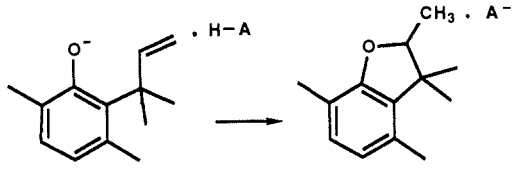
Intramolecular Nucleophilic Addition of Phenolate Oxygen to Double Bonds Activated by Carboxyl and Carboxylate Groups. Relative Reactivity, Stereochemistry, and Mechanism

Tina L. Amyes and Anthony J. Kirby*

Contribution from the University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. *Received February 16, 1988*

Abstract: The cyclization reactions of substituted 4-methyl-4-(2-hydroxyphenyl)pent-2-enoic acid derivatives (**7**) in water involve intramolecular nucleophilic attack of phenolate oxygen on the activated double bond. Activation by COO^- and COOH groups gives rate enhancements over a hydrogen substituent of 4000 and 10^8, respectively, for the unsubstituted acid. Both mono- and dianion reactions are general-acid-catalyzed by protonated amines ($\alpha \approx 0.2$). The stereochemistry of these latter reactions (syn addition of phenol O and general-acid H) is in remarkable contrast with the trans addition observed for the water-catalyzed reaction, and the (primary) solvent deuterium isotope effects (less than 2 for buffer acids, compared with ~5 for water) are also very different. The most likely mechanisms involve rate-determining protonation of mono- or dianions of carboxylic acid enolates, thus formally, reverse $(E1cB)_1$ reactions.

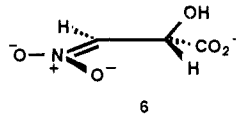
We recently described the rapid cyclization of a series of phenol olefins, e.g., **1**, involving intramolecular nucleophilic addition of phenolate oxygen to the unactivated double bond of a monoalkyl ethylene.[1] In this situation, with cyclization favored by the release



1 2

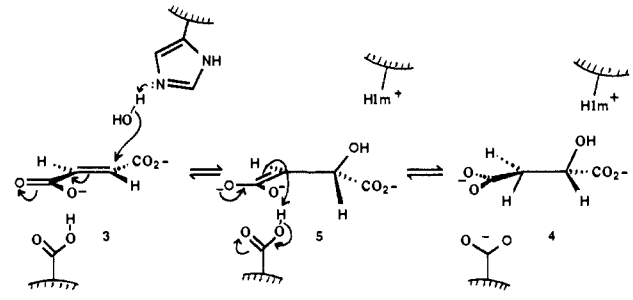
of ground-state strain, the alkene clearly prefers to act as an electrophile. Nucleophilic addition requires the presence of a preassociated general acid, but proton transfer is not far advanced in the transition state, though of course it plays an essential role in avoiding the formation of a primary alkyl carbanion in water. These results define the basic requirements for the addition of an oxygen nucleophile like water to an unactivated double bond,[1] a reaction catalyzed by a number of interesting enzymes.

The hydration catalyzed by fumarase (EC 4.2.1.2) (**3** ⇌ **4**)[2] involves a double bond activated by a carboxylate or carboxyl group. Several mechanisms have been proposed. Early work with halofumarate substrates led to the suggestion of a pathway involving a carbocation,[3] and this was supported by isotope-exchange results.[4] Rose,[5] however, considering the reverse reaction, argued that the relative timing of C-H and C-OH bond cleavage is not easy to assess from such studies and that concerted and carbanion mechanisms could not be excluded. More recent work by Lowe et al.[6] provides kinetic evidence for a concerted pathway. But a comprehensive isotope effect study led Blanchard and Cleland[7] to favor the carbanion mechanism (Scheme I). Independent support for a carbanion intermediate comes from the observation[8] that **6** is a tight-binding competitive inhibitor of the enzyme.

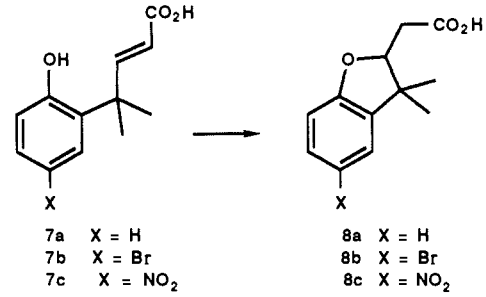


6

Scheme I

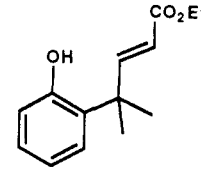


Scheme I raises some interesting questions, particularly concerning the viability of the carbanion intermediate (**5** is formally a carboxylic acid dianion) in a protic medium. If such an intermediate has a significant lifetime in water, it should be generated by an intramolecular cyclization reaction (cf. **1** → **2**). So we have prepared and studied the cyclization (**7** → **8**) of a series of substituted 4-methyl-4-(2-hydroxyphenyl)pent-2-enoic acid derivatives.



7a X = H
7b X = Br
7c X = NO_2

8a X = H
8b X = Br
8c X = NO_2



9

Experimental Section

Materials. Diisopropylamine was distilled from and stored over calcium hydride. Triethyl phosphonoacetate was from Lancaster Synthesis. Diisobutylaluminum hydride (DIBAL) was from Aldrich. Dichloromethane was distilled from phosphorus pentoxide. Tetrahydrofuran (THF) was predried by distillation from lithium aluminum hydride, stored over sodium wire, and redistilled from sodium-benzophenone. Acetonitrile was distilled from phosphorus pentoxide. Inorganic buffer

(1) Evans, C. M.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1259.
(2) Hill, R. L.; Teipel, J. W. *Enzymes, 3rd ed.* **1971**, *5*.
(3) (a) Teipel, J. W.; Hass, G. M.; Hill, R. L. *J. Biol. Chem.* **1968**, *243*, 5684. (b) Nigh, W. G.; Richards, J. H. *J. Am. Chem. Soc.* **1969**, *91*, 5847.
(4) Hansen, J. N.; Dinovo, E. C.; Boyer, P. D. *J. Biol. Chem.* **1969**, *244*, 6270.
(5) Rose, I. A. *Enzymes, 3rd ed.* **1970**, *2*.
(6) Jones, V. T.; Lowe, G.; Potter, B. V. L. *Eur. J. Biochem.* **1980**, *108*, 433.
(7) Blanchard, J. S.; Cleland, W. W. *Biochemistry* **1980**, *19*, 4506.
(8) Porter, D. J. T.; Bright, H. J. *J. Biol. Chem.* **1980**, *255*, 4772.

0002-7863/88/1510-6505$01.50/0

salts were of AnalaR grade and were used without further purification, apart from drying in vacuo where necessary. Piperidine was distilled from calcium hydride, and ethanolamine and propanolamine were distilled before use. Other amines were obtained as, or converted to, the hydrochlorides and then recrystallized. Distilled water was distilled twice more from all-glass apparatus. Unless stated otherwise, all other reagents were of analytical grade.

Synthesis. ^{1}H NMR spectra were recorded at 60 MHz on a Varian EM 360 spectrometer, at 90 MHz on a Varian EM 390 spectrometer, at 80 MHz on a Bruker WP 80 spectrometer, and at 250 MHz on a Bruker WM 250 spectrometer. Chemical shifts are reported as δ (ppm) downfield of an internal tetramethylsilane standard at 0 ppm. High-resolution mass spectra were recorded on an AEI MS30 mass spectrometer. Infra-red spectra were recorded on a Perkin-Elmer 297 spectrophotometer. Ultraviolet spectra were recorded on a Gilford 2600 spectrophotometer. Melting points were determined with a Köfler hot stage apparatus and are uncorrected. Column chromatography was carried out using Merck Kieselgel 60 (70–230 mesh). Chromatographic solvents were distilled before use.

3,3-Dimethyl-2(3*H*)-benzofuranone (10) was prepared by lactonization of *o*-hydroxyphenylacetic acid followed by methylation with methyl iodide using a published procedure[9] to give the dimethylated lactone as an oil: bp 63 °C (0.4 mmHg) (lit.[10] bp 101–102 °C (2 mmHg); IR (liquid film) 1800 cm^{-1} (C=O); ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.1–6.6 (4 H, m, Ar), 1.47 (6 H, s, CH_3); MS (found M$^+$ 162.0682, $C_{10}H_{10}O_2$ requires M 162.0681), *m/z* 162 (50, M$^+$), 134 (91, M – CO), 119 (88), 91 (100).

2,3-Dihydro-3,3-dimethyl-2-benzofuranol (11). DIBAL (40 mL of a 1 M solution in heptane, 40 mmol) was added to a stirred solution of the lactone **10** (5 g, 31 mmol) in dry dichloromethane (80 mL) under nitrogen at −78 °C. Stirring was continued for 1 h, and the mixture was treated with hydrochloric acid to dissolve the aluminum salts formed. The mixture was extracted with dichloromethane (3 × 100 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (200 g) eluting with 2/11 ethyl acetate/hexane to give the lactol **11** (4.2 g, 83%) as needles: mp 56–58 °C; IR (CCl_4) 3600 cm^{-1} (OH); ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.1–6.5 (4 H, m, Ar), 5.4 (1 H, d, J = 6 Hz, CH), 3.1 (1 H, d, J = 6 Hz, OH), 1.33 (3 H, s, CH_3), 1.27 (3 H, s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.2, 135.4, 128.1, 122.6, 121.4, 110.0 (Ar), 108.5 (OCO), 45.2 (C), 27.7 (CH_3), 20.2 (CH_3); MS (found M$^+$ 164.0834, $C_{10}H_{12}O_2$ requires M 164.0837), *m/z* 164 (46, M$^+$), 135 (100). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.1; H, 7.35. Found: C, 73.0; H, 7.30.

