Acid-Catalyzed Hydrolysis of 3-Alkoxy-4′-substituted Crotonophenones

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The acid-catalyzed hydrolysis of 3-alkoxy-4′-substituted crotonophenones (**1–6**) to para-substituted benzoylacetones and alcohol is characterized by (1) rate constants which are smaller than those for hydrolysis of 3-methoxy-4′-substituted acrylophenones, which hydrolyze via an A-2 mechanism, and are similar to those for hydrolysis of 3-alkoxycrotonic acid derivatives, which hydrolyze via an ASE-2 mechanism, (2) $\rho = 0.15 \pm 0.12$, (3) $k(D_3O^+)/k(H_3O^+) = 1.4–3$, and (4) catalysis by carboxylic acids with $k(HA)/k(DA) = 1.4$. These data were interpreted to indicate the simultaneous operation of two pathways to products, the one an A-2 pathway which involves rate-limiting reaction of carbonyl oxygen-protonated **1–6** with water and the other an ASE-2 pathway which involves rate-limiting protonation of the olefin bond.

The hydrolysis of β-substituted oxy-α,β-unsaturated ketones (eq 1) has been shown to be a specific acid-catalyzed

$$ROCH{=}CHCOR' + H_2O \rightarrow R'COCH{=}CHOH\ (\text{etc.}) + ROH \quad (1)$$

process which was presumed to involve rapid protonation of the carbonyl oxygen atom of the reactants followed by a rate-limiting attack of water at the β carbon to give an intermediate (SOH_3^+) which leads to products (Scheme I).[1,2] On the other hand, hydrolysis of several β-substituted oxy-α,β-unsaturated carboxylic acid derivatives (eq 1, R′ = OH, NH_2, OR″, SR‴) is general acid-catalyzed with the first and rate-limiting step being protonation of the olefin bond (Scheme II).[3] Fast reaction of water with the intermediate oxocarbonium ion (SH^+, Scheme II) and fast breakdown of the hemiacetal (SOH_2, Scheme II) lead to products. The difference in reaction mechanism between the two classes of compounds was attributed to a greater ease of "enol" formation for ketones vs. acids, esters, and amides.[3] It could be expected, however, that for an appropriate ketone high carbonium ion stability coupled with unfavorable nucleophilic attack of water at the β carbon of the carbonyl oxygen-protonated ketone (SH^+, Scheme I) could lead to a mechanism change to rate-limiting protonation of the olefin bond of β-substituted oxy-α,β-unsaturated ketones. In an attempt to see if such a mechanism change could be brought about, we synthesized a series of 3-alkoxy-4′-substituted crotonophenones (**1–6**) [4′-X-C_6H_4COCH=C(OR)CH_3: R = CH_3, X = CH_3O (**1**); R = X = CH_3 (**2**); R = CH_3, X = H (**3**); R = CH_3, X = Cl (**4**); R = CH_3, X = NO_2 (**5**); and R = C_2H_5, X = CH_3O (**6**)]

Scheme I

$$R_1OCH{=}CHCOR_2 + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{(SH^+)}{R_1OCH{=}CHCOHR_2^+} + A^-$$

$$SH^+ + H_2O \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{(SOH_3^+)}{R_1OCH(OH_2)CH{=}COHR_2^+}$$

$$\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \underset{(SOH_2)}{R_1OCH(OH)CH{=}COHR_2} + H^+$$

$$SOH_2 \xrightarrow{k_4} R_2COCH{=}CHOH\ (\text{etc.}) + R_1OH$$

Scheme II

$$R_1OCH{=}CHCOXR_2 + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{(SH^+)}{R_1OCHCH_2COXR_2^+} + A^-$$

$$(SH^+) + H_2O \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{(SOH_3^+)}{R_1OCH(OH_2)CH_2COXR}$$

$$\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \underset{(SOH_2)}{R_1OCH(OH)CH_2COXR_2} + H^+$$

$$SOH_2 \xrightarrow{k_4} R_2XCOCH_2CHO\ (\text{etc.}) + R_1OH$$

and examined the kinetics of the acid-catalyzed hydrolysis of these compounds.

