J. Chem. Research (S), 1999, 146–147†

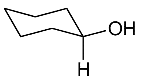
Kinetic Isotope Effects in the Chromium(VI) Oxidation of Bicyclic Alcohols†

J. Hodge Markgraf,* Jordan S. Dubow, Jessica A. Charland and Elliott H. Sohn

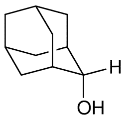
Department of Chemistry, Williams College, Williamstown, MA 01267, USA

Pseudo first-order rate constants are determined for the oxidation of a series of secondary alcohols and their monodeutero analogues by ammonium chromate in aqueous acidic solution at several temperatures; the relative rates and activation parameters are consistent with a cyclic, symmetrical transition state.

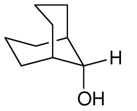
The oxidation of alcohols by chromium(VI) reagents is widely utilized in synthetic and mechanistic studies.[1–4] Fifty years ago the seminal papers by Westheimer and coworkers on the kinetic isotope effect (KIE) for the oxidation of [$^2H_1$]propan-2-ol identified the rate-determining step.[5] Subsequently, studies of cyclohexyl and bicyclic alcohols correlated relative rates with structures.[6,7] While KIEs have been reported for the chromic acid oxidation of cycloalkanols,[8] the only similar datum in the bicyclic series was the reaction of norbornanols with silver carbonate on Celite (Fetizon's reagent).[9] The latter process is problematic for kinetic studies, given the difficulties of controlling reaction parameters in heterogeneous systems.[10] In the present work rate coefficients, activation parameters, and KIEs are reported for the chromic acid oxidation of cyclohexanol (**1**), 2-adamantol (**2**), 9-bicyclo-[3.3.1]nonanol (**3**), 2-bicyclo[2.2.2]octanol (**4**), and 2-*endo*-norbornanol (**5**).



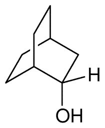
1



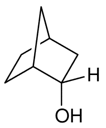
2



3



4



5

Results

The aqueous, acidic oxidation of secondary alcohols is first-order in both alcohol and chromate ion. Use of a 20-fold excess of the alcohol permits pseudo first-order rate constants to be derived from the rate of disappearance of chromate ion followed spectrophotometrically. Rate coefficients and relative rates for oxidations of **1**–**5** at several temperatures in 0.01 M H_2SO_4 in 80% (v/v) aqueous acetic acid are shown in Table 1. The activation parameters are shown in Table 2. Rate coefficients and KIEs for oxidations of the deuterated analogues of **1**–**5** are shown in Table 3.

The deuterated analogs of **1**–**4** were prepared by reduction of the corresponding ketones with $LiAlD_4$. With norbornanone, however, this reagent was not stereospecific; the product was a 92:8 mixture of 2-*endo*-norbornanol-2d_1 and 2-*exo*-norbornanol-2d_1. The desired **5**-2d_1 was obtained in >99.5% epimeric purity by the use of $LiEt_3BD$.[11]

Table 1 Pseudo first-order rate coefficients for the chromium(VI) oxidation of **1**–**5**[a]

Alcohol	T/°C	$10^4\ k/s^{-1}$	k_{rel}	$t_{1/2}$/min
1	15.00	0.688	1.00	168
	25.00	1.729		
	35.00	3.401		
2	7.50	2.372		
	15.00	3.293	4.79	35.1
	25.00	9.149		
3	5.47	2.406		
	15.00	3.723	5.41	31.0
	23.00	8.399		
4	3.80	3.243		
	8.53	5.048		
	15.00	6.958	10.11	16.6
5	0.31	3.633		
	4.90	5.526		
	15.00	10.166	14.78	11.4

[a] Rate coefficients were reproducible to ±2%.

Discussion

The relative rates of oxidation of **1**–**3** and **5** are comparable to the literature values.[7] The rate of **4**, which has not previously been reported, places its reactivity only slightly less than that of **5**. The hydroxyl substituent in **2**–**5** is in an axial position, which is known to be the more reactive conformation for this oxidation. The activation parameters parallel those previously reported for **1** and **2**.[7,8] The data in Table 2 extend these correlations to **3**–**5**. The KIEs (Table 3) are consistent with the values reported for **1** with chromium(VI) reagents.[8,12] With Fetizon's reagent the KIE for **5** was 3.6;[9] however, use of Celite has been shown to decrease KIE values.[10]

Oxidations of secondary alcohols by chromium(VI) are considered to proceed by an acid-catalyzed pre-equilibrium formation of a chromate ester, followed by a slow breaking of the α C–H bond *via* a planar cyclic transition state. In particular, substantial primary KIEs and large, negative $\Delta S^\ddagger$ terms implicate a concerted symmetrical arrangement for the six electron process in which the hydrogen transfer is linear.[13] Earlier work established that the transition state for **2** and **3** is late, *i.e.*, product-like.[14] The strain of non-bonded steric interactions is thereby relieved as rehybridization occurs from sp^3 to sp^2. The present data establish that the

Table 2 Activation parameters for the chromium(VI) oxidation of **1**–**5** at 15.0 °C[a]

Alcohol	$\Delta H^\ddagger$/kcal mol^{-1} [b]	$\Delta S^\ddagger$/kcal mol^{-1} [b]
1	13.5	–30.5
2	12.9	–29.8
3	11.0	–36.1
4	10.1	–37.8
5	10.2	–36.7

[a] Values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are considered accurate to within ±200 cal mol^{-1} and ±0.8 cal mol^{-1} K^{-1}, respectively.
[b] 1 cal = 4.184 J.

---

*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1999, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 3 Kinetic isotope effects for the chromium(VI) oxidation of **1**–**5**[a]

Alcohol	$T/°C$	$10^4\ k/s^{-1}$	k_G/k_D
1	25.00	1.729	
1–2d_1	25.00	0.294	5.88
2	15.00	3.293	
2–2d_1	15.00	0.421	7.82
3	15.00	3.723	
3–9d_1	15.00	0.623	5.98
4	15.00	6.958	
4–2d_1	15.00	1.150	6.05
5	15.00	10.166	
5–2d_1	15.00	1.194	8.51

[a] Rate coefficients were reproducible to ±2%.

pathway for additional bicyclic alcohols conforms to this interpretation.

Experimental

GC–MS analyses were performed on a Hewlett Packard 5890II gas chromatograph with a SPB-5 polydiphenyl (5%)–dimethyl (95%) siloxane column (30 m × 200 μm with 0.2 μm film) and Hewlett Packard 5971A mass spectrometer (EI, 70 eV). IR spectra were obtained on a Nicolet 550 FT-IR spectrophotometer. Melting points (uncorrected) were determined in sealed capillaries on a modified Hershberg apparatus with matched Anschutz thermometers.

Compounds **1**, **2** and **5** were obtained commercially; **1** was redistilled. Compound **3** was prepared by the method of Schleyer and Nicholas:[15] mp 206.5–207.3 °C (lit.,[16] 206–208 °C). Compound **4** was prepared by the methods of Goering *et al.*,[17] and Mislow and Berger:[18] mp 210–212 °C (lit.,[19] 210–212 °C). Purities of **1**–**4** by GC-MS analysis were >99%; **5** was 98.5% *endo* isomer. The deuterated analogs of **1**–**4** were prepared by reduction of the corresponding ketones with lithium aluminium deuteride.[20] The ketones were obtained commercially, except for 2-bicyclo[2.2.2]octanone which was prepared by the chromic acid oxidation of **4**.[19] The deuterated analogue of **5** was prepared by reduction of 2-norbornanone with lithium triethylborodeuteride.[11] In all cases, GC–MS analysis of the deuterated alcohols showed purities >99%. All deuterated alcohols exhibited an IR peak in the range 2160–2093 cm^{-1}.

Rate Measurements.—Reaction rates were determined on a Hewlett Packard 8452A diode array spectrophotometer at 350 nm in a water-jacketed cell connected to a Lauda K-2/R constant temperature bath; the cell block was connected to a Neslab RTE-100 constant temperature bath. The temperature of the reaction solution was monitored continuously by an Omega HH 41 digital thermometer with an ON-403-PP probe in the solution; temperature control was ±0.01 °C. To the cell were added a temperature-equilibrated solution (1.50 mL) of 0.0200 M substrate in 0.0100 M sulfuric acid (acetic acid–water, 4:1 v/v) and then a temperature-equilibrated solