Mechanism of the Base-Catalyzed Elimination of Para-Substituted Phenoxides from 4-(Aryloxy)azetidin-2-ones

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4-(Aryloxy)azetidin-2-ones **4–7** react in dilute aqueous alkali to give 3-hydroxyacrylamide oxyanion and para-substituted phenolate ions. Similarly, 4-(aryloxy)-3,3-dimethylazetidin-2-ones **8–11** give 2,2-dimethylcarboxaldoacetamide and para-substituted phenolate ions. Reactivity is proportional to the fraction of (aryloxy)azetidin-2-one anions, $K_a/(K_a + [H^+])$. Kinetic pK_a's of **4–11** and first-order k_2's for (suggested) reversible E1cB elimination of para-substituted phenoxide ions from N-1 anions are reported. Reactions are further characterized kinetically by solvent deuterium isotope effects: k_{OH}/k_{OD} = ca. 0.5, $\rho(k_2)$ = 2.2 for **4–7** and $\rho(k_2)$ = 2.7 for **8–11**, and β_{lg} = –0.65 for **4–7** and β_{lg} = –0.75 for **8–11**.

Base-catalyzed α,β-elimination from 4-oxy-substituted 2-butanones proceeds in water via the E1cB mechanism. With weakly basic leaving groups such as para-substituted benzoate ions, the mechanism is $E1cB_I$.[1] With strongly basic leaving groups such as methoxide ion, the mechanism is $E1cB_R$.[2] With moderately basic leaving groups such as para-substituted phenoxide ions, partitioning of carbanions is kinetically detectable and the mechanism changes from $E1cB_I$ at low amine catalyst concentration to $ElcB_R$ at high amine catalyst concentration.[3] For this group of reactions the only obtainable rate constant is that for carbanion formation.

It was of interest to examine a system that reacted via the $E1cB_R$ mechanism (eq 1) and permitted measurement of rate constants for departure of leaving groups. Such a system could provide nucleofugalities of diverse leaving groups in elimination reactions.

$$SH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S^- + H^+ \qquad S^- \xrightarrow{k_2} \text{products} \qquad (1)$$

Separation of the constant for the preequilibrium ionization step, K_a ($\equiv k_1/k_{-1}$), from that for the nucleofugic step, k_2, in an $E1cB_R$ reaction requires that the substrate ionize appreciably in the pH range of the experiments. When this occurs, the rate of the reaction is proportional to the mole fraction of anion and equals $(k_2K_a/(K_a + [H^+]))$[substrate]. The constants can be evaluated (vide infra).

As a first step we sought to establish the $E1cB_R$ mechanism for an appropriate candidate system. We chose the predictably acidic 4-oxy-substituted azetidin-2-ones to test for the $E1cB_R$ mechanism and the feasibility of measuring K_a, for ionization of NH, and k_2. In dilute aqueous alkali, 4-acetoxyazetidin-2-one (**1**) gives 3-hydroxyacrylamide oxyanion (**2**) and acetate ion (eq 2). 4-(Aryloxy)azetidin-2-ones (Table I) similarly react to give **2** and substituted phenolate ions. Here we attempt to show that the $E1cB_R$ mechanism is used and that the system is potentially useful for determining nucleofugalities in elimination reactions.

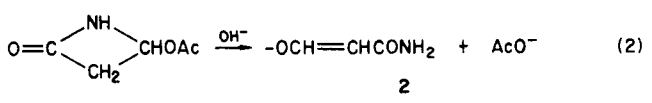

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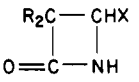
Table I. Structures of 4-Substituted Azetidin-2-ones 1 and 4–11



compd	R	X
1	H	CH_3CO_2
4	H	p-$CH_3OC_6H_4O$
5	H	C_6H_5O
6	H	p-ClC_6H_4O
7	H	p-$NO_2C_6H_4O$
8	CH_3	C_6H_5O
9	CH_3	p-ClC_6H_4O
10	CH_3	p-CNC_6H_4O
11	CH_3	p-$NO_2C_6H_4O$

Experimental Section

Equipment. A Gilford Model 2400 spectrophotometer coupled to an Apple II computer with disk drive and printer, a Cary 118C spectrophotometer, a Radiometer PHM 26 with GK 2401B combination electrode, a Tamson TE9 constant temperature circulating bath, and a Mel-Temp apparatus were used. Elemental analyses were performed by Atlantic Microlab, Inc.