Experimental Section

Reagents and Compounds. Certified ACS grade inorganic salts were purchased from Fisher Scientific Co. Tap distilled water was redistilled through a Corning AG-la still. Organic reagents were purchased from Aldrich Chemical Co. and Distillation Products Industries. Deuterated solvents were obtained from Diaprep, Inc., and Stohler Isotope Chemicals. *p*-Methoxy- and *p*-nitrobenzoylacetone were prepared by the method of Sabnis et al.,[4] *p*-methylbenzoylacetone was prepared by the method of Walker et al.,[5] and *p*-chlorobenzoylacetone was prepared by a general procedure described for benzoylacetone.[6] Compounds **1–6** were obtained from the appropriately substituted benzoylacetones by either the method of Weygand[7] (A) or that of Eistert and Merkel[8] (B). Analytical data are given in Table I. Compounds **2** and **3** were chromatographed on neutral alumina with benzene as eluent prior to final distillation. In order to distinguish **1–6** from the isomeric 4-(4′-substituted phenyl)-4-alkoxy-3-buten-2-ones, compounds **1** and **5** were hydrogenated in ethanol on 10% Pd/C and their products examined using NMR. 3-Methoxy-4′-methoxybutyrophenone, the product from **1**, showed a doublet (J = 6 Hz, 3 H) at δ 1.16 ($CDCl_3$, Me_4Si) for the ω-methyl group, as well as other signals consistent with the assigned structure. Similarly, 3-methoxy-4′-aminobutyrophenone, the product from **5**, showed a doublet (J = 6 Hz, 3 H) at δ 1.08 ($CDCl_3$, Me_4Si) for the ω-methyl group, as well as other signals consistent with the assigned structure. In addition, when **3** was allowed to react with hydroxylamine in aqueous methanolic KOH, the expected 3-phenyl-5-methylisoxazole [mp 39 °C; λ_{max} (CH_3OH) 242.5 nm (lit.[8] mp 42 °C, λ_{max} (CH_3OH) 240 nm)] was obtained rather than the isomeric 3-methyl-5-phenylisoxazole [mp 68 °C, λ_{max} (CH_3OH) 265 nm].[8]

Apparatus. A Gilford Model 2400 spectrophotometer was used for the collection of rate data. Ultraviolet scans were taken on a Beckman Model DB-G spectrophotometer. Temperature was maintained in the cuvettes by circulating water through thermospacers from a Tamson TE-3 water bath. pH was measured with a Radiometer Model PHM-22 pH meter equipped with a PHA 630 scale expander and a GK 2302B combination electrode. Melting points were taken in open capillary tubes using a Mel-Temp apparatus and are uncorrected. NMR spectra were taken on a Varian A 60 spectrometer. Calculations were performed on a Hewlett-Packard 9100 A calculator using the least-squares and mean standard deviation programs from the program library provided.

Kinetics. The courses of the reactions were monitored by following the loss of absorbance vs. time at the indicated wavelength: **1** (302 nm), **2** (291 nm), **3** (289 nm), **4** (291 nm), **5** (300 nm), **6** (304 nm). Reactions, carried out under pseudo-first-order conditions at concentrations of **1–6** of ~5×10^{-5} M, were initiated by addition of a microdrop of **1–6** in methanol or dioxane to 3-mL cuvettes containing the appropriate HCl (DCl)–KCl buffer or carboxylic acid–carboxylate salt buffer solutions previously equilibrated to 30 ± 0.1 °C. Pseudo-first-order rate constants were obtained by multiplying slopes of plots of log $(OD_0 - OD_\infty)/(OD_t - OD_\infty)$ vs. time by 2.303; reactions were monitored to completion, and the pseudo-first-order plots were generally linear to at least 2 half-lives for runs made in water solution. For runs in deuterium oxide solutions which contained high D_3O^+ concentrations, pseudo-first-order plots were not as good, and deviations from linearity were to be found at about 50% reaction. Ionic strength was