Ethyl 2,3-Dihydro-3,3-dimethyl-2-benzofuranacetate (12a). Triethyl phosphonoacetate (5.38 g, 24 mmol) in dry THF (25 mL) was added dropwise to a stirred solution of oil-free sodium hydride (0.96 g of a 60% dispersion, 24 mmol) in dry THF (10 mL) under nitrogen at 0 °C. The mixture was stirred for 10 min at room temperature, after which the lactol **11** (1.5 g, 9 mmol) in dry THF (10 mL) was added. The mixture was stirred at room temperature for 20 h and saturated ammonium chloride (20 mL) added. The THF was removed under reduced pressure and the residue extracted with ether (3 × 50 mL). The combined extracts were washed with water (50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatograph on silica gel (200 g) eluting with 2/11 ethyl acetate/hexane to give the ester **12a** (2 g, 93%) as an oil: IR (liquid film) 1740 cm^{-1} (C=O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.14–6.77 (4 H, m, Ar), 4.73 (1 H, dd, J = 4.4, 9.3 Hz, OCH), 4.23 (2 H, q, J = 7 Hz, CH_2CH_3), 2.75 (1 H, dd, J = 9.3, 15.7 Hz, CH_AH_B), 2.61 (1 H, dd, J = 4.4, 15.7 Hz, CH_AH_B), 1.36 (3 H, s, CH_3), 1.30 (3 H, t, J = 7 Hz, CH_2CH_3), 1.14 (3 H, s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.0 (C=O), 157.8, 136.7, 128.0, 122.3, 120.8, 109.9 (Ar), 88.4 (OCH), 60.8 (CH_2CH_3), 43.7 (C), 35.6 (CH_2CO_2Et), 26.8 (CH_3), 23.5 (CH_3), 14.2 (CH_2CH_3); MS (found M$^+$ 234.1254, $C_{14}H_{18}O_3$ requires M 234.1256), *m/z* 234 (46, M$^+$), 219 (36, M – Me), 145 (100).

Ethyl 5-Bromo-2,3-dihydro-3,3-dimethyl-2-benzofuranacetate (12b). Bromine (13 mL of a 0.5 M solution in CCl_4, 6.5 mmol) was added to a stirred solution of the ester **12a** (1.53 g, 6.5 mmol) in CCl_4 (10 mL) in an open flask at 0 °C. The mixture was stirred at room temperature for 4 h and the CCl_4 removed under reduced pressure. The residue was taken up into dichloromethane (50 mL), washed with sodium thiosulfate solution (20 mL) and with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was distilled to give the ester **12b** (1.95 g, 95%) as an oil: bp 185 °C (0.1 mmHg); IR (liquid film) 1730 cm^{-1} (C=O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.2–7.14 (2 H, m, Ar), 6.65 (1 H, d, J = 8.3 Hz, Ar), 4.73 (1 H, dd, J = 4.4, 9.2 Hz, OCH), 4.20 (2 H, q, J = 7 Hz, CH_2CH_3), 2.72 (1 H, dd, J = 9.2, 15.8 Hz, CH_AH_B), 2.61 (1 H, dd, J = 4.4, 15.8 Hz, CH_AH_B), 1.33 (3 H, s, CH_3), 1.28 (3 H, t, J = 7 Hz, CH_2CH_3), 1.11 (3 H, s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.7 (C=O), 156.9, 139.1, 125.5, 112.6, 111.6 (Ar), 88.9 (OCH), 60.9 (CH_2CH_3), 44.0 (C), 35.4 (CH_2CO_2Et), 26.6 (CH_3), 23.3 (CH_3), 14.3 (CH_2CH_3); MS (found M$^+$ 312.0374, $C_{14}H_{17}BrO_3$ requires M 312.0361), *m/z* 312 (44, M$^+$), 297 (25, M – Me), 225 (100), 223 (87).

Ethyl 2,3-Dihydro-3,3-dimethyl-5-nitro-2-benzofuranacetate (12c). **12a** (5 g, 21.4 mmol) and silver nitrate (3.99 g, 23.5 mmol) were stirred together in dry acetonitrile (30 mL) at 0 °C. Acetyl chloride (1.67 mL, 23.5 mmol) in dry acetonitrile (20 mL) was added dropwise, followed by more dry acetonitrile (20 mL). The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 0.5 h. Water (10 mL) was added and the mixture extracted with dichloromethane (3 × 200 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (300 g) eluting with 2/11 ethyl acetate/hexane to give the ester **12c** (4.11 g, 69%) as a yellow solid: mp 89–91 °C; IR (CCl_4) 1740 (C=O), 1530 (NO_2), 1350 cm^{-1} (NO_2); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.09 (1 H, dd, J = 2.4, 8.8 Hz, Ar), 7.97 (1 H, d, J = 2.4 Hz, Ar), 6.82 (1 H, d, J = 8.8 Hz, Ar), 4.91 (1 H, dd, J = 4.5, 9.2 Hz, OCH), 4.23 (2 H, q, J = 7.1 Hz, CH_2CH_3), 2.76 (1 H, dd, J = 9.2, 16 Hz, CH_AH_B), 2.65 (1 H, dd, J = 4.5, 16 Hz, CH_AH_B), 1.42 (3 H, s, CH_3), 1.30 (3 H, t, J = 7.1 Hz, CH_2CH_3), 1.19 (3 H, s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.2 (C=O), 163.1, 142.5, 138.2, 125.7, 119.0, 109.9 (Ar), 90.5 (OCH), 61.6 (CH_2CH_3), 43.5 (C), 35.4 (CH_2CO_2Et), 26.8 (CH_3), 23.5 (CH_3), 14.1 (CH_2CH_3); MS (found M$^+$ 279.1086, $C_{14}H_{17}NO_5$ requires M 279.1107), *m/z* 279 (18, M$^+$), 264 (24, M – Me), 190 (100). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.2; H, 6.15; N, 5.0. Found: C, 60.0; H, 6.35; N, 4.80.

2,3-Dihydro-3,3-dimethyl-2-benzofuranacetic Acid (8a). Ester **12a** (0.55 g, 2.4 mmol), potassium hydroxide (0.44 g, 7.9 mmol), water (30 mL), and THF (30 mL) were heated under reflux for 21 h. The THF was removed under pressure and the mixture acidified with concentrated hydrochloric acid. The mixture was extracted with ether (3 × 20 mL) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was recrystallized from ether/hexane to give the acid **8a** (0.37 g, 76%) as prisms: mp 106 °C; IR (CCl_4) 3500–2500 (OH), 1710 cm^{-1} (C=O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.16–6.80 (4 H, m, Ar), 4.73 (1 H, dd, J = 4.1, 9.4 Hz, OCH), 2.79 (1 H, dd, J = 9.4, 16 Hz, CH_AH_B), 2.69 (1 H, dd, J = 4.1, 16 Hz, CH_AH_B), 1.38 (3 H, s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.1 (C=O), 157.6, 136.4, 128.1, 122.3, 121.0, 110.0 (Ar), 88.0 (OCH), 43.8 (C), 35.2 (CH_2), 26.9 (CH_3), 23.4 (CH_3); MS (found M$^+$ 206.0940, $C_{12}H_{14}O_3$ requires M 206.0943), *m/z* 206 (23, M$^+$), 191 (24, M – Me), 145 (100). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.85. Found: C, 69.6; H, 6.80.

Prepared in a similar fashion were the following. **5-Bromo-2,3-dihydro-3,3-dimethyl-2-benzofuranacetic acid (8b)**: prisms; mp 125–126 °C; IR ($CHCl_3$) 3500–2500 (OH), 1710 cm^{-1} (C=O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.23–7.16 (2 H, m, Ar), 6.68 (1 H, d, J = 8.4 Hz, Ar), 4.74 (1 H, dd, J = 4.2, 9.4 Hz, OCH), 2.77 (1 H, dd, J = 9.4, 16 Hz, CH_AH_B), 2.67 (1 H, dd, J = 4.2, 16 Hz, CH_AH_B), 1.36 (3 H, s, CH_3), 1.15 (3 H, s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.6 (C=O), 156.8, 139.0, 131.0, 125.6, 112.9, 111.7 (Ar), 88.6 (OCH), 44.1 (C), 35.1 (CH_2), 26.8 (CH_3), 23.3 (CH_3); MS (found M$^+$ 284.0040, $C_{12}H_{13}BrO_3$ requires M 284.0048), *m/z* 284 (75, M$^+$), 269 (50, M – Me), 223 (100). Anal. Calcd for $C_{12}H_{13}BrO_3$: C, 50.5; H, 4.60. Found: C, 50.6; H, 4.50. **2,3-Dihydro-3,3-dimethyl-5-nitro-2-benzofuranacetic acid (8c)**: yellow needles; mp 199–200 °C; IR ($CHCl_3$) 1710 cm^{-1} (C=O); ^{1}H NMR (250 MHz, Me_2SO-d_6) δ 8.14–8.06 (2 H, m, Ar), 6.98 (1 H, d, J = 8.8 Hz, Ar), 4.83 (1 H, dd, J = 3.5, 9.9 Hz, OCH), 2.86 (1 H, dd, J = 3.5, 16.3 Hz, CH_AH_B), 2.61 (1 H, dd, J = 9.9, 16.3 Hz, CH_AH_B), 1.40 (3 H, s, CH_3), 1.15 (3 H, s, CH_3); ^{13}C NMR (62.9 MHz, Me_2SO-d_6) δ 171.8 (C=O), 163.0, 141.7, 138.9, 125.6, 119.3, 109.8 (Ar), 91.9 (OCH), 43.0 (C), 35.0 (CH_2), 26.0 (CH_3), 23.1 (CH_3); MS (found M$^+$ 251.0804, $C_{12}H_{13}NO_5$ requires M 251.0794), *m/z* 251 (28, M$^+$), 236 (51, M – Me), 190 (100). Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.4; H, 5.20; N, 5.6. Found: C, 57.7; H, 5.30; N, 5.5.

***trans*-4-Methyl-4-(2-hydroxyphenyl)pent-2-enoic Acid (7a).** *n*-Butyllithium (0.76 mL of a 1.6 M solution in hexane, 1.2 mmol) was added to a stirred solution of diisopropylamine (0.17 mL, 1.2 mmol) in dry THF (2 mL) under nitrogen at −78 °C. After 10 min, **8a** (0.1 g, 0.49 mmol) in dry THF (3 mL) was added and stirring continued for 1 h. The mixture was acidified with concentrated HCl and extracted with dichloromethane (3 × 15 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a greater than 90% yield of **7a**, contaminated with starting material **8a**. This material was not purified further: ^{1}H NMR (80 MHz, $CDCl_3$) δ 7.40 (1 H, dd, J = 15.9 Hz, CH=$CHCO_2H$), 7.28–6.65 (4 H, m, Ar), 5.80 (1 H, d, J =

(9) Elix, J. A.; Ferguson, B. A. *Aust. J. Chem.* **1973**, *26*, 1079.
(10) Gripenberg, J.; Hase, T. *Acta Chem. Scand.* **1966**, *20*, 1561.

15.9 Hz, CH=C*H*CO_2H), 1.52 (6 H, s, CH_3).

Prepared in a similar fashion was ***trans*-4-methyl-4-(5-bromo-2-hydroxyphenyl)pent-2-enoic acid (7b)**: IR (liquid film) 1690 cm^{-1} (C=O); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25–7.20 (2 H, m, Ar), 7.14 (1 H, d, J = 15.9 Hz, C*H*=CHCO$_2$H), 6.76 (1 H, d, J = 6 Hz, Ar), 5.58 (1 H, d, J = 15.9 Hz, CH=C*H*CO$_2$H), 1.43 (6 H, s, CH_3).