Materials. 4-Acetoxyazetidin-2-one (**1**), 4-acetoxy-3,3-dimethylazetidin-2-one (**3**), 4-(*p*-methoxyphenoxy)azetidin-2-one (**4**), 4-phenoxyazetidin-2-one (**5**), 4-(*p*-chlorophenoxy)azetidin-2-one (**6**), and 4-(*p*-nitrophenoxy)azetidin-2-one (**7**) were synthesized by the method of Clauss et al.[4] 3,3-Diethoxypropionamide was synthesized by the method of Israel et al.[5] NMR spectra and melting points agreed with those reported. 4-(Aryloxy)-3,3-dimethylazetidin-2-ones were synthesized from **3** by the method of Clauss et al.[4]

4-Phenoxy-3,3-dimethylazetidin-2-one (8): mp 116 °C (ethanol–pentane); ^1H NMR ($CDCl_3$) δ 1.28 (s, CH_3), 1.42 (s, CH_3), 5.32 (s, CH), 6.77–7.47 (m, aryl and NH).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 69.01; H, 6.86.

4-(*p*-Chlorophenoxy)-3,3-dimethylazetidin-2-one (9): mp 121–122 °C (ethanol–pentane); ^1H NMR ($CDCl_3$) δ 1.30 (s, CH_3), 1.42 (s, CH_3), 5.23 (s, CH), 6.76 (d, J = 9 Hz, aryl and NH), 7.28 (d, J = 9 Hz, aryl).

Anal. Calcd for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.36. Found: C, 58.56; H, 5.38.

4-(*p*-Cyanophenoxy)-3,3-dimethylazetidin-2-one (10): mp 142–143 °C (ethanol–pentane); ^1H NMR ($CDCl_3$) δ 1.32 (s, CH_3), 1.47 (s, CH_3), 5.37 (s, CH), 6.91 (d, J = 9 Hz, aryl and NH), 7.63 (d, J = 9 Hz, aryl).

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60. Found: C, 66.58; H, 5.60.

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4-(*p*-Nitrophenoxy)-3,3-dimethylazetidin-2-one (11): mp 133.5–134 °C (ethanol–pentane); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, CH_3), 1.50 (s, CH_3), 5.43 (s, CH), 6.95 (d, J = 9 Hz, aryl and NH), 8.25 (d, J = 9 Hz, aryl).

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.92; H, 5.12. Found: C, 55.75; H, 5.12.

Kinetics. The pHs of reaction solutions in the pH range 8.5–11.5 were maintained with (dimethylamino)ethanol, *N*-methylpiperidine, or quinuclidine buffers. In the concentration range 0.005–1.0 M KOH, no additional buffers were used. The pHs remained constant during runs. At low pHs, the concentration of hydroxide ion was determined from the relationship $[OH^-] = (1.3 \pm 0.1)10^{pH-14}$ and the pH reading.[6] Similarly, for reactions in D_2O, $[OD^-] = (1.5 \pm 0.1)10^{pH-14.87}$ was used.[6] The pD was determined from the pH meter reading by adding 0.4 to it.[7] Reactions were initiated by adding 10 μL of the appropriate azetidin-2-one in CH_3CN to aqueous reactant solution (μ = 1.0 M, KCl) contained in 3-mL cuvettes at 25 ± 0.1 °C.

Production of **2** and phenolate ions from azetidin-2-ones were followed spectrophotometrically at the wavelengths (nm) indicated: **2** (265), *p*-methoxyphenolate (238, 265), phenolate (240), *p*-chlorophenolate (240), *p*-cyanophenolate (245, decrease; 273), *p*-nitrophenolate (400).