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Table I. 3-Alkoxy-4′-substituted Crotonophenones

compd (method)	mp or bp (mm), °C	% yield	recryst[a] solvent	calcd % C	calcd % H	found[b] % C	found[b] % H
1 (A)	89	35	P–B	69.89	6.84	69.84	6.78
2 (B)	115–117 (0.15)	61		75.76	7.42	75.69	7.35
3 (A)[7]	155 (10) [lit.[7] 147–148 (13)]	34					
4 (A)	47	17	P	62.72[c]	5.26	62.87[d]	5.23
5 (A)	129–131	27	P–B	59.73[e]	5.01	59.90[f]	5.09
6 (A)	87–88.5	28	P–B	70.89	7.32	70.68	7.36

[a] P = petroleum ether, B = benzene. [b] Galbraith Microanalytical Laboratories. [c] % Cl = 16.83. [d] % Cl = 17.02. [e] % N = 6.33. [f] % N = 6.17.

Table II. Rate Constants for the Reactions of 3-Alkoxy-4′-substituted Crotonophenones (1–6) with Aqueous Hydrochloric Acid Solution[a]

compd	k_H,[b] M^{-1} min^{-1}	pH range	no. of k_{obsd}
1	2.55 ± 0.11	1.06–2.05	18
2	3.11 ± 0.14	1.04–2.01	6
3	3.81 ± 0.13	1.04–2.02	6
4	2.49 ± 0.09	1.02–2.01	6
5	4.25 ± 0.23	1.06–2.06	18
5	6.01 ± 0.21[c]	0.08–0.75	5
6	4.44 ± 0.26	1.03–2.02	6

[a] Solvent is water; t = 30 °C; μ = 0.1 M (KCl). [b] Errors are standard deviations. [c] μ = 1.0 M (KCl).

maintained at 0.1 M (KCl), and pH, determined before and after each run, remained constant (±0.02 pH unit). pD was determined from the pH meter reading by adding 0.39 to it.[9] The pK of 2,6-dimethyl-γ-pyrone in D_2O–D_2SO_4, 0.45, was determined by the NMR method of Levy et al.[10]

Products. The ultraviolet spectra of solutions containing reacted 1–6 were identical with those of authentic para-substituted benzoylacetones and quite different from those of authentic para-substituted acetophenones and para-substituted benzoic acids. In 0.1 M HCl, 4 was converted to *p*-chlorobenzoylacetone in 94% yield as determined from the ratio of the molar extinction coefficients (ε product/11 490) at 264 nm.

Results

Compounds 1–6 undergo hydrolysis in dilute aqueous acid solution to give para-substituted benzoylacetones and alcohol (eq 2) and follow the rate law of eq 3. At constant pH

$$1\text{–}6 + H_2O \rightarrow p\text{-}XC_6H_4COCH_2COCH_3 + ROH \quad (2)$$

$$v/[1\text{–}6] = k_{obsd} = k_H a_H \quad (3)$$

pseudo-first-order conditions obtain. From linear plots of k_{obsd} vs. a_H values, second-order rate constants, k_H (Table II), were calculated. Hydrolyses of 1–6 in deuterium oxide gave anomalous kinetic results. Plots of k_{obsd} vs. a_D values for the compounds of this study curve downward, although the rate constants obtained for reactions in this solvent, when a_D is small, remain larger than those obtained from reactions run in water of comparable acidity. The operational rate law for reactions run in deuterium oxide is that of eq 4. The second-

$$v/[1\text{–}6] = k_{obsd} = ka_D/(K + a_D) \quad (4)$$

order rate constants, k_D (Table III), are given by the value k/K obtained from the linear plots of $1/k_{obsd}$ vs. $1/a_D$, from which the slope K/k and intercept $1/k$ may be calculated. Values of k_D/k_H (Table III) range from 1.4 for 6 to 3 for 3. Carboxylic acids catalyze the hydrolysis of 1, 5, and 6 (Table IV), and for these reactions the Brønsted α values are −0.7, −0.78 ± 0.21, and −0.68 ± 0.11, respectively. For hydrolysis of 6 catalyzed by chloroacetic acid, k_{HA}/k_{DA} = 1.4. For 1–5, the Hammett ρ = 0.15 ± 0.12; a better correlation is obtained with the σ^+ values of Brown and Okamoto,[11] and ρ^+ = 0.098 ± 0.005.

