_2–O cleavage of the oxirane ring occurs was established in each case. Aromatization of toluene 1,2-oxide occurs only by the pathway involving C_1–O cleavage.[1] Although C_1–O cleavage is the predominant pathway for aromatization of the 1,2-oxide of benzyl alcohol, 8–17% of the reaction occurs by C_2–O cleavage, and substituent loss rather than migration is observed when C_2–O cleavage occurs.[2]

The 1,2-oxides of phenylacetic acid and *trans*-cinnamic acid are of interest since they, or the arene 2,3-oxides, may be intermediates in the ortho hydroxylation of the corresponding aromatic substrates in biological systems. Feeding studies with *A. chinensis* by Kindl[5] have shown that formation of (*o*-hydroxyphenyl)acetic acid (**1**) from phenylalanine involves substituent migration; phenylpyruvic acid is probably an intermediate and the substituent migration during hydroxylation is analogous to that observed in the transformation of tyrosine to homogentisic acid via (*p*-hydroxyphenyl)pyruvic acid.[6] On the other hand, substituent migration was not observed by Kindl in the formation of **1** by hydroxylation of phenylacetic acid.[5] Similarly, the results of Ellis and Amrhein indicate that formation of *o*-coumaric acid in plants by hydroxylation of *trans*-cinnamic acid does not involve substituent migration.[7]

Scheme I



Our interest in these biological transformations derives from the question of whether arene 1,2-oxides are likely intermediates in such ortho-hydroxylation reactions. Described herein are the preparation and aromatization reactions of the arene 1,2-oxides of methyl phenylacetate (**2**) and methyl *trans*-cinnamate (**3**). The 1,2-oxide of phenylacetic acid was too unstable for isolation by the synthetic route investigated. The 1,2-oxide of *trans*-cinnamic acid could be isolated only in impure form for aromatization studies.

Arene oxide **2** was prepared as indicated in Scheme I. Birch reduction of phenylacetic acid by a modification of the literature procedure followed by esterification afforded

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