As reactions proceeded, voltages proportional to absorbances and times were conducted to the Apple II computer and stored. These data were then manipulated by the computer using a kinetics program that gave the pseudo-first-order rate constant with standard error, correlation coefficient, and a least-squares plot of ln $(a - x)$ vs. time. Plots were linear to at least 75% reaction and usually were linear to more than 90% reaction. Pseudo-first-order rate constants were generally reproducible to ±5%, except for very rapid reactions for which reproducibility was generally ±10%.

Products. Reaction of **1** in weakly alkaline solution is characterized spectroscopically by an absorbance increase at 265 nm. The amount of absorbance is pH dependent from ca. pH 7.5 (low ϵ) to pH 12 (high ϵ) where it is maximal. This absorbance can be eliminated by acidification of the reaction mixture, and the absorbance can be regenerated by subsequent addition of base. The pH-dependent absorbance is characteristic of that of a highly absorbing enolate anion, **2**, which upon acidification reverts to carboxaldoacetamide (and its enol). Carboxaldoacetamide was generated in situ from 3,3-diethoxypropionamide[2] and dilute HCl. Addition of an aliquot of this carboxaldoacetamide solution to aqueous KOH gave **2**, λ_{max} 265 nm (log ϵ 4). When acidified, this solution showed no 265-nm absorbance, but absorbance was immediately regenerated when the acidic solution was made basic. At constant concentration of **2**, a plot of absorbance vs. pH has a sigmoid shape from which an apparent pK_a of 9.33 ± 0.03 was determined. 4-Acetoxy-3,3-dimethyazetidin-2-one can react in the same manner as **2**, but it cannot form an enol. As expected, reaction of **3** in dilute aqueous base shows no absorbance in the UV.

Reactions of 4-(aryloxy)azetidin-2-ones **4–7** in aqueous base give UV spectra that are the sum of 3-hydroxyacrylamide anion (**2**) and corresponding phenolate anion. Acidification of these solutions gives the spectrum of the corresponding phenol, and subsequent basification gives the original product spectrum. Reactions of 4-(aryloxy)-3,3-dimethylazetidinones **8–11** in aqueous base give the UV spectra of only the corresponding phenolate ion.

3,3-Dimethyl-4-acetoxyazetidin-2-one (**3**) in D_2O was titrated with 1 equiv of KOD: NMR (D_2O) δ 1.28 (s, CH_3), 2.10 (s, CH_3CO_2) 5.0 (s, HOD), 8.66 (s, CHO).

The reactions appear to be quantitative, with yields of 90% or better as estimated by UV–vis spectrophotometry.

Results

In aqueous alkaline solution, 4-acetoxy and 4-aryloxyazetidin-2-ones (**1**) give 3-hydroxyacrylamide anion (**2**) and acetate (eq. 2) or phenolate ions. This reaction is specific base catalyzed and therefore dependent only on the concentration of hydroxide ion. Reactions **7** in 0.02–0.1 M (dimethylamino)ethanol solutions, pH 9.34, give k_{obsd} = 0.0223 ± 0.0003 s^{-1}. Reactions of **7** in 0.02–0.20 M ethanolamine solutions, pH 9.79, give k_{obsd} = 0.0612 ± 0.0007 s^{-1}. Similarly, reactions of **11** in 0.06–0.20 M piperidine, pH 11.10, give k_{obsd} = 0.0487 ± 0.0005 s^{-1}.

In weakly alkaline solution, the observed pseudo-first-order rate constant is directly proportional to hydroxide ion concentration and the rate law is that of eq 3. There

$$k_{obsd} = k_{OH}[OH^-] \quad (3)$$

is no detectable spontaneous (water) reaction.