Dipotassium *trans*-4-Methyl-4-(5-nitro-2-hydroxyphenyl)pent-2-enoate (7c). **8c** (50 mg, 0.2 mmol) was added to a stirred solution of potassium *tert*-butoxide (100 mg, 0.89 mmol) in dry THF (4 mL) under nitrogen, and the mixture was heated under reflux for 20 h. The mixture was filtered and the solid washed with THF (3 × 5 mL). This material was not purified further: UV (1 M aqueous KOH) 425 nm (ϵ 10000); ^{1}H NMR (90 MHz, Me_2SO-d_6) δ 7.73–7.60 (2 H, m, Ar), 6.72 (1 H, d, J = 16.5 Hz, C*H*=CO_2K), 5.87 (1 H, d, J = 10 Hz, Ar), 5.48 (1 H, d, J = 16.5 Hz, CH=C*H*CO_2K), 1.33 (6 H, s, CH_3).

Kinetics. Rate constants were measured at 39 °C in water at ionic strength 1.0 M (KCl) on a Gilford 2600 spectrophotometer equipped with a Thermoset temperature control unit. Some data for **7a** were measured at an ionic strength of 0.2 M. The change in ionic strength does not affect the rate significantly. Kinetic runs were started by injecting ~1 μL of a stock solution of the substrate into 0.25 mL of preheated buffer solution in 0.3-mL capacity quartz cuvettes. Stock solutions of **7a** and **7b** (ca. 20 mg/mL) were made up in dioxane and acetonitrile, respectively. For **7c**, the solution (ca. 10 mg/mL of the dipotassium salt) was in dimethyl sulfoxide. In all cases the medium contained <1% of organic solvent. All reactions were followed under pseudo-first-order conditions and gave good linear first-order plots over at least 3 half-lives. For **7c**, cyclization of the monoanion gave only a small change in absorbance, so aliquots were taken at various times and rapidly injected into 0.25 M KOH solution, and the absorbance at 420 nm was recorded. For the (slow) runs in HCl, the solutions were degassed with argon prior to use.

Ionization Constants. Ionization constants were measured for the substrates **7** by the spectrophotometric technique,[11] with absorbances extrapolated back to zero time where necessary and wavelengths of 294, 310, and 420 nm for the phenol groups of **7a**, **7b**, and **7c**, respectively. For the COOH group of **7a**, a wavelength of 246 nm was used.

Products. For both **7a** and **7b**, a 10-mg sample was incubated in buffer (5 mL) for 10 half-lives and the mixture acidified (HCl) and extracted with ether. The ether extract was dried and evaporated and the product examined by ^{1}H NMR (250 MHz).

Isotope Effects. Kinetic solvent isotope effects were measured in buffers made up with 99.8% D_2O (Aldrich). Commercial KOD solutions in D_2O (Aldrich) were diluted and estimated by titration with HCl. Exchangeable protons of buffer constituents were exchanged by prior treatment with D_2O. Product isotope effects were determined by running reactions in 1:1 (M/M) H_2O/D_2O solutions. After 10 half-lives the reactions were quenched with HCl and extracted with ether. The concentrated products were treated with KOH solution and reextracted to convert the carboxyl group to the COO*H* form, before analysis by mass spectrometry. Control experiments run for 20 half-lives gave identical results.

Stereochemistry. Deuteriated buffers were the same as those used for the kinetic experiments. A sample of **7a** or **7b** (2–5 mg) was incubated for 10 half-lives in buffer in D_2O (3 mL) at 39 °C. The reaction mixture was acidified and the product isolated by ether extraction and examined by 250-MHz ^{1}H NMR. Controls run for 20–50 half-lives gave identical results.

Exchange Experiments. **8a** (33.7 mg) was dissolved in 1.069 M KOD in D_2O (0.5 mL) with a small amount of 3-(trimethylsilyl)propionate-*2,2,3,3-d*$_4$ as an internal standard. The ^{1}H NMR spectrum was recorded and integrated at 90 MHz, the solution was then incubated in the NMR tube in a water bath at 39 °C, and spectra were recorded at intervals.

Results

Synthesis. The system **7** was chosen because we had found[12] that ester **9**, incorporating the full "trialkyl lock",[13] could not be isolated because it cyclizes inconveniently fast. The preparation of **7a** is shown in Scheme II. Elimination occurs when the dianion of **8a** is generated with lithium diisopropylamide, and **7a** is obtained on acidification. This material (generally >90% phenol olefin) was used directly for the kinetic studies, since rapid cyclization prevented further purification.

The substituted compounds **7b** and **7c** were obtained by bromination or nitration of **12a**, followed by alkaline hydrolysis to give the corresponding carboxylic acids. Ring opening of the acid proceeded as before for **8b**, but for **8c**, potassium *tert*-butoxide had to be used, and **7c** was obtained as the dipotassium salt.

Scheme II

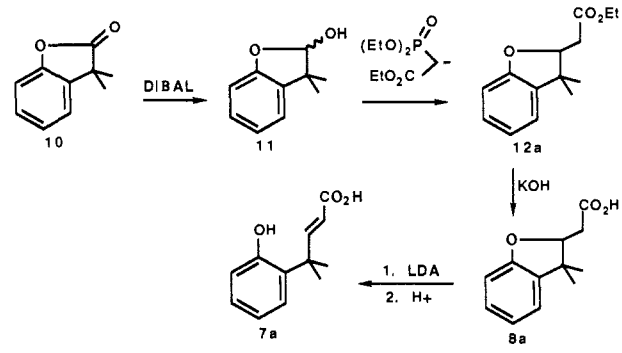


Table I. pK_a's of Substrates **7**, at 39 °C and Ionic Strength 1.0 M (KCl)

compd	pK_a^1	pK_a^2
7a	4.56 ± 0.04	10.69 ± 0.03
7a (in D_2O)	5.09 ± 0.08	11.37 ± 0.02
7b	4.50 ± 0.10[a]	10.04 ± 0.03
7c	4.30 ± 0.10[b]	7.21 ± 0.03

[a] Estimated; see text. [b] Apparent pK_a from pH–rate profile.

Identification of Products. NMR spectra of the isolated products from cyclization of **7a** and **7b** were identical with those of authentic samples of **8a** and **8b**. The reaction of **7c** ⇌ **8c** is reversible: mixtures are obtained at pH 12–14, but a quantitative yield of **7c** or **8c** may be obtained at higher or lower pH, respectively.

Ionization Constants. The ionization constants for the carboxylic acid (K_a^1) and phenol (K_a^2) groups are defined as the first- and second-ionization constants of the substrate, respectively. For **7a**, they were determined as described in the Experimental Section, but for **7b** and **7c**, no significant change in spectrum was apparent on ionization of the COOH group, so the pK_a's were estimated as follows. For **7c**, the apparent pK_a^1 given by the pH–rate profile for cyclization was used. For **7b**, the pK_a^1 was obtained by interpolation on the two-point Hammett plot for ionization of **7a** and **7c**. The results are given in Table I.

Buffer Catalysis. The cyclizations of all three species—free acid, monoanion, and dianion—of **7a** are buffer-catalyzed. Catalysis was studied with a more limited range of buffers for **7b** and **7c** also. Plots of observed pseudo-first-order rate constants against buffer concentration were always linear, and pH–rate profiles for cyclization (Figure 1) were obtained by extrapolation to zero buffer concentration.

General-acid catalysis of the cyclization of **7a** by cyanoacetic acid was observed at pH 1.8, but buffer catalysis was not studied further for the reactions of the neutral species of **7**.

Catalysis of the mono- and dianion reactions is complicated, because (i) there exists the problem of kinetic ambiguity and (ii) there are significant pH regions of overlap of the two reactions. For reasons described in the Discussion, we have calculated second-order rate constants for buffer catalysis in terms of general-acid-catalyzed reactions of the mono- and dianion species (rather than the kinetically equivalent general-base-catalyzed reactions of the free acid and monoanion). But this cannot be done successfully in certain pH regions if catalysis is assumed to represent exclusively the reaction of the mono- or the dianion: the resulting second-order rate constants vary with pH, as expected if the reactions of both species are catalyzed.

To perform the calculations we measured second-order rate constants for catalysis by buffers of pK_a > 8 in carrier buffers, in the region of pH where the substrate is present almost exclusively as the monoanion and the buffer is in the conjugate acid form. The results are summarized in Table II. These rate constants, representing (>99%) general-acid catalysis of the cyclization of the monoanion only, were then used to correct those

(11) Albert, A.; Serjeant, E. P. *Ionization Constants of Acids and Bases*; Methuen: London, 1962.
(12) Evans, C. M. Thesis, Cambridge University, 1982.
(13) Milstien, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158.

Table II. Observed Second-Order Rate Constants for the Cyclization of the Monoanion of **7a** Catalyzed by General Acids in Carrier Buffers, at 39 °C and Ionic Strength 1.0 M (KCl)

conjugate base of general acid	no. of runs (concn range, M)	carrier buffer (% free base), pH	10^4k_0[a], s^{-1}	10^4k_2[b], M^{-1} s^{-1}
quinuclidine	6 (0–0.6)	25 mM MES[c] (80), 6.63	2.89 ± 0.42	18.7 ± 0.80
ethylamine	6 (0–0.5)	50 mM MES (35), 5.82	2.57 ± 0.04	3.79 ± 0.14
3-propanolamine	6 (0–0.5)	50 mM MES (35), 5.82	2.51 ± 0.03	7.71 ± 0.10
ethanolamine	6 (0–0.5)	50 mM MOPS[d] (80), 7.65	2.28 ± 0.13	10.5 ± 0.40
ethanolamine	4 (0.2–0.8)	0.10 M MOPS (50), 7.06	3.71 ± 0.44[e]	9.32 ± 0.81
ethanolamine	6 (0–0.5)	50 mM MES (80), 6.64	2.39 ± 0.18	10.0 ± 0.50
ethanolamine	5 (0.1–0.5)	50 mM MES (50), 6.03	3.00 ± 0.06	9.97 ± 0.17
ethanolamine	6 (0–0.5)	50 mM MES (35), 5.82	2.57 ± 0.05	9.91 ± 0.17
3-quinuclidinol	5 (0.2–0.6)	25 mM MOPS (50), 7.03	5.25 ± 0.50	42.0 ± 1.20
3-chloroquinuclidine	6 (0.05–0.30)	25 mM MES (50), 6.25		61.0 ± 3.20

[a] Intercept and [b] slope of plots of pseudo-first-order rate constants against general-acid (generally >99% acid form) concentration; carrier buffer concentration is constant. [c] MES, *N*-morpholinoethanesulfonate. [d] MPOS, *N*-morpholinopropanesulfonate. Correlation coefficients of second-order plots are better than 0.996, except for [e] $r = 0.993$.