Discussion

The question of the site of protonation in molecules capable of undergoing either oxygen or carbon protonation was previously examined.[1–3] For 3-alkoxy-4′-substituted acrylophenones and related β-oxy-α,β-unsaturated ketones, the finding of specific acid catalysis of hydrolysis led to the proposed mechanism of Scheme I. For similarly structured β-oxycrotonic acid derivatives, hydrolysis is initiated by protonation of carbon, typical of vinyl ether hydrolysis (Scheme II).[3] Seemingly, protonated β-oxy ketones react with water to form enols more readily than do β-oxycarboxylic acid derivatives, as is the case for α,β-unsaturated ketones[24] and α,β-unsaturated carboxylic acids.[25,26]

The presumed greater ease of enol formation of ketones vs. thiol esters was crudely approximated[3] by comparing the rate constant for hydrolysis of 4-methoxy-3-buten-2-one (k_H = 43.5 M^{-1} min^{-1}) with that for hydrolysis of *tert*-butyl 3-ethoxythiolacrylate (k_{HA} = 0.02 M^{-1} min^{-1}) and the rate constant for hydrolysis of 4-methoxy-3-penten-2-one (k_H = 11.1 M^{-1} min^{-1}) with that for hydrolysis of *tert*-butyl 3-ethoxythiolcrotonate (k_{HA} = 2.65 M^{-1} min^{-1}). The former rate ratio, 2175, corresponds to ~4.6 kcal mol^{-1} in activation energy, favoring ketone hydrolysis via the mechanism of Scheme I which involves enol formation, while the latter ratio, 4.2, corresponds to only ~0.9 kcal mol^{-1}. Based on these comparisons, it had been hoped that if any of compounds 1–6 showed a smaller k_H than those for analogous crotonate esters, $k_{HA} \approx$ 1–11 M^{-1} min^{-1}, a mechanism change could result. In fact, 1–6 do hydrolyze slower than many of the crotonate esters, but it appears unlikely that a mechanism change from A-2 to ASE-2 occurred.

The decrease in reactivity of 1–6 vs. β-methoxyacrylophenones is predictable by the mechanism of Scheme I. Based on the tenfold greater basicity of acetophenone than benzaldehyde,[10] the concentrations of the conjugate acids of 1–6 are estimated to be about 10 times greater than those of β-methoxyacrylophenones, and based on the 90-fold decrease in reactivity of 5 vs. 3-methoxy-4′-nitroacrylophenone toward aminoethanol,[12] a reaction postulated to involve rate-limiting attack of amine at the 3 carbon, the reactivity of 1–6 with water is estimated to be ~0.011 that of β-methoxyacrylophenones. The predicted reactivity of 1–5 is ~0.11 that of β-methoxyacrylophenones, and this estimate is within 10% of the actual value, 0.12.

The deuterium solvent kinetic isotope effects, $k_{HA}/k_{DA} \approx$ 2–4, for acid-catalyzed hydrolysis of vinyl ethers signal rate-limiting protonation of the olefin bond of these compounds.[13–15] In contrast, the deuterium solvent kinetic isotope effects, k_D/k_H = 1.4–3,[16] for acid-catalyzed hydrolysis of 1–6 indicate rapid protonation of the carbonyl oxygen of 1–6, followed by some rate-limiting event which, for compounds of the β-oxy-α,β-unsaturated ketone type, could be attack by water at the 3 carbon (Scheme I). However, the somewhat smaller isotope effects for 1 (1.7) and 6 (1.4) than for 2–5 and β-oxyacrylophenones, may indicate the existence of a com-

Table III. Rate Constants for the Reactions of 3-Alkoxy-4′-substituted Crotonophenones (1–6) with Deuterium Oxide–Deuteriochloric Acid Solution[a]

compd	$1/k$, min	K/k, M min	k_D,[b] M^{-1} min^{-1}	k_D/k_H	r[c]	pD range	no. of k_{obsd}
1	1.45 ± 0.23	0.236 ± 0.005	4.24 ± 0.08	1.7	0.997	1.04–2.08	18
2	2.35 ± 0.27	0.138 ± 0.006	7.26 ± 0.33	2.3	0.996	1.0–1.94	6
3	3.01 ± 0.28	0.088 ± 0.006	11.40 ± 0.76	3	0.978	1.07–2.03	12
4	1.68 ± 0.37	0.144 ± 0.009	6.94 ± 0.42	2.8	0.993	1.0–1.95	6
5	0.83 ± 0.09	0.095 ± 0.002	10.52 ± 0.21	2.5	0.997	1.03–1.99	15
6	0.99 ± 0.05	0.160 ± 0.005	6.26 ± 0.20	1.4	0.998	0.98–1.94	6