In more strongly alkaline solutions (0.005–1.0 M KOH), k_{OH} decreases as the concentration of hydroxide ion increases. This suggests that k_{obsd} is dependent on the mole fraction of azetidin-2-one anions, $K_a/(K_a + [H^+])$. At high pH, the rate law is that of eq 4. It may be seen that eq 3 is a limiting form of eq 4. Specifically, $k_2K_a/K_w = k_{OH}$ when $[H^+] > K_a$.

$$k_{obsd} = k_2K_a/(K_a + [H^+]) \quad (4)$$

In the concentration range 0.005–1.0 M KOH, plots of k_{obsd} vs. $[OH^-]$ are hyperbolas (Figure 1). Plots of $1/k_{obsd}$ vs. $1/[OH^-]$ (Figure 1) gave $1/k_2$'s as intercept and K_w/k_2K_a as slope, from which k_2's and K_a's were obtained (Table II).

Reactions are faster in D_2O than in H_2O. Values of k_{OD}/k_{OH} for **6**, **7**, **8**, and **11** are provided in Table II.

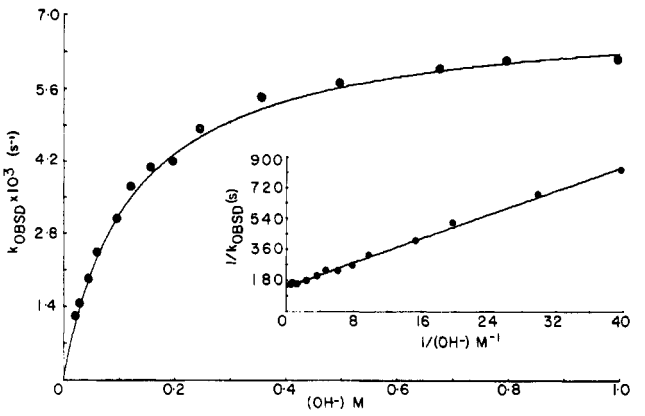

Figure 1. Plot of the pseudo-first-order rate constants vs. the molar concentration of hydroxide ion for reactions of 4-phenoxy-3,3-dimethylazetidin-2-one (**8**) (t = 25 ± 0.1 °C; μ = 1 M KCl). The solid line was constructed from eq 4 using the constants of Table II. Inset: plot of $1/k_{obsd}$ vs. $1/[OH^-]$ for this reaction. The solid line is the least-squares line.

Table II. Rate Constants for Reactions of 4-Substituted Azetidin-2-ones in Dilute Aqueous Alkaline Solutions[a]

compd	k_{OH}, M^{-1} s^{-1}	k_2, s^{-1}	pK_a	k_{OH}/k_{OD}
1	(5 ± 0.25) × 10^3	[b]	[b]	
4	1.43 ± 0.02	0.20 ± 0.0919	13.15	
5	2.62 ± 0.07	0.25 ± 0.02	13.00	
6	10.5 ± 0.48	1.1 ± 0.20	12.98	0.50
7	796 ± 21	20 ± 10[d]	12.40	0.57
8	(5.68 ± 0.1) × 10^{-2}	(7.14 ± 0.25) × 10^{-3}	13.10	0.55
	(0.102 ± 0.0006)[c]	((7.25 ± 0.20) × 10^{-3})[c]	(13.72)[c]	
9	0.23 ± 0.0006	(2.54 ± 0.059) × 10^{-2}	13.03	
10	6.9 ± 0.18	0.32 ± 0.019	12.70	
11	30 ± 1.84	0.94 ± 0.092	12.50	0.56

[a] t = 25 ± 0.1 °C; μ = 1.0 M KCl. [b] Not determined. **1** was too reactive to study at high $[OH^-]$ where eq 4 applies. [c] Determined in KOD/D_2O. [d] The large uncertainty in k_2 is due to the large uncertainty in the intercept of the double reciprocal plot. That intercept is only 0.04% of the maximum $1/k_{obsd}$ value of the set. The accuracy of k_2's value could be improved by running reactions of **7** in more concentrated KOH solutions, which would require stopped-flow equipment.

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The Hammett constant for k_2's of 4–7 is 2.20 ± 0.3 (r = 0.978). When σ^n and σ^- constants are used, ρ = 1.49 ± 0.01 (r = 0.993). In the 3,3-dimethyl series (8–11), ρ = 2.67 ± 0.12 (r = 0.998). When σ^n and σ^- constants are used, ρ = 1.67 ± 0.06 (r = 0.999).