Table III. Observed Rate Constants for the Buffer-Catalyzed Cyclization of **7a**, at 39 °C and Ionic Strength 1.0 M (KCl)

buffer (% free base)	no. of runs (concn. range, M)	pH	10^4k_0[a], s^{-1}	10^4k_2[b], M^{-1} s^{-1}	buffer (% free base)	no. of runs (concn. range, M)	pH	10^4k_0[a], s^{-1}	10^4k_2[b], M^{-1} s^{-1}
quinuclidine (20)	5 (0.1–0.5)	10.52	52.1 ± 0.50[d]	26.2 ± 1.50	ethanolamine (20)	4 (0.1–1.0)	8.68	3.59 ± 0.23	11.1 ± 0.40
ethylamine (15)	5 (0.2–1.0)	9.70	13.0 ± 0.40	13.0 ± 0.60	TRIS[c] (80)	4 (0.04–0.4)	8.57	2.63 ± 0.04	4.41 ± 0.18
n-propylamine (15)	5 (0.2–1.0)	9.62	12.9 ± 0.20	6.95 ± 0.28	TRIS (50)	4 (0.05–0.5)	7.95	1.89 ± 0.04	6.77 ± 0.14
3-propanolamine (35)	5 (0.2–1.0)	9.67	13.1 ± 0.40	13.9 ± 0.60	TRIS (20)	4 (0.05–0.5)	7.35	1.84 ± 0.06	8.93 ± 0.22
ethanolamine (80)	4 (0.1–1.0)	9.91	21.7 ± 0.10	7.81 ± 0.24	TRIS (10)	5 (0.05–0.25)	7.01	1.82 ± 0.05	9.75 ± 0.29
ethanolamine (65)	5 (0.2–1.0)	9.64	11.2 ± 0.30	12.6 ± 0.50	3-quinuclidinone (20)	5 (0.01–0.05)	6.71	1.92 ± 0.07	9.26 ± 2.20
ethanolamine (50)	4 (0.1–1.0)	9.33	7.76 ± 0.13	12.2 ± 0.20	acetic acid (50)	5 (0.1–0.5)	4.61	0.954 ± 0.042	6.23 ± 0.13
ethanolamine (35)	4 (0.2–0.8)	9.12	5.17 ± 0.18	12.2 ± 0.30	cyanoacetic acid (20)	5 (0.2–1.0)	~1.8	0.279 ± 0.008	0.321 ± 0.011

[a] Intercept and [b] slope of plot of pseudo-first-order rate constants against total buffer concentration. [c] TRIS, tris(hydroxymethyl)aminomethane hydrochloride. Correlation coefficients for second-order plots were all better than 0.997, except for [d] $r = 0.995$.

Table IV. Calculation of Second-Order Rate Constants (M^{-1} s^{-1}) for the Buffer-Catalyzed Cyclization of the Dianion of **7a**, at 39 °C and Ionic Strength 1.0 M (KCl)

buffer (% free base)	pK_{BH}	10^4k^{mono}[a] (a)	10^4k_{obsd}[b] (b)	pH	f^{di}[c] (c)	$10^4k^{mono}f^{mono}$[d] (d)	10^3k^{di}[e] (e)
quinuclidine (20)	11.5	18.9	26.2	10.52	0.403	9.03	5.33
ethylamine (15)	10.5	3.99	13.0	9.70	0.093	3.08	12.6
3-propanolamine (35)	9.9	8.12	13.9	9.67	0.087	4.82	16.1
ethanolamine (80)	9.4	10.1	7.81	9.91	0.142	1.73	21.4
ethanolamine (65)	9.4	10.1	12.6	9.64	0.082	3.25	32.5

[a] Apparent second-order rate constant for general-acid catalysis of the cyclization of the monoanion. Data from Table II corrected for the small amount of substrate present in the neutral acid form. [b] Data from Table III. [c] Fraction of **7a** present as dianion at pH given. [d] Contribution from the buffer acid-catalyzed reaction of the monoanion. Subtracting this from the figure in column (b) gives the corresponding contribution from the dianion reaction. [e] Calculated (in column headings) as (b–d)/c, which is finally divided by the fraction of free acid in the buffer.

Table V. Derived Second-Order Rate Constants k_{BH^+} (M^{-1} s^{-1}) for the Buffer-Catalyzed Cyclization of **7a**, **7b**, and **7c**, at 39 °C and Ionic Strength 1.0 M (KCl)

		7a		**7b**		**7c**	
buffer base, B	pK_{BH}[a]	monoanion[b]	dianion	monoanion[b]	dianion	monoanion[b]	dianion
quinuclidine	11.5	2550	5.33×10^{-3}	582	2.01×10^{-3}	2.13	1.47×10^{-5}
ethylamine	10.5	538	1.26×10^{-2}	148	1.89×10^{-3}	0.385	1.08×10^{-5}
3-quinuclidinol	10.0	5670		1376		5.75	
3-propanolamine	9.9	1095	1.61×10^{-2}	231	3.55×10^{-3}	0.80	1.97×10^{-5}
ethanolamine	9.4	1360	2.70×10^{-2}	333	5.75×10^{-3}	0.92	3.58×10^{-5}
3-chloroquinuclidine	9.0	8230		2226		11.1	
3-quinuclidinone	7.5	16500		4240		18.0	
acetate	4.6	3180		720		2.86	

[a] pK_a's of quinuclidines at 25 °C, ionic strength 1.0 M (KCl) taken from Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963. pK_a's of primary amines and acetate calculated from the observed pH values of buffer solutions. [b] Second-order rate constants calculated for the reaction of the minor (phenol O^-/COOH) ionic form.

obtained at higher pH (for the reaction of the dianion) for the monoanion reaction. Because the second pK_a of **7a** is so high (10.69), only a very limited range of general acids could be used, and only measurements made above pH 9.5 (>5% of dianion) were useful. The full set of data for buffer catalysis of the cyclization of **7a** is given in Table III, and the calculation of the rate constants for the dianion reaction, from data sets measured at pH >9.5, is summarized in Table IV. As discussed below, it is reasonable to assume that the monoanion reacts through the thermodynamically less favorable phenolate–COOH tautomer. The derived rate constants for general-acid catalysis of the reactions of the monoanions of **7a**, **7b**, and **7c** given in Table V have been calculated on this basis and can thus be compared directly with those for the corresponding dianion reactions.

Isotope Effects. Data for the kinetic solvent isotope effects appear in Table VI. The isotope effects for the water-catalyzed dianion reactions were determined in the region of pH where the substrates were completely ionized ($[H^+] \ll K_a^2$) so that no correction for substrate ionization is necessary. For the buffer-catalyzed reactions, the isotope effects were determined from the

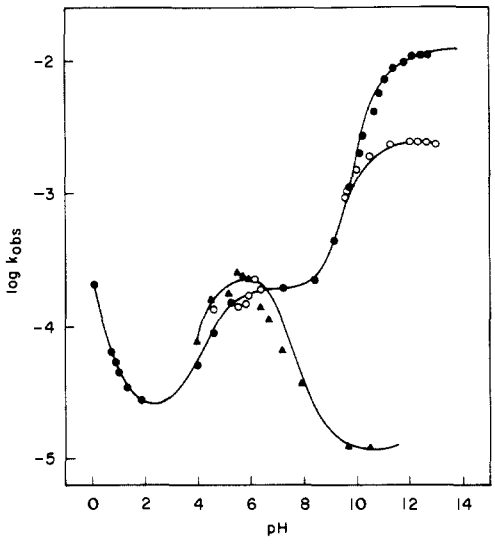


Figure 1. pH–Rate profiles for the cyclization of **7a** (●), **7b** (○), and **7c** (▲), at 39 °C and ionic strength 1.0 M (KCl). The points are experimental and the curves calculated by using the pK_a's given in Table I and the following rate constants. For **7a**: neutral species, $k_{H^+} = 1.86 \times 10^{-4}$ M^{-1} s^{-1}, $k_0 = 2.6 \times 10^{-5}$ s^{-1}; monoanion, $k_0 = 1.84 \times 10^{-4}$ s^{-1}; dianion, $k_0 = 1.15 \times 10^{-2}$ s^{-1}. For **7b**: monoanion, $k_0 = 1.68 \times 10^{-4}$ s^{-1}; dianion, $k_0 = 2.49 \times 10^{-3}$ s^{-1}. For **7c**: monoanion, $k_0 = 2.40 \times 10^{-4}$ s^{-1}; dianion, $k_0 = 1.19 \times 10^{-5}$ s^{-1}. Many of the large number of experimental points defining the curve for **7a** between pH 5 and 10 are omitted in the interest of clarity.

Table VI. Kinetic and Product Deuterium Isotope Effects (k_H/k_D) on the Cyclization of **7** at 39 °C and Ionic Strength 1.0 M (KCl)

compd	7a	7b	7c
k_0(dianion)[a]	5.10 ± 0.10 (4.93)[g]	5.37 ± 0.03	~5
k_2(BH^+)(dianion)[b,d]	1.34 ± 0.05	1.66 ± 0.03	
k_0(monoanion)[a,c]	4.38 ± 0.11	4.14 ± 0.15	4.50 ± 1.2
k_2(BH^+)(monoanion)[c]	2.38 ± 0.43 (2.02)[g]	1.76 ± 0.06	1.93 ± 0.09

[a] All kinetic isotope effects represent k_{H_2O}/k_{D_2O}. [b] B is quinuclidine. [c] B is 3-quinuclidinone[e] (**7a**) or *N*-morpholinoethanesulfonate[f] (**7b**, **7c**). [d] Quinuclidine buffer, 20% free base, 0.1–0.5 M, pH 10.52, pD 11.15. [e] 3-Quinuclidinone buffer, 20% free base, 0.01–0.05 M, pH 6.69, pD 7.37. [f] *N*-morpholinoethanesulfonate buffer, 40% free base, 0.1–0.5 M, pH 5.95, pD 6.52. [g] Product isotope effect, single measurement (see text).

ratios of slopes of buffer plots in H_2O and D_2O. The pK_a values for the phenol group of **7a** in H_2O and D_2O differ by 0.68 unit. For quinuclidine, the difference calculated from pH and pD measurements is 0.65. The close match of these two values means that little or no correction of the observed isotope effect for substrate ionization is necessary. Isotope effects for the water-catalyzed monoanion reactions were determined from the ratios of intercepts of buffer plots in H_2O and D_2O, and for the buffer-catalyzed reactions the ratio of slopes was again used.

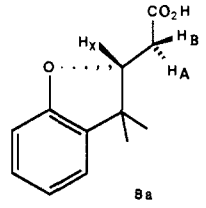
Product isotope effects, also given in Table VI, were determined as described in the Experimental Section.

Stereochemistry of Reaction. A study of the ^1H NMR spectra of the cyclization products of **7a** and **7b** in D_2O provided detailed information about the stereochemistry of the reaction.

The relevant chemical shifts and coupling constants for the cyclization product **8a** and the two monodeuteriated diastereoisomers A (H_B = D) and B (H_A = D) are given in Table VII. The assignment of the conformation shown is based on the Karplus equation.[14] These data allow us to specify the stereochemistry of the cyclization reaction with some precision. Sources of inaccuracy were (i) traces of protium in the D_2O solvent, which contribute disproportionately to product isotope ratios because

(14) Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry, 3rd ed.*; McGraw Hill: London, 1980.

Table VII. ^1H NMR Data (250 MHz, $CDCl_3$) for **8a** and its Deuteriated Derivatives A and B (δ ppm, J Hz)



	H_A,H_B			
	H,H	H,D	D,H	D,D
		A	B	
δ_A	2.80	2.78		
δ_B	2.69		2.67	
δ_X	4.73	4.72	4.72	4.71
J_{AB}	16	*a*	*a*	
J_{AX}	9.4	10	*a*	*a*
J_{BX}	4.1	*a*	3	*a*

[a] Couplings to deuterium were not resolved.

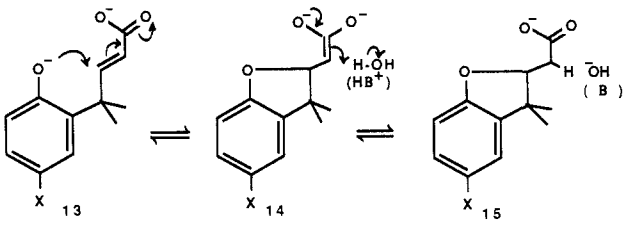
of the large primary isotope effects (k_H/k_D up to 5), and (ii) the small amounts of dihydrogen compound **8**, always present because the final ring opening of the synthesis of **7** (**8** → **7**, Scheme II) is not quite quantitative. Product ratios were obtained from the spectra by plotting the H_A and H_B peaks between δ 2.6–2.8, greatly expanded, onto high-quality paper. Peaks were then cut out and weighed. Since H_A and H_B are in closely similar chemical environments, it was assumed that they have similar relaxation times and pulse-delay procedures were not employed. Where signals were well-resolved integration gave closely similar results.

Cyclization of **7a** in 0.2 M KOD in D_2O gave almost exclusively diastereoisomer A, as determined from peaks in the regions δ 2.6–2.8 and 4.6–4.8. Within the uncertainties discussed above we can say that the reaction is at least 90% stereospecific. When the same reaction was run in buffered (piperidine, quinuclidine) solution in D_2O, a mixture of diastereoisomers A and B was obtained, suggesting a dependence of the stereochemistry on the general acid. When the cyclization of **7a** was carried out in D_2O in the presence of increasing concentrations (0.1, 0.3, 0.5, 1.0 M) of 20% free base quinuclidine buffer, increasing amounts of diastereoisomer B, the product of syn addition, were obtained. From the observed rate equation under the conditions ($k_{obsd} = 1.17 \times 10^{-3} + 1.95 \times 10^{-3}$[buffer]) we can calculate the percent of buffer-catalyzed reaction as 28, 42, 52, and 66% in the four runs. Observed percentages of syn products were 14, 33, 46, and 63. The data are not of high precision, but we are confident that for the cyclization of the dianion of **7a** the water-catalyzed reaction gives ≥90% trans addition and the reaction catalyzed by the conjugate acid of quinuclidine >90% syn.

Results for the cyclization of the monoanion are less precise, because buffer was always present between pH 4 and 8. But the situation is clearly similar. (i) In experiments with 3-quinuclidinone and *N*-morpholinoethanesulfonate buffers, the percentage of syn addition product increases with increasing buffer concentration. (ii) In 0.25 M quinuclidinone, 50% free base, where ~90% of the reaction is attributable to buffer catalysis, ~90% syn addition product is obtained. (iii) In the presence of low concentrations (0.1 M) of phosphate and acetate buffers, where buffer catalysis accounts for less than 50% of observed reaction, over 50% trans addition is observed.

Exchange Experiments. The rate constant for exchange for deuterium of the β-hydrogens of **8a** was determined by ^1H NMR. Spectra were recorded at intervals over a period of 6 days, by which time ~1.3 of the two β-hydrogens had been exchanged for deuterium. The rate constant for exchange of the first hydrogen estimated from the integrated spectra is 1×10^{-5} M^{-1} s^{-1}. The sample was then quenched with HCl and extracted with ether and its NMR spectrum recorded at 250 MHz. This showed a mixture of monodeuterio diastereoisomer A (Table VII) and the dideuterio compound. When the region δ 2.6–2.8 (signals for CHD com-

Scheme III



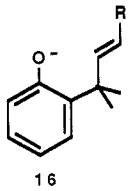
pounds only) was examined at 400 MHz, a small amount of diastereoisomer B could be seen to be present. Comparison of peak areas gave a ratio [A] to [B] of ~13:1, so the exchange of the first proton of **8a** is ≥93% stereospecific.

When **8c** was incubated under similar conditions for 19 h in KOD/D_2O, only the elimination product **7c** was observed in the NMR. No incorporation of deuterium accompanied elimination of aryl oxide.

Discussion

Relative Reactivity of the Carboxyl- and Carboxylate-Activated Double Bonds. The pH–rate profile for the cyclization of **7a** (Figure 1; ●) shows four distinct regions, corresponding to four separate reactions: acid-catalyzed and uncatalyzed cyclizations of the free acid phenol below pH 3 and faster reactions of the monoanion (pH 4–8.5) and dianion (pH >9). The last three are all buffer-catalyzed. The cyclization of the free acid phenol is catalyzed by cyanoacetic acid/cyanoacetate buffer, presumably acting as a general acid: if the H_3O^+-catalyzed reaction involves the same mechanism, the Brønsted α-value must be low (0.16 from the two-point plot). These low pH reactions, involving the undissociated phenolic OH group, are relatively inefficient and have not been studied further.

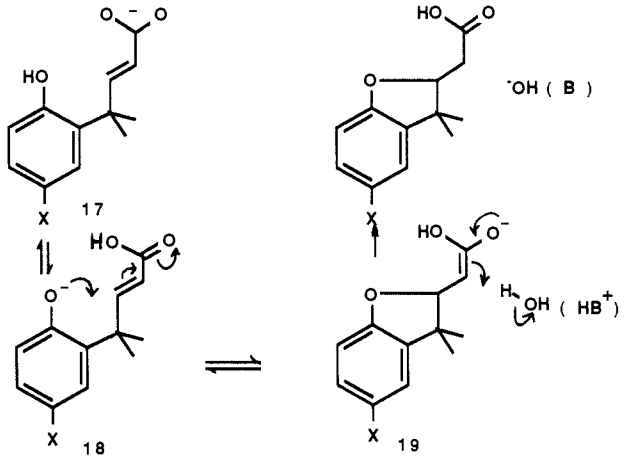
The cyclization of the dianion, observed at high pH, is of particular interest. A stepwise mechanism (Scheme III) must involve a carboxylic acid dianion (**14**) as an intermediate. This would be expected to have a very short lifetime in water. Nevertheless, it would certainly be substantially more stable than the putative primary alkyl carbanion generated by the addition of an aryl oxide to a monoalkylethylene. Such an intermediate is not observed[1] in the cyclization of **1**, because its lifetime is less than the time for a bond vibration (~10^{-13} s) and therefore cannot be said to exist.[15] As discussed below, we believe that the spontaneous cyclizations of **7** do indeed involve carbanion intermediates, and we can set a minimum value on the stabilization of the carbanion available from delocalization into the CO_2^- group by comparing the rate constant for the cyclization of the dianion of **7a** (thus **16**, R = CO_2^-) with that (2.08×10^{-6} s^{-1} at 39 °C in



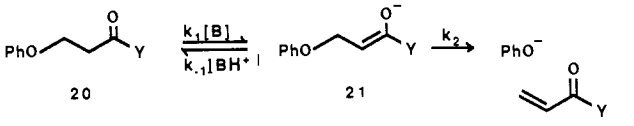
0.2 M KOH in 1:1 (v/v) $MeCN/H_2O$)[12] for the corresponding reaction of **16**, R = H. The ratio is 4×10^3, a direct measure of the capacity of an ionized carboxyl group to stabilize and adjacent negative charge.

The shapes of the pH–rate profiles for the cyclization of **7b** and **7c** (Figure 1; ○ and ▲, respectively) are very different. The aromatic substituent has a large effect ($\rho^- = 2.4$) on the observed rates of cyclization of the dianions—affecting the nucleophilicity of the phenolate oxygen in the expected way—but almost none ($\rho^- = +0.1$) on the corresponding monoanion reactions. This is simply explained, since the predominant ionic form of the monoanion is that (**17**; Scheme IV), with the carboxyl group ionized,

Scheme IV



Scheme V



whereas the reactive species is **18**, with the phenol oxygen in its more nucleophilic anion form and the undissociated carboxyl group activating the side-chain double bond toward nucleophilic attack (Scheme IV). [For this reason we have calculated final rate constants for the monoanion reactions (Table V) in terms of this minor tautomer.] The equilibrium constant for **17** ⇌ **18** is (to a first approximation) the ratio of the observed dissociation constants K_a^2/K_a^1, and the effect of substituents on this equilibrium is opposite, and almost equal to, that on the cyclization reaction of **18**. For example, for X = H the concentration of **18** is $10^{-6.13}$ times that of **17**, so that the true rate constant for the water-catalyzed cyclization of **18** is 1.84×10^{-4} $s^{-1} \times 10^{6.13} = 250$ s^{-1}, 2×10^4 times faster than that of the dianion. Relative to **16**, R = H; therefore, the activating effects of COO^- and COOH substituents, R, are 4000 and 8×10^7, respectively. The effects are large and represent the first direct measurement of the activating effects of both the ionized and un-ionized carboxyl group in carbanion-forming reactions.

Relevant Previous Work. Mechanistic work on related systems has generally involved the reverse base-catalyzed elimination of aryl oxide. Fedor and Glave[16] established that the ready general-base-catalyzed reaction of **20**, Y = CH_3, involves the E1cB mechanism (Scheme V). For a better leaving group than phenoxide ($RCOO^-$) enolization was the slow step,[17] while for methoxide k_2 was rate-determining and only specific-base catalysis could be observed.[18] For the phenoxy compound **20**, Y = CH_3, the rate-determining step could be changed from k_1 to k_2 simply by increasing the concentration of the general base.[16]

Our reactions show a large dependence on the nature of the activating group, general-species catalysis, and almost complete neutralization of the negative charge on the phenolate oxygen in the transition state, as judged by the Hammett ρ^- value. We believe that at least the water-catalyzed cyclizations of the mono- and dianion species involve carbanion intermediates, with the advantage of the protonated carboxyl group over carboxylate $k_{COOH}/k_{COO^-} = 2 \times 10^4$. For a similar system, Crosby and Stirling[19] found that the ratio of rate constants for the ethoxide-catalyzed elimination of phenoxide from **20**, Y = OEt, and **20**, Y = O^-, was 10^6. Although it was demonstrated that **20**, Y = OEt, used the E1cB mechanism, no further studies of **20**, Y

(15) (a) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161. (b) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345.

(16) Fedor, L. R.; Glave, W. R. *J. Am. Chem. Soc.* **1971**, *93*, 985.
(17) Cavestri, R. C.; Fedor, L. R. *J. Am. Chem. Soc.* **1970**, *92*, 4610.
(18) Fedor, L. R. *J. Am. Chem. Soc.* **1969**, *91*, 908.
(19) (a) Crosby, J.; Stirling, C. J. M. *J. Chem. Soc. B* **1970**, 671. (b) Crosby, J.; Stirling, C. J. M. *J. Chem. Soc. B* **1970**, 679.

= O^-, have been published, and so this factor may not represent the true advantage of carboxyl over carboxylate in a stepwise process.

Bada and Miller[20] studied the hydration of fumaric acid at elevated temperatures and observed addition of hydroxide ion to fumarate dianion to give malate. The ratio of rate constants for addition of hydroxide to the neutral and dianion species was 3 × 10^7 at 135 °C. The corresponding value for the addition of ammonia was only 3 × 10^4. The discrepancy of 10^3 was explained by an adverse electrostatic interaction incurred in bringing together the charged dianion and hydroxide species from infinite separation. Such an effect may also contribute to Stirling's value of 10^6. Any electrostatic effect involving the single carboxylate of the phenol–olefin system is expected to be less severe than that in fumarate dianion and will in any case be much reduced in the intramolecular case because the two anionic centers are already in close proximity in the ground state.

Surprisingly, the cyclizations of the mono- and dianions of **7** show similar responses to all the usual mechanism probes, while the water-catalyzed and general-acid-catalyzed reactions differ significantly. So we discuss the reactions of mono- and dianions for each type of catalysis together.

Water-Catalyzed Cyclization of Mono- and Dianions. In the absence of an added general acid the proton required to convert the enolate dianion (**14**; Scheme III) to product monoanion (**15**) must come from solvent water or H_3O^+. All the evidence is consistent with the simple two-step mechanisms shown in Schemes III and IV for the cyclizations of both mono- and dianions. Substantial solvent deuterium isotope effects (k_{H_2O}/k_{D_2O}) between 4 and 5.4 (Table VI) indicate that the proton-transfer step is rate-determining.[21] And the entropies of activation are substantial and negative for both ionic forms. For **7a** mono- and dianions, $\Delta S^\ddagger$ = −22 ± 4 and −25 ± 1 eu (−94 ± 5 and −107 ± 3 J K^{-1} mol^{-1}), respectively, consistent with the involvement of a molecule of water in the transition state. The apparent enthalpies of activation (19 ± 1 and 15 ± 0.3 kcal mol^{-1}, 81 ± 5 and 65 ± 1 kJ mol^{-1}) show $\Delta H^\ddagger$ somewhat larger for the monoanion, but the true value for the cyclization of the reactive form (**18**, X = H) of the monoanion is about half this figure.

For **7a**, the product isotope effect is equal to the kinetic solvent isotope effect for the cyclization of the dianion, as expected if the product and rate-determining steps are the same. Thus, an intermediate (**14**) must be stable enough to discriminate between H_2O and D_2O and is thus at least partially solvent equilibrated. Full diffusional equilibrium is not established, as shown by the much reduced isotope effects for protonation by added general acids, but rotation within the solvent shell appears to be possible. Protonation could also include reversible proton transfer to *oxygen* ("trapping" **14**·BH^+ as **19**·B): This would be kinetically "invisible" because the slower proton transfer to carbon is the observed rate-determining step, but would extend the lifetime of the intermediate substantially. It is also a possible (partial) explanation of the remarkable similarities between the cyclizations of the mono- and dianions, which involve intermediates (**19** and **14**, respectively) of such apparently different stabilities.

Finally, both reactions are stereospecific. The dianion (**13**, X = H) is cyclized in KOD in D_2O to give almost exclusively (≥90%) monodeuterio diastereoisomer A (Table VII): as expected for anti addition of phenol O and solvent D. We obtained complementary stereochemical information for the reverse, elimination reaction from exchange experiments on the ring-closed compound **8a**. For **8a** (and **8b**), exchange of the β-hydrogens for deuterium occurs via slow base-catalyzed elimination of aryl oxide to give the dianion **13**, followed by very rapid recyclization to give **15**. Again, for **8a**, monodeuterio diastereoisomer A is formed preferentially (≥93%). No exchange accompanied the OD^--catalyzed opening of **8c** → **13** in D_2O.

(20) Bada, J. L.; Miller, S. L. *J. Am. Chem. Soc.* **1969**, *91*, 3948.
(21) For **8c** it is possible to measure the rate of the reverse, ring-opening reaction in KOH (cf. **15** → **13**). This reaction is faster in D_2O, with k_{OD^-}/k_{OH^-} = 1.38, similar to isotope effects observed previously for related E1cB eliminations of PhO^-.[17]

Table VIII. Structure–Reactivity Parameters for the Cyclization of **7a**, **7b**, and **7c**, Catalyzed by General Acids BH^+, at 39 °C and Ionic Strength 1.0 M (KCl)

(A) Variation of Leaving Group[a]

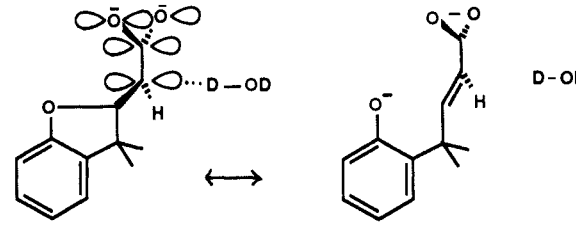
buffer base, B	pK_{BH}	Brønsted β_{nuc}	Hammett ρ^-
monoanion			
acetate	4.6	0.86 ± 0.01	−2.37 ± 0.04
quinuclidine	11.5	0.88 ± 0.02	−2.41 ± 0.06
3-quinuclidinol	10.0	0.86 ± 0.01	−2.35 ± 0.04
3-chloroquinuclidine	9.0	0.82 ± 0.01	−2.25 ± 0.04
3-quinuclidinone	7.5	0.85 ± 0.02	−2.32 ± 0.06
ethylamine	10.5	0.91 ± 0.01	−2.48 ± 0.02
water[b]	15.7	0.88 ± 0.01	−2.41 ± 0.05
dianion			
ethanolamine	9.4	0.86 ± 0.05	−2.34 ± 0.14
3-propanolamine	9.9	0.86 ± 0.04	−2.34 ± 0.12
ethylamine	10.5	0.88 ± 0.05	−2.41 ± 0.16
water[b]	15.7	0.85 ± 0.04	−2.33 ± 0.12

(B) Variation of General Acid[c]

compd	**7a**	**7b**	**7c**
aromatic substituent	H	Br	NO_2
pK_{nuc}	10.69	10.04	7.21
Brønsted α for monoanion	0.20 ± 0.01	0.21 ± 0.02	0.23 ± 0.03

[a] See Table V for original data. [b] In this case, water = BH^+ and the data are from Figure 1. [c] Brønsted α values are based on the data for the four 3-substituted quinuclidine buffers.

The same result—almost exclusively anti addition—is observed for the cyclization of the monoanion also, though the data in this care are more complicated (see Results). This is the result expected on stereoelectronic grounds, if the stabilizing π–σ^*_{C-O} interaction in the intermediate (indicated by the arrows in **22**) gives rise to an unsymmetrical distribution of charge over the two faces of the π-system—including perhaps partial pyramidalization at the α-carbon. The same stereochemistry is of course expected



22 **23**

if the cyclization and proton-transfer steps are concerted, but the reverse E2 mechanism can be ruled out with some confidence on the basis of the effects of aromatic substituents (X). Hammett ρ^- values (based on σ^-) are identical for both the mono- and dianion reactions (−2.41 ± 0.05, −2.33 ± 0.12, respectively) and close to equilibrium values for protonation of ArO^- (cf. ρ^- values of 2.11[22] and 2.23[23] for the ionization of phenols in water). The aryl oxide pK_a's for our three compounds **7** are correlated by σ^-, with ρ^- = 2.74 ± 0.03. This last figure may be affected by the interaction of the phenolic OH (or O^-) with the side-chain carboxylate group, but even if it is, the ρ^- values observed for the cyclization reactions are still consistent with reactions via an intermediate, because of the contribution to its structure from the π–σ^*_{C-O} interaction (**22** ↔ **23**) described above.[24,25]

Thus, the water-catalyzed cyclizations of **7a**, **7b**, and **7c** mono- and dianions involve the reverse $(E1cB)_1$ mechanism.[26] In one case, that of **7c**, we have been able to study the reaction in the elimination direction and show that the ring-opening reaction of **8c** in KOD is not accompanied by H–D exchange. This is consistent with an $(E1cB)_1$ mechanism.

(22) Jaffé, H. H. *Chem. Rev.* **1953**, *53*, 161.
(23) Barlin, G. B.; Perrin, D. D. *Q. Rev., Chem. Soc.* **1966**, *20*, 75.
(24) Alunni, S.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 2052.
(25) Keeffe, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1983**, *105*, 265.
(26) For classifications of elimination reaction mechanisms, see: (a) Banthorpe, D. V. *Elimination Reactions*; Elsevier: Amsterdam, 1963; Chapter 4. (b) Bunnett, J. F. *Surv. Prog. Chem.* **1969**, *5*, 53.