[a] Solvent is deuterium oxide; t = 30 °C; μ = 0.1 M (KCl). [b] k_D is the ratio k/K obtained from eq 4 for the condition $K > a_D$. [c] Correlation coefficient for the double reciprocal plots; errors are standard deviations.

Table IV. Rate Constants for the Reactions of 3-Alkoxy-4′-substituted Crotonophenones (1, 5, 6) with Aqueous Carboxylic Acids[a]

compd	acid[b]	k_{HA},[c] M^{-1} min^{-1}	fraction acid	pH	no. of k_{obsd}
1	Cl_2CHCO_2H	0.144 ± 0.049	0.5	1.67	6
1	$CH_3OCH_2CO_2H$	0.0062 ± 0.0021	0.77	2.96	6
5	$ClCH_2CO_2H$	0.017 ± 0.012	0.55, 0.82, 0.91	2.78, 2.18, 1.98	18
5	$CH_3OCH_2CO_2H$	0.0039 ± 0.0016	0.55, 0.91	3.45, 2.55	12
5	CH_3CO_2H	0.0028 ± 0.0007	0.93	3.62	6
6	$ClCH_2CO_2H$	0.032 ± 0.013	0.55, 0.82, 0.91	2.78, 2.18, 1.98	18
6	$ClCH_2CO_2D$	0.023 ± 0.007	0.5, 0.8	3.22, 2.64[d]	12
6	$CH_3OCH_2CO_2H$	0.018 ± 0.003	0.55, 0.91	3.45, 2.55	12
6	CH_3CO_2H	0.0018 ± 0.0008	0.66, 0.92	4.47, 3.68	12

[a] Solvent is water; t = 30 °C; μ = 0.1 M (KCl). [b] pK_a values of dichloroacetic acid, chloroacetic acid, methoxyacetic acid, and acetic acid are 1.25, 2.87, 3.53, and 4.75, respectively: A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases", Methuen and Co. Ltd, London, 1962, p 124. [c] Errors are standard deviations. [d] Solvent is deuterium oxide; pD values are given.

peting hydrolytic pathway, which is olefin bond protonation (Scheme II). This process would be most favorable for 1 and 6.

The hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran shows a deuterium solvent kinetic isotope effect k_D/k_H of 1.3 for hydronium ion catalysis, but formic acid serves as a general acid catalyst.[23] Here an ASE-2 process or combined ASE-2–A-1 processes may be associated with an inverse or composite isotope effect. For hydrolysis of **1–6**, support for the suggestion of competitive pathways to products is provided by the result that carboxylic acids catalyze the hydrolysis of **1, 5,** and **6**.[17] For hydrolysis of **6** catalyzed by chloroacetic acid, k_{HA}/k_{DA} = 1.4, a normal, if small, isotope effect for an ASE-2 reaction.[13] The Brønsted coefficients, −0.71, −0.78, and −0.68 for **1, 5,** and **6**, respectively, based on few measurements, fall within the range of 0.6 to 0.8 for hydrolysis of a number of vinyl ethers, including *tert*-butyl 3-ethoxythiolcrotonate, catalyzed by carboxylic acids.[3,15] The results of hydrolysis of **1, 5,** and **6** catalyzed by carboxylic acids support the existence of general acid catalysis in hydrolysis and the existence of competitive pathways to products.

The insensitivity of **1–5** toward electronic effects of para substituents is typical of specific acid-catalyzed hydrolysis reactions of carbonyl compounds,[18–20] including β-methoxyacrylophenones, and the ρ value 0.15 ± 0.12, although less than that for β-methoxyacrylophenones (0.31 ± 0.09), is reasonable for the A-2 type mechanism of Scheme I; an ASE-2 mechanism would require a negative ρ.[21,22] Nevertheless, the smaller ρ for **1–5** could signal a component of an ASE-2 reaction together with a more favorable A-2 type reaction. Also, the poorer fit of the rate constants k_H and k_D for **1–5** to the Hammett equation could mean that these constants reflect hydrolysis by two different mechanisms.

We conclude that the results of this study do not support a mechanism change from A-2, as suggested for β-oxyacrylophenones, to ASE-2, as suggested for β-oxycrotonic acid derivatives; the apparent catalytic effect of carboxylic acids during hydrolysis of **1, 5,** and **6** does, however, provide evidence for the existence of an ASE-2 pathway as a minor route to products.

Registry No.—**1,** 69706-14-5; **2,** 69745-16-0; **3,** 42392-88-1; **4,** 69706-15-6; **5,** 69706-16-7; **6,** 69706-17-8; *p*-methoxybenzoylacetone, 4023-80-7; *p*-methylbenzoylacetone, 4023-79-4; benzoylacetone, 93-91-4; *p*-chlorobenzoylacetone, 6302-55-2; *p*-nitrobenzoylacetone, 4023-82-9; dichloroacetic acid, 79-43-6; methoxyacetic acid, 625-45-6; chloroacetic acid, 79-11-8; acetic acid, 64-19-7; $ClCH_2CO_2D$, 1837-59-8; 3-methoxy-4′-methoxybutyrophenone, 69706-18-9; 3-methoxy-4′-aminobutyrophenone, 69706-19-0; 3-phenyl-5-methylisoxazole, 1008-74-8; hydrochloric acid, 7647-01-0; deuteriochloric acid, 7698-05-7.

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(16) We can not explain the curved k_{obsd} vs. a_D plots, although several possible explanations were investigated. Solubility differences and salt effects peculiar to deuterium oxide seem not to contribute to curvature. Pseudo-first-order rate constants for reactions of **4** in DCl–D_2O with LiCl to maintain ionic strength were virtually identical with those for which KCl was used to maintain ionic strength. No evidence was found for a change from protio to deuterio 4-methoxy-3-penten-2-one[2] when this compound was allowed to react with dilute DCl in D_2O for 1.5 half-lives; following quenching of the reaction, examination of the recovered starting material using NMR revealed no diminution of the vinyl signal compared to the signal for the hydrogens of the 4-methoxy group. Formation of an intermediate which undergoes acid-dependent partitioning to reactant and product seems unlikely because

curvature should be obtained for reactions run in water. A plot of k_{obsd} vs. a_H for reactions of **5** in 0.1–1.0 M HCl was linear, and differences in partitioning ratios in the two solvents would have to be much larger than sensible to account for curvature. It is unlikely that the values of K_{SH} and K_{SD}, the dissociation constants for protonated and deuterated **1–6**, are in the acidity range of this study. However, if they were, then K_{SH} would have a predicted value 2–5 times greater than that of K_{SD}, and should be kinetically detectable in the acidity range of the study. Regarding this point, the pK_a of 2,6-dimethyl-γ-pyrone, a stable model for **1–6**, is only ~0.15 pK_a unit larger in D_2O than in H_2O and a similar pK_a difference between SH^+ and SD^+ would require that K_{SH} be kinetically detectable if K_{SD} is.

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Base-Catalyzed Carbon-to-Oxygen Acyl Rearrangement via an Aromatic Transition State[1]

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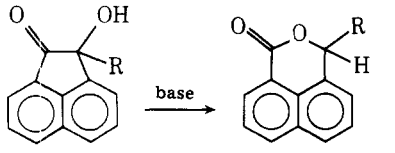
Homologues of 2-hydroxyacenaphthenone undergo a facile base-catalyzed carbon-to-oxygen acyl rearrangement to peri ring-expanded naphthalides. The several examples studied include rearrangement of the cyanohydrin of acenaphthenequinone. The rearrangement is catalyzed by nonnucleophilic bases such as the bicyclic tertiary amidine DBU, and the naphthalide product can be crystallized directly from the reaction mixture under hydroxide catalysis. Consequently, the reaction does not appear to proceed via nucleophile-induced peri ring cleavage to an intermediate hydroxynaphthoic acid followed by lactonization. An alternative mechanism is proposed that involves base-catalyzed formation of an intermediate α-oxanol followed by bridgehead carbon–carbon bond cleavage to an aromatic carbanion isoelectronic with the 14 π-electron phenalenyl carbanion.