For 4–7, β_{lg} = −0.65 ± 0.06 (r = 0.993); for 8–11, β_{lg} = −0.75 ± 0.04 (r = 0.997). Here β_{lg} is the slope of a plot of log k_2 against the pK_a of the conjugate acid of the leaving group.[21,22]

Discussion

Potentially, 4-acetoxy- and 4-(aryloxy)azetidin-2-ones can react in alkaline solution via several paths. These include β-lactam hydrolysis, nucleophilic displacement of acetate or phenoxide ions, 3,4-elimination, and 1,4-elimination of acetate and phenoxide ions. The $\Delta^{3,4}$- and $\Delta^{1,4}$-azetin-2-one formed in the latter two reactions would add nucleophiles to give further products, such as **2**.

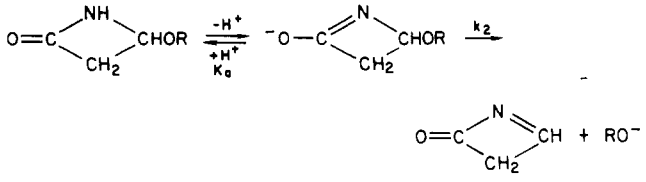
β-Lactam hydrolysis, which is favorable in the case of comparatively strained penicillins, is less favorable in the case of azetidin-2-one. Thus, k_{OH} = 8.54 × 10^{-2} M^{-1} s^{-1} (30 °C)[8] for hydrolysis of benzylpenicillin while k_{OH} = 2.17 × 10^{-3} M^{-1} s^{-1} (50 °C)[9] for hydrolysis of azetidin-2-one in 0.5 M KOH in 85% alcohol.

Clauss et al.[4] showed that under basic conditions **1** readily reacted with nucleophiles to give 4-substituted azetidin-2-ones. For example, compounds **4–7** of this study were synthesized from **1** and potassium phenolates in water.[4] 4-Methoxyazetidin-2-one was synthesized from **1** and methanolic magnesium methoxide.[4] In the presence of 2 equiv of piperidine, **1** gave 3-piperidinyl acrylamide.[4] These results show that the 4-acetoxy group is easily "displaced" and our results show that the 4-aryloxy group is also easily "displaced". The rate constants of Table II show that this chemistry is easier than lactam ring opening.

The simplest displacement mechanism is an S_N2 reaction at C-4 followed by further chemistry. The result that ethanolamine and piperidine do not catalyze transformations of **7** and **11** indicates that this mechanism does not operate efficiently.

Yet another path to products (eq 2) is via 3,4-elimination followed by addition of hydroxide ion at C-4, etc. Predictably, C-3 proton abstraction should be general base catalyzed with $k_{OH} \approx 5$ M^{-1} s^{-1}.[3] In fact, representative primary, secondary, and tertiary amines used in this study are not catalysts and k_{OH}'s for **1**, **4–7** are much greater than 5 M^{-1} s^{-1} (Table II). That C-3 proton loss is unessential for reactions of **1** and **4–11** is shown by the result that 3,3-dimethyl derivatives **8–11** react to give 2,2-dimethylcarboxaldoacetamide and phenolate ions.

Predictably, the easier proton transfer is from N-1 and we suggest that **1** and **4–11** react via the reversible E1cB mechanism shown.[2,10–12] Rapid reaction of $\Delta^{1,4}$-azetin-2-



one with hydroxide ion and decomposition of the resultant 4-hydroxyazetidin-2-one would give **2**. This mechanism predicts that product formation is proportional to the fraction of azetidin-2-one anion, $K_a/(K_a + H^+)$, as required by eq 4. The result that ethanolamine does not catalyze the reaction supports rate-determining leaving group expulsion rather than nucleophilic attack on $\Delta^{1,4}$-azetin-2-one at C-4.

