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Are the Halogenations of Simple Enols in Aqueous Solution Really Diffusion-Controlled Reactions?

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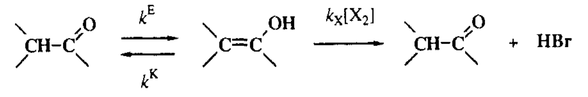
There is much current interest in chemical reactions that occur with rates at or near the diffusion-controlled limit in solution.[2] One such process is the addition of halogens to simple enols. This has been studied by examining the acid-catalyzed halogenation of the corresponding carbonyl compounds in aqueous solution, eq 1,

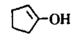
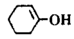
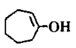
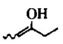
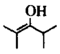
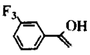
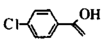
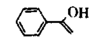
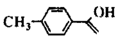
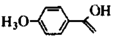

(1)

at very low halogen concentrations where the halogenation step is partly rate-determining, i.e., $k_X[X_2] \approx k^K$.[3] Rates of reaction under these conditions were found to depend upon the concentration but not the identity of the halogen, and the conclusion was drawn that the rate of halogenation was limited only by the rate of diffusion. Apparent second-order bromination rate constants, $k_{11}^{Br_2} = (k^E/k^K)k_{Br}$, were then used to calculate keto-enol equilibrium constants, K_E ($=k^E/k^K$), by assuming a constant value of $k_{Br} = 5 \times 10^9$ M^{-1} s^{-1} for a series of simple enols. We have now found, however, that rate constants for this step do not have a constant value, as might be expected for a process governed by diffusion, but rather vary in a way expected for a process requiring input of chemical activation energy.

We have determined accurate values of K_E, free of any assumption, by making separate measurements of k^E and k^K, the latter with enols generated by flash photolytic methods based upon Norrish type II photoelimination,[4] photooxidation of alcohols,[5] and photohydration of acetylenes.[6] With this information in hand, we are able to reverse the previous calculation[3b] and to obtain experimental values for the rate constant of enol bromination, k_{Br}.[7] The results are listed in Table I.

These rate constants are very large. Yet the fact that they are less than those found for the reaction of some other organic substrates with Br_2 in aqueous solution,[8] e.g., $k = 6.2 \times 10^9$ M^{-1} s^{-1} for *o*-bromophenoxide ion,[9a] $k = 7.9 \times 10^9$ M^{-1} s^{-1} for the anion of 3-methyluracil,[9b] and $k = 8.3 \times 10^9$ M^{-1} s^{-1} for the anion of malononitrile,[2d] suggests that they are not completely diffusion-controlled values. These rate constants, moreover, vary with enol structure in a way typical of electrophilic addition to carbon–carbon double bonds, as exemplified by the acid-catalyzed hydrolysis of vinyl ethers, a process whose rates are many orders of magnitude too slow to be diffusion-controlled. For instance, the cyclic enols (first three entries of Table I) show a ring-size effect similar to the alternating reactivity of five-, six-, and seven-membered ring cyclic vinyl ethers,[10] and successive methyl substitution at the β-carbon (entries 4 to 6) retards the rate, again as in vinyl ether hydrolysis.[11]

Table I. Enolization Constants K_E and Rate Constants k_{Br} for the Reaction of Simple Enols with Bromine in Aqueous Solution at 25 °C

enol	pK_E[a]	k_{Br},[b] 10^9 M^{-1} s^{-1}
	7.94 ± 0.01[c]	4.4 ± 0.1
	6.39 ± 0.02[c]	2.8 ± 0.2
	8.00 ± 0.01[c]	4.0 ± 0.1
	8.33 ± 0.02[d]	4.0 ± 0.4
	7.43 ± 0.02[c]	2.8 ± 0.2
	7.52 ± 0.02[c]	1.5 ± 0.1
	7.38 ± 0.02[e]	2.0 ± 0.2
	7.77 ± 0.02[e]	2.8 ± 0.2
	7.97 ± 0.03[e,f]	3.3 ± 0.3
	8.34 ± 0.03[e]	3.8 ± 0.4
	8.80 ± 0.02[e]	4.3 ± 0.3

[a] Ionic strength $I = 0.1$ M; error limits are standard deviations of sample means, df > 10. [b] Calculated as $k_{11}^{Br_2}/K_E$ ($I = 1$ M),[7] taking second-order rate constants $k_{11}^{Br_2}$ from ref 3b. [c] Reference 5. [d] Revision of value given in ref 4a; Chiang, Y.; Schepp, N. P., unpublished work. [e] Calculated as $-\log(k^E/k^K)$ with the values for acid-catalyzed enolization, k^E, given in Table II of ref 3b and the rate of acid-catalyzed ketonization, k^K, determined in this work. [f] The average of two independent determinations of this value in acidic[4c] and basic[4b] solution is 7.96 ± 0.04.