Cyclic, unsaturated ketol homologues of 2-hydroxyacenaphthenone undergo a facile, frequently quantitative carbon-to-oxygen acyl rearrangement[3] to peri ring-expanded naphthalides. In earlier reports of the overall reaction,[4,5] the rearrangement was interpreted as first involving nucleophile (hydroxide)-induced cleavage of the peri carbon–carbon bond, giving an open-chain hydroxynaphthoic acid, followed by lactonization to the naphthalide. The purpose of the present paper is threefold: to report several new examples of the rearrangement, to present evidence that the reaction does not proceed via the open-chain hydroxy acid intermediate, and to propose alternatively that this facile rearrangement proceeds via a cyclic, aromatic transition state.

Results and Discussion

The new examples of the reaction are shown in Chart I. Cyanohydrin **1**, precursor of acenaphthenones **2** and **3**, is prepared by addition of HCN to acenaphthenequinone (ACQ) at pH 5.0. The compound is thermodynamically unstable and at neutral pH is decomposed by water and methanol (and presumably basic solvents in general); at higher pH, the ketol rearranges to naphthalide **8**. However, the compound is kinetically stable at low pH and may be recrystallized from acetic acid–water. Acenaphthenones **4–7** are prepared by appropriate Grignard addition to ACQ; the mesityl and tipyl (2,4,6-triisopropylphenyl) homologues have previously been reported.[6] Unlike acenaphthenones **1–7**, naphthalides **8–14** exhibit intense blue fluorescence under UV light, and this allows convenient monitoring of the rearrangement by TLC.

Chart I. Base-Catalyzed Carbon-to-Oxygen Acyl Rearrangement



1, R = CN	**8**, R = CN
2, R = $CONH_2$	**9**, R = $CONH_2$
3, R = CO_2Et	**10**, R = CO_2Et
4, R = Ph	**11**, R = Ph
5, R = Mes	**12**, R = Mes
6, R = Tip	**13**, R = Tip
7, R = CH_3	**14**, R = CH_3

Carbon-to-oxygen acyl rearrangement of **1–7** occurs under generally mild base catalysis and in high yield. That the reaction is not observably acid catalyzed is demonstrated by the failure of ketol **3** to rearrange under the acidic conditions of its synthesis. In contrast, base-catalyzed rearrangement occurs readily at low temperature with nonnucleophilic bases such as DBU (1,5-diazabicyclo[5.4.0]undec-5-ene)[7] in DMF solution and KH suspended in benzene. Under homogeneous hydroxide catalysis, the naphthalide product can be crystallized directly from the strongly basic reaction mixture. (The solvent or substrate must provide a proton, and hence the Grignard adducts giving **4–7** do not rearrange.) Rearrangement of the deuterioxy-labeled ketol **5** by *tert*-butoxide in benzene solution can be used to label the naphthalide with deuterium in the 3 position.[8] The rate of acyl rearrangement decreases as a function of substituent R in the order $CO_2Et > CONH_2 \gg Ar \gg CH_3$ and decreases as a function of solvent under *tert*-butoxide catalysis in the order $Me_2SO >$ benzene > *tert*-butyl alcohol.

A reaction mechanism involving nucelophile-induced carbon–carbon bond cleavage to an open-chain hydroxy acid intermediate is unlikely under the above conditions. The bicyclic tertiary amidine DBU, chosen as a base because of its nonnucleophilicity, is probably not sufficiently nucleophilic to cleave the peri ring of acenaphthenones[9] at room temperature. Likewise, rearrangement of overcrowded ketol **5** by KH suspended in benzene would require that the nucleophile be the conjugate base of the substrate, an unlikely event since the hydroxyl and outside methyl groups of that compound in-

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