Generally, specific base-catalyzed reactions are faster in D_2O than in H_2O. This is widely interpreted to mean that a reactant undergoes fast proton exchange with solvent prior to the rate determining step.[13–15] In the present study we measured k_{OH}/k_{OD} in 1.5 × 10^{-4} M OD^-/D_2O and found the values to be 0.50 (**6**), 0.57 (**7**), and 0.56 (**11**), consistent with our finding of specific base catalysis. Further, for **8** we dissected k_{OH}/k_{OD} into its component parts. That ratio is equal to $(k_2^H/k_2^D)(K_a^H/K_a^D)(K_w^D/K_w^H)$ and from the data of Table II, (k_2^H/k_2D) = 1.02 and (K_a^H/K_a^D) = 4.18. The value of (K_w^D/K_w^H) is 0.13[16] and for **8**, k_{OH}/k_{OD} = 0.55. The solvent isotope effect on k_2 is ca. 1 as predicted by the mechanism, and K_a and K_w are seen to be the contributors to the measured isotope effect.

The standard Hammett ρ values for k_2 for 4–7 (2.20 ± 0.3) and for 8–11 (2.67 ± 0.12) indicate an increase in negative charge in the leaving phenoxide ions in the transition state, consistent with rate-determining formation of $\Delta^{1,4}$-azetin-2-ones and the E1cB mechanism. It is noteworthy that 3,3-dimethylazetidin-2-ones 8–11 are more sensitive to electronic effects than are 4–7. The implication is that the critical transition states for 8–11 are reached later than those for 4–7. Expectedly, electron releasing methyl groups should destabilize transition states. This is reflected in the greater reactivity of **5**, **6**, and **7** vs. **8**, **9**, and **11**. (The reactivities of **5**, **6**, and **7** are related to those of **8**, **9**, and **11** by the equation, log k_2 (**5**, **6**, and **7**) = 0.88 ± 0.08 log k_2 (**8**, **9**, **11**) + 1.35 ± 0.12 (r = 0.996)).

In a related study[11] of the hydrolysis of aryl *N*-aryl carbamates, which undergo hydrolysis via a reversible E1cB mechanism similar to that postulated here, $\rho(k_2)$ = 2.9 based on σ and σ^- constants. The comparable values of ρ's for 4–7 and 8–11 are 1.49 ± 0.01 and 1.67 ± 0.06, respectively. It appears that E1cB elimination from sp^2 carbon involves more C–O bond breaking in the critical transition state than elimination from sp^3 carbon in 3-(aryloxy)azetidin-2-ones.

The picture of the transition state that emerges from consideration of ρ's is reinforced by the result that β_{lg} = −0.65 ± 0.06 for 4–7 and β_{lg} = −0.75 ± 0.04 for 8–11. Here, as for ρ's, the 3,3-dimethylazetidin-2-ones 8–11 are more sensitive to this measure of relative reactivity, and the implication is that transition states for 8–11 are reached later than those for 4–7. For aryl and alkyl arylcarbamates,[11] β_{lg} = 1.34, indicating again that transition states for the latter are reached later than for 4-(aryloxy)azetidin-2-ones.

We believe that our results straightforwardly support the reversible E1cB mechanism for reactions of **4–11** in aqueous base. It is noteworthy that pK_a's of 4-(aryloxy)azetidin-2-ones were measurable, albeit by kinetics means. They range from 12.4 for **7** to 13.15 for **4** and may be compared with 15.1 for acetamide.[18] To our knowledge, acetamide is the only amide whose pK_a has been directly measured, although estimates of pK's in water of other

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amides have been made.[18,19]

It has been pointed out that nucleofugality in 1,2-elimination reactions has been little studied.[20,21] This is because it is difficult to separate unambiguously deprotonation from departure of the leaving group.[20] In the present study, these processes have been separated in the few examples studied and we suggest that 4-substituted azetidin-2-ones could be useful probes to determine the nucleofugalities of diverse nucleofuges.

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Registry No. 1, 28562-53-0; 4, 31898-90-5; 5, 31898-84-7; 6, 31898-86-9; 7, 31898-87-0; 8, 93280-78-5; 9, 93280-79-6; 10, 93280-80-9; 11, 93280-81-0; D_2, 7782-39-0.