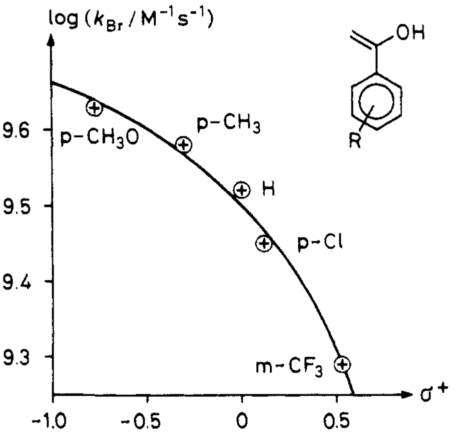


Figure 1. Hammett plot of relative rates of bromination for substituted acetophenone enols.

Perhaps most telling of all is the regular increase in the bromination rate constant, k_{Br}, shown by acetophenone enols, as increasingly electron-supplying substituents are introduced into the aromatic ring (last five entries of Table I). This systematic trend surely reflects changes in chemical reactivity. As shown

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(1) (a) Universität Basel. (b) University of Toronto.

(2) See, for example: (a) Tapuhi, E.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 5758-5765. (b) Guthrie, J. P.; Cossar, J.; Klym, A. *Ibid.* **1984**, *106*, 1351-1360. (c) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *Ibid.* **1984**, *106*, 1361-1372. Richard, J. P.; Jencks, W. P. *Ibid.* **1984**, *106*, 1373-1383. Bednar, R. A.; Jencks, W. P. *Ibid.* **1985**, *107*, 7117-7126. (d) Hojatti, M.; Kresge, A. J.; Wang, W.-H. *Ibid.* **1987**, *109*, 4023-4028.

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(4) (a) Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460-462. (b) Chiang, Y.; Kresge, A. J.; Wirz, J. *Ibid.* **1984**, *106*, 6392-6395. (c) Keefe, J. R.; Kresge, A. J.; Toullec, J. *Can. J. Chem.* **1986**, *64*, 1224-1227.

(5) Keeffe, J. R.; Kresge, A. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1988**, *110*, 1993-1995.

(6) Chiang, Y.; Kresge, A. J.; Capponi, M.; Wirz, J. *Helv. Chim. Acta* **1986**, *69*, 1331-1332.

(7) Rate constants $k_{11}^{Br_2}$ were determined at ionic strength $I = 1$ M;[3b] enolization constants K_E are concentration quotients determined at $I = 0.1$ M. The calculated rate constants k_{Br} refer to $I = 1$ M, assuming that salt effects on K_E are small. In any case, salt effects should hardly affect the trends in k_{Br} values which are of prime interest here.

(8) de la Mare, P. B. D. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, England, 1976. Ridd, J. H. *Adv. Phys. Org. Chem.* **1978**, *16*, 1.

(9) (a) Tee, O. S.; Bennett, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 269-274. (b) Tee, O. S.; Berks, C. G. *J. Org. Chem.* **1980**, *45*, 830-835.

(10) Kresge, A. J.; Sagatys, D. S.; Chen, H.-L. *J. Am. Chem. Soc.* **1977**, *99*, 7228-7233.

(11) Chiang, Y.; Chwang, W. K.; Kresge, A. J.; Szilagyi, S. *Can. J. Chem.* **1980**, *58*, 124-129.

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in Figure 1, the rates exhibit a monotonous but distinctly curved free-energy relationship when plotted versus σ^+ substituent constants.[12] Such behavior is expected, if the process is not entirely diffusion-controlled, with the rate constants at the high end leveling off toward a limiting diffusive value. Admittedly, the curvature could, in part, be attributed to coincidental scatter or to the somewhat arbitrary choice of substituent constants (the curvature—but not the trend—is largely eliminated through a bilinear Yukawa-Tsuno[13] regression). However, there is independent evidence that the rate is approaching the diffusion-controlled limit for the more reactive enols. First, the absolute values of k_{Br} are close to those expected for a diffusive process in aqueous solution. Second, the low sensitivity of the reaction rate to substituent effects indicates that the changes in chemical reactivity are diluted by the influence of nonchemical diffusive steps: a straight line through the points of Figure 1 has a slope of $\rho = -0.26$ which is 1 order of magnitude less than, e.g., the slope of $\rho = -2.2$ found for the hydrolysis of a corresponding series of vinyl ethers[14] or $\rho = -4.4$ for the bromination of styrene derivatives through the carbonium ion pathway.[15]

We conclude that the bromination of simple enols is not quite—though almost—a diffusion-controlled process. A similar analysis based on rates of halogenation of acetone[2a,b] and substituted acetophenones[16] in alkaline solutions suggests that the absolute rate constants for the reaction of the hypohalous acids with enolate ions also fall short of the limit of diffusion.

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[15] Ruasse, M. F.; Argile, A.; Dubois, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 7645-7652.

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Prorocentrolide, a Toxic Nitrogenous Macrocycle from a Marine Dinoflagellate, *Prorocentrum lima*[†]

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Marine dinoflagellates are a source of chemically and pharmacologically significant compounds, e.g., saxitoxin, maitotoxin, and the brevetoxins. We have previously isolated okadaic acid[1] and its esters[2] from a benthic dinoflagellate, *Prorocentrum lima*.

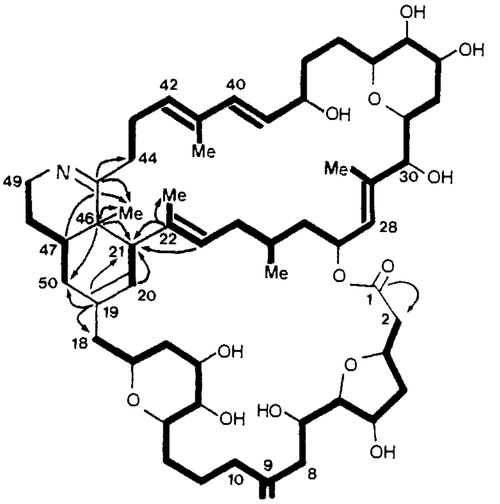

Figure 1. Connectivities established by ^1H–^1H COSY, ^{13}C–^1H COSY, and long-range ^{13}C–^1H COSY. Heavy lines indicate the connectivities assigned on the basis of ^1H–^1H and ^{13}C–^1H COSY (dimethyl sulfoxide-d_6, 500 MHz, AM-500). Arrows denote the correlation between carbons (tail) and protons (head) around the quaternary carbons observed in the long-range ^{13}C–^1H COSY (dimethyl sulfoxide-d_6, 500 MHz, GN-500). The other correlations are omitted for clarity.

From the same organisms we have isolated prorocentrolide (**1**), which is a toxic macrocycle formed from a C_{49} fatty acid and incorporating a C_{27} macrolide and a hexahydroisoquinoline in its unique structure.

The dinoflagellate was isolated at Sesoko Island, Okinawa in 1985 and cultured in seawater enriched with ES-1 nutrient[3] at 25 °C for 5 weeks. Algal cells (2.7×10^{10}) harvested from 1000 L of the culture were extracted with acetone and methanol. The combined extracts were evaporated, the residue was partitioned between diethyl ether and water, and the aqueous layer was extracted with 1-butanol. The butanol solubles were successively chromatographed with the following columns and solvents: silica gel 60, chloroform/methanol (1:1); Toyopearl HW-40 (Tosoh), methanol/water (1:1); silica gel 60, chloroform/methanol/water (25:10:1); Develosil ODS-5 (Nomura Chem.), a linear gradient elution from acetonitrile/0.05 N acetic acid (1:9) to (3:7). The toxin in the eluates was monitored by ip mouse lethality.

Prorocentrolide (70 mg), an amorphous solid, had a mouse lethality of 0.4 mg/kg (ip):[4] $[\alpha]^{23}_D$ +136.5° (c 0.147, CH_3OH); UV max (CH_3OH) 235 nm (ε 13 600); IR (KBr) 3400, 1715, 1670, 1640, 1200, and 1060 cm^{-1}. HR-FABMS and total number of carbons determined by ^{13}C NMR spectra suggested a probable molecular formula of $C_{56}H_{85}NO_{13}$ (MH^+, m/z 980.6100; found, m/z 980.6168). Positive Dragendorff's test, elemental analysis for nitrogen (1.39%), and an IR band at 1670 cm^{-1} suggested the presence of an imine group.

The proton connectivities were elucidated by detailed analyses of ^1H–^1H and ^{13}C–^1H COSY experiments. Long-range proton couplings via sp^2 carbons such as H_2-51/H_2-8, H_2-51/H_2-10, H-28/H-30, H-40/H-42, and H_2-44/H_2-49 were clearly indicated by cross-peaks. Eventually, four partial structures (C2-C18, C20-C21, C22-C44, and C49-C50) were obtained as shown in Figure 1. The fragments terminating in quaternary carbons (C1, C19, C22, C45, and C46) were assembled by a long-range ^{13}C–^1H COSY,[5] designed to detect $^{2,3}J_{CH}$ (Figure 1). Hetero couplings of C45/H-44 and C45/H_3-56 observed in the spectrum indicated that C45 (δ 169.9) was alkylated by two sp^3 carbons (C44 and C46) and presumably assignable to an imine group; no other carbons adjacent to two sp^3 carbons give rise to the signals in that region. The other nitrogen-bearing carbon was deduced to be C49 because of its typical chemical shift (δ 48.3) for $N-CH_2$ and because of homoallylic couplings between H_2-49 and H_2-44.

[†] Presented at the 16th International Symposium on the Chemistry of Natural Products (IUPAC), May 29-June 3, 1988, Kyoto, Japan.

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