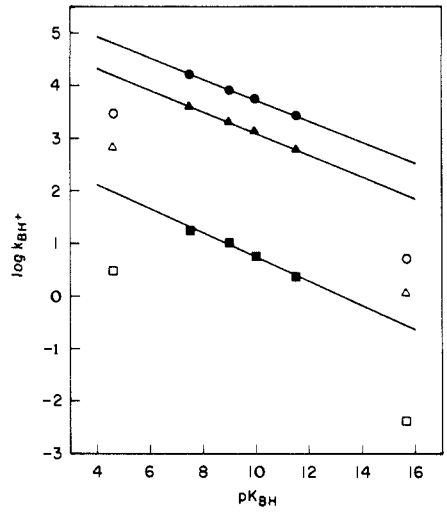


Figure 2. Brønsted plots for general-acid catalysis by protonated 3-substituted quinuclidines of the monoanion cyclization of **7a** (●), **7b** (▲), and **7c** (■). Points for neutral catalysts (acetic acid and water) are shown with open symbols. Data for buffer acids are from Table V. Data for water are from Figure 1.

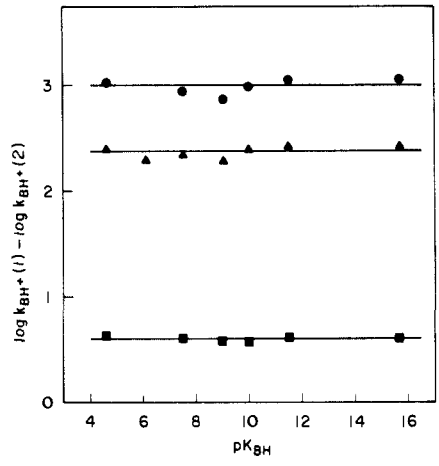


Figure 3. Plots of difference in log k_{BH^+} against pK_{BH} for the monoanion reaction of any two substrates 1 and 2: (●) (1) = **7a**, (2) = **7c**; (▲) (1) = **7b**, (2) = **7c**; (■) (1) = **7a**, (2) = **7b**. Buffer acid data are from Table V. Data for water are from Figure 1. The slopes of the lines define $p_{xy} = \partial\alpha/\partial pK_{BH} \simeq 0$.

General-Acid Catalysis. The cyclizations of all our compounds **7**, both mono- and dianions, show general-acid catalysis, and no curvature in buffer plots up to 1 M total buffer was observed. Thus, proton transfer remains rate-determining for reactions of general acids stronger than water. Most efficient are the conjugate acids of unhindered tertiary amines. The second-order rate constant for quinuclidinone is greater than that calculated for H_2O by a factor of 3450 for the monoanion reaction of **7a**. So the lifetime of the carbanion intermediates could be significantly reduced in these reactions, leading to the possibility of a change in mechanism. To examine this question we have varied both general acid and aromatic substituent X, looking for evidence of coupling between the C–O bond-forming and proton-transfer steps, in the shape of a significant cross-interaction coefficient p_{xy}.[25,27] The results are summarized in Table VIII. For the cyclization of the monoanion there is no change in Hammett ρ^- or Brønsted β_{nuc} over a range of 11 units of the pK_a of the general acid, pK_{BH}, and the values observed for catalysis by R_3NH^+ are identical with those for the water-catalyzed reactions. Correspondingly, no change in Brønsted α for general-acid catalysis by the four 3-substituted quinuclidine conjugate acids with changing aromatic substituent X (pK_{nuc}) is observed (Figure 2; Table VIII). Although

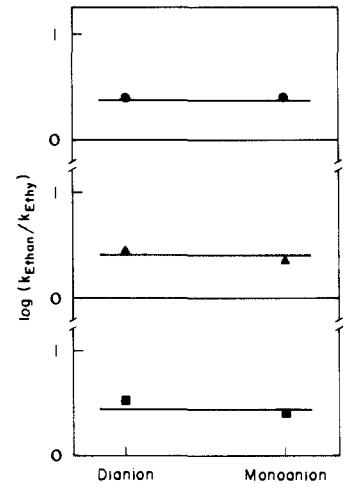


Figure 4. Diagram to show the relationship between the log of the ratio of rate constants for catalysis by the conjugate acids of ethanolamine and ethylamine, log (k_{ethan}/k_{ethy}), of the monoanion and dianion reactions of **7a** (●), **7b** (▲), and **7c** (■). Data are from Table V. The horizontal lines drawn through the points show that the α value for general-acid catalysis of the monoanion cyclization reaction is not detectably different from that for the dianion reaction.

the α values varied slightly (and actually in the direction expected for a concerted reaction) the "difference" plots (Figure 3) show unequivocably that $p_{xy} = \partial\beta_{nuc}/\partial pK_{BH} \simeq 0$ for this reaction. Here the difference in the quantity log k_{BH^+} for any two substrates is plotted against the pK_a of the general acid (pK_{BH}).[28] The horizontal lines drawn through the points illustrate the lack of interaction between the base and the leaving group (in the reverse direction) over a large range of base strength.

For the dianion reactions, data are available for only a few buffer acids. The pK_a range of the three RNH_3^+ general acids is only 1.1 units and therefore too small for useful Brønsted correlations. Thus, the α values for the dianion reactions were estimated indirectly by comparing the ratio of the rate constants for the conjugate acids of ethanolamine and ethylamine for the mono- and dianion reactions of any given substrate: This quantity log (k_{ethan}/k_{ethy}) is a measure of the α value in each case. Figure 4 shows the results in a graphical form, and a horizontal line can be drawn through the points for the dianion and monoanion for each substrate. This indicates that the α value for the dianion reaction is not detectably different from that for the monoanion reaction of the same substrate, and hence p_{xy} is also indistinguishable from zero for the dianion reaction. Also, β_{nuc} (ρ^-) is again identical for catalysis by the three primary ammonium compounds and for water.

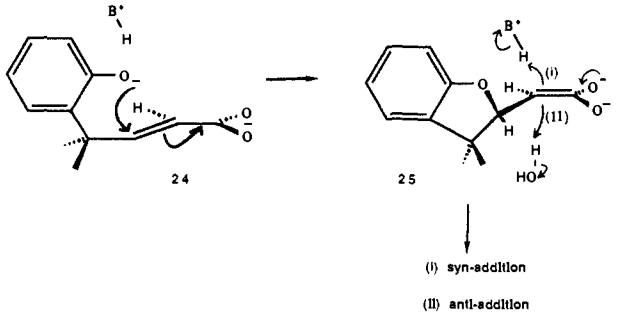
There is thus no significant coupling between C–O bond formation and proton transfer in the rate-determining transition state, and we can rule out any recognizable E2 mechanism for the general-acid-catalyzed cyclization of **7**. As for the water-catalyzed reaction, the evidence is also consistent with a reverse $(E1cB)_1$ mechanism. In other respects, the reactions catalyzed by protonated amines differ sharply from the water-catalyzed cyclizations. The kinetic and product deuterium isotope effects fall in the range 1–2, compared with 4–5 for the $H_2O(D_2O)$-catalyzed reactions (Table VI). Entropies of activation are significantly more positive: For the cyclization of **7a** catalyzed by protonated 3-quinuclidinone, $\Delta S^{\ddagger}$ is −13 ± 2 eu (56 ± 10 J K^{-1} mol^{-1}), compared with −30.3 eu (127 J K^{-1} mol^{-1}) calculated for the (second-order) water-catalyzed reactions. And the stereochemistry of addition changes from anti to syn.

As discussed above, the cyclization of **7a** in KOD/D_2O gives almost exclusively the product of anti addition of phenol O and solvent D (diastereoisomer A in Table VII). When the reaction of the dianion is run in buffered solution, the proportion of anti addition product falls with increasing buffer concentration. The

(27) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.

(28) Gandler, J. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 1937.

Scheme VI



analysis is accurate enough to show that the water-catalyzed reaction gives ≥90% anti addition and the cyclization of the dianion catalyzed by the conjugate acids of piperidine and quinuclidine ≥90% syn addition product. Results for the cyclization of the monoanion catalyzed by protonated quinuclidinone, phosphate, and acetic acid gave similar results.

Thus, the proton-transfer process is qualitatively as well as quantitatively different for the two reactions. Our best explanation hinges on the expected short lifetimes of the carbanion intermediates and involves stepwise preassociation mechanisms[15] for the cyclization of both the mono- and dianions of **7** catalyzed by added general acids. Intermediate carboxylic acid enolate mono- and dianions (**19**, **14**) are formed reversibly (Schemes III and IV), and are stable enough to discriminate ($k_{H_2O}/k_{D_2O} \sim 5$) between H_2O and D_2O at least in the solvation shell. Activation-limited proton transfer to carbon is thus rate-determining for the spontaneous reaction, as generally observed for the ketonizations of more stable enolates. But both enolates must break down by elimination of aryl oxide faster than the diffusion limit. (This is readily predictable for the dianion **14** from the results of Fedor and Glave[16] who estimated the rate constant for the loss of PhO^- from the free enolate **21**, Y = CH_3, to be $\sim 10^6$ s^{-1}: less so for the monoanion, though we know that it breaks down to starting materials faster than it removes a proton from water.) Only preassociated general acids, already present in the encounter complex, would then be in a position to deliver a proton to the carbanion before it reverts to starting material.

The low sensitivity (Brønsted $\alpha \sim 0.2$) to the pK_a of the general acid may represent either a very early transition state for proton transfer to carbon (not readily distinguishable from hydrogen bonding to the intermediate **22**)[15] or the effect of the strength of the general acid on the preassociation equilibrium. This could involve H bonding to the ground-state phenolate oxygen and is expected to be favored electrostatically for cationic general acids: as discussed previously for other reactions[1,29] in which very short-lived (or nonexistent) carbanion species are generated from oxy anions in the presence of preassociated general acids. In the latter reactions, catalysis is observed specifically for positively charged general acids. In the present case the cyclization of the monoanion at least is catalyzed by both phosphate and acetic acid.

A preassociation equilibrium in which the general acid is associated specifically with the (more localized) phenolate anion might also be thought to explain the observed stereochemistry of addition (Scheme VI). If the intermediate breaks down faster than the associated general acid can diffuse away, it is reasonable that it does not have time either to migrate within the encounter complex (**24**) from one face of the double bond to the other. So the carbanion would be generated (**25**) with the general acid associated specifically with the face syn to the phenolate O^-, notwithstanding the stereoelectronic preference for protonation from the opposite, anti face. However, this explanation can be ruled out by considering the reaction in the reverse (elimination) direction. Since the C–O bond is not broken at all in the rate-determining transition state, any advantage of syn elimination via a stabilizing $BH^+\cdots O$–C interaction is expected to be much smaller than the observed syn/anti ratio of ≥100. An alternative explanation is that approach to the stereoelectronically favored anti face is hindered by the *gem*-dimethyl group of the newly formed ring, so that more sterically demanding general acids than water are directed to the opposite face. That a β'-methyl group can have a large shielding effect on proton abstraction (in the elimination direction) has been demonstrated by Bailey and Saunders[30] in their study of the E2 elimination reactions of 3-hexyltrimethylammonium ions, and there is some literature precedent for conformational control in E1cB reactions.[31] However, more results are needed before we can say that this remarkable (and unprecedented) change in stereochemistry of addition reflects the fundamental chemistry of the intermediate, rather than the special steric requirements of one particular system.

Enzyme-Catalyzed Hydration Reactions. We suggested previously[1] that the key factor in the hydration of an unactivated C=C double bond under physiological conditions is the generation of negative charge on an oxygen atom in "appropriate proximity" to the π-system. For activated systems like fumarate and other α,β-unsaturated acid derivatives, the chemical case for the nucleophile-led mechanism is stronger still.

Enzyme-catalyzed hydration–dehydration reactions are generally stereospecific, and many examples of both syn and anti addition are well-established. The fumarase reaction involves the anti addition of water,[2] while β-hydroxydecanoyl thioester dehydrase catalyzes the syn addition of water to α,β-unsaturated thioesters.[32] (The latter enzyme is known to use a single active site histidine,[33] an obvious pointer to syn addition.) A generalization suggested to relate the stereochemistry of the addition–elimination process to substrate structure is a correlation with the nature of the activating group. Where this is a ketone or thioester, the stereochemistry is syn, whereas for α,β-unsaturated acids anti addition of water is observed,[34] as it is also where no activating group is present.[1,35]

Our results show that E1cB mechanisms can explain the important features of most of these reactions, including the observed stereospecificity. Kinetically the most difficult step of all those involved in hydration/dehydration—given that appropriate proximity can make C–O bond formation rapid—is the initial removal of the C–H proton in the elimination direction. This will be faster for ketones and thioesters, more difficult for carboxylic acid anions, and impossible, without concerted cleavage of the C–O bond, for alcohols without activating groups. These more difficult reactions must make maximum use of any structural feature of the substrate that maximum stabilize the carbanion, and thus the transition state leading to it. The one such feature always present is the σ_{C-H}–σ^*_{C-O} interaction (becoming π–σ^*_{C-O} in the delocalized carbanion **22**), which accounts for the significant effect of the leaving group *on proton removal* observed in several $(E1cB)_1$ reactions.[24,25] In the cyclizations studied in this work, involving COO^- (COOH) activation, we can calculate a value of β_{1g} on the proton removal step in the elimination direction of –0.14 (0.86–1; Table VIII). Since it is well-established that two-electron stabilizing interactions of this sort are most effective when the orbitals concerned are *antiperiplanar*,[36] it seems clear that there is a stereoelectronic advantage for anti elimination *by the* $(E1cB)_1$ *mechanism*, which becomes relatively more important with decreasing stability of the carbanion intermediate. (The culmination of this trend, of course, is a recognizable E2 mechanism.)

Also paralleling the stability of the carbanion intermediate is the ease of C–O cleavage. The more stable the intermediate the

(29) Thibblin, A.; Jencks, W. P. *J. Am. Chem. Soc.* **1979**, *101*, 4963.

(30) Bailey, D. S.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 6904.
(31) (a) Redman, R. P.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1978**, 43. (b) Cabaleiro, M. C.; Garay, R. O. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1091.
(32) Schwab, J. M.; Habib, A.; Klassen, J. B. *J. Am. Chem. Soc.* **1986**, *108*, 5304.
(33) Helmkamp, G. M.; Bloch, K. *J. Biol. Chem.* **1969**, *244*, 6014.
(34) Widlanski, T. S.; Bender, S. L.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 1873.
(35) Niehaus, W. G., Jr.; Kisic, A.; Torkelson, A.; Bednarczyk, D. J.; Schroepfer, G. J., Jr. *J. Biol. Chem.* **1970**, *245*, 3790.
(36) Epiotis, N. D.; Cherry, W. R.; Shaik, S.; Yates, R. L.; Bernardi, F. *Structural Theory of Organic Chemistry*; Springer-Verlag: Berlin, 1977.

slower this step will be, and thus the more important that it is catalyzed effectively. In a single-base enzyme, this can be done by the general acid generated by the removal of the C–H proton, as long as the leaving group oxygen is syn to it. For an unstable intermediate, spontaneous (water-catalyzed) C–O cleavage would be faster and anti stereochemistry more necessary, as described above. Eventually, as the general level of catalytic efficiency rose, evolutionary pressure would increase for catalysis even of relatively fast C–O cleavage, leading to enzymes with a second active site catalytic group, but naturally retaining anti stereochemistry.

Acknowledgment. We are grateful to the Science and Engineering Research Council for a studentship to T.L.A. and to Dr. J. P. Richard for helpful discussion.

Rate and Equilibrium Constants of Ionization of (α-Cyanodiphenylmethane)bis(tricarbonylchromium(0)) in Me_2SO–Water Mixtures. Unusual Solvent Effect on the Intrinsic Rate Constant

Claude F. Bernasconi,*,‡ Richard D. Bunnell,‡ and François Terrier†

Contribution from the Thimann Laboratories of the University of California, Santa Cruz, California 95064, and the Laboratoire de Physicochimie des Solutions, UA CNRS 403, ENSCP, 11 Rue Curie, 75231 Paris Cedex 05, France. *Received March 17, 1988*

Abstract: The kinetics of the ionization of (α-cyanodiphenylmethane)bis(tricarbonylchromium(0)) by carboxylate ions, primary amines, and the piperidine/morpholine pair have been measured in 50%, 70%, and 90% aqueous Me_2SO. The Brønsted plots for the carboxylate ion reactions in 70% and 90% Me_2SO show some downward curvature which is reminiscent of recent reports of such curvature in the ionization of acetylacetone and 1,3-indandione, and is attributed to a solvation effect. Intrinsic rate constants, defined as $k_0 = k_1^B/q = k_{-1}^{BH}/p$ at $\Delta pK + \log(p/q) = 0$, were determined by suitable interpolation or extrapolation of the Brønsted plots. For the piperidine/morpholine pair in 50% Me_2SO $\log k_0 = 3.30$. Even if one allows for a rate lowering steric effect of up to one log unit, giving a corrected $\log k_0 \approx 4.3$, this value is still close to that for 4-nitrophenylacetonitrile ($\log k_0 = 3.95$). This suggests that the resonance effect of the $Cr(CO)_3$–phenyl groups is substantial and comparable to that of the combination of a 4-nitrophenyl and a cyano group, in agreement with some literature reports but in disagreement with others. The effect of increasing the Me_2SO content of the solvent is to significantly decrease k_0 for both the carboxylate ion and amine reactions. This contrasts with either sharp *increases* in k_0 or solvent independent k_0 values with six other carbon acids for which similar data are available. The decrease in k_0 can be attributed to carbanion solvation being substantially stronger in Me_2SO than in water, as confirmed by measurements of the solvent activity coefficient for the transfer from 50% to 70% and from 50% to 90% Me_2SO. Since it appears that carbanion solvation generally lags behind proton transfer at the transition state, this lag produces a decrease in k_0 in the better solvating medium. Surprisingly, the solvent effect on k_0 is essentially independent of the ionizing agent, again in contrast to findings in other systems where the addition of Me_2SO enhanced k_0 for the carboxylate ion reactions more strongly than for the amine reactions. A possible explanation of our results is that the main factor usually responsible for the larger solvent effects in the carboxylate ion reactions, i.e., the lag of the proton transfer behind the desolvation of the carboxylate ion, becomes insignificant because proton transfer is nearly complete at the transition state, as implied by very high Brønsted β-values.

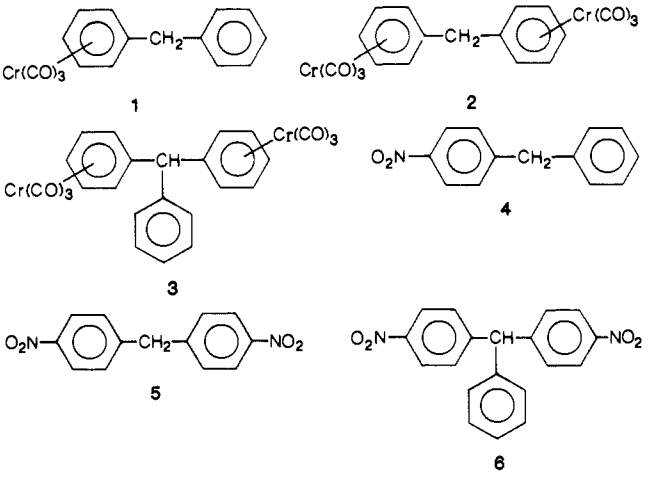
The tricarbonylchromium(0) group ($Cr(CO)_3$) is known to be strongly electron withdrawing as reflected in a pK_a value of $Cr(CO)_3$–phenylacetic acid that is virtually identical with that of 4-nitrophenylacetic acid.[1] Despite its strong electronic effect it has not been widely used as an activating group in the study of proton transfers from carbon acids. In a first quantitative study Terrier et al.[2] recently compared kinetic and thermodynamic acidities of the $Cr(CO)_3$-substituted di- and triphenylmethanes **1**–**3** with the corresponding 4-nitro-substituted analogues **4**–**6** in Me_2SO–methanol mixtures. Their major findings can be summarized as follows.

(1) The nitro group is more effective in stabilizing the diphenyl and triphenylmethane anions as reflected in much higher acidity constants of **4** vs **1**, **5** vs **2**, and **6** vs **3**.

(2) One $Cr(CO)_3$–phenyl group is *kinetically* more acidifying than one 4-nitrophenyl group, as reflected in an approximately 3-fold higher rate constant of deprotonation of **1** vs **4** by methoxide ion.

(3) In the comparisons **2** vs **5** and **3** vs **6** the respective nitro compound is deprotonated slightly more rapidly than the $Cr(CO)_3$ compound, but if the results are adjusted to compensate for the different thermodynamic acidities, **2** is faster than **5** while **3** and **6** show comparable kinetic reactivities.

Chart I



‡University of California.
†UA CNRS 403, ENSCP.

(1) Nicholls, B.; Whiting, M. C. *J. Chem. Soc.* **1959**, 551.

0002-7863/88/1510-6514$01.50/0