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Liquid and Supercritical Carbon Dioxide as Organic Solvents

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The nature of carbon dioxide in its liquid and supercritical states as a solvent for organic compounds was explored. Visible spectroscopy of solvatochromic dyes, infrared spectroscopy of ketones and pyrrole, and the exo:endo ratio of a Diels–Alder reaction in CO_2 solutions were employed as probes of solvent polarity. It was found for both liquid and supercritical CO_2 that $E_T(30) \simeq 33.8$ kcal/mol and $\Omega \simeq 0.50$; π^* is near −0.5. It is concluded that CO_2 in these states behaves very much like a hydrocarbon solvent with very low polarizability.

The central importance of solvents in chemical technology is well recognized. Indeed, scarcely a chemical process exists in which a solvent is not intimately involved in both synthesis and separation stages.[1] In most organic reactions, choice of solvents is of pivotal importance; often the solvent is the major component. The search for new solvents having wider-ranging properties continues to be a significant part of organic research.

The use of liquified gases, such as NH_3, SO_2, and HF, as reaction media is well established, and the question of whether liquified carbon dioxide has properties that make it suitable for use as a solvent in organic chemistry is a reasonable one. Carbon dioxide is readily available, inexpensive, nontoxic, nonflammable, chemically inert under many conditions, environmentally acceptable, and liquefiable at reasonable pressures.

The purpose of this paper is to present results of studies designed to assign a place for CO_2 in the series of conventional organic solvents. Literature data on the solubility of organic compounds in compressed CO_2 are augmented and summarized, and the question of the effective polarity of liquid and supercritical CO_2 is addressed. Although one might a priori expect CO_2 to be similar in CS_2 or, perhaps, to ketone solvents, it was thought that investigation of the spectroscopic properties of solvatochromic materials and of the behavior of solvent-sensitive reactions in CO_2 would give a useful picture of the nature of this unconventional solvent.

Supercritical and Subcritical Phases. The critical point of carbon dioxide is at 31 °C and 73 atm. Below this point, liquid CO_2 can be maintained under relatively modest pressure (about 950 psi at 25 °C). Above 31 °C, no amount of pressure will serve to liquify CO_2—there exists only the supercritical fluid phase that behaves as a gas, although when highly compressed, this fluid is denser than liquid CO_2 (ca. 0.47 g cm^{-1}). The subcritical liquid phase of CO_2 behaves like any other liquid; the supercritical fluid phase can also act as a solvent, but it has higher diffusivity, lower viscosity, and lower surface tension than does the liquid phase. A small but rapidly growing body of literature deals with the use of supercritical CO_2 as an extraction medium (vide infra). Current research centers upon CO_2 in the supercritical phase because it is thought to have, in general, better solvent properties than does CO_2 in the subcritical liquid phase. Indeed, the well-known solubility/pressure curve of naphthalene in CO_2 (Figure 2, ref 22b) demonstrates the type of behavior commonly encountered—solubility increases dramatically with increasing pressure above the critical point. Implicit in some current literature is the idea that the supercritical fluid phase is intrinsically different as a solvent from the subcritical liquid phase. This idea appears quite reasonable in view of the significant discontinuities in many physical properties, such as diffusivity, surface tension, viscosity, and even dielectric constant, near the critical point. But while it should be understood that supercritical CO_2 offers advantages over liquid CO_2 as a solvent (higher solubilities with increasing pressure, wider range of operating temperatures and pressures available, and density variable over a wide range), it has not been demonstrated that the solvent behavior of supercritical CO_2 is intrinsically different from that of subcritical CO_2. In fact, some recent work by Alwani has shown that the solubility of α-tocopheryl acetate in both subcritical and supercritical CO_2 increases with increasing pressure and that no significant changes in the solubility of tocopheryl acetate occur when subcritical CO_2 solutions are heated above the critical temperature at constant pressure.[2] Work is conducted in the supercritical region because useful temperatures,

(1) Dack, M. "Techniques of Chemistry"; Weissburger, A., Ed.; Wiley-Interscience: New York, 1975; Vol. VIII, Parts 1 and 2.
(2) Alwani, Z. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 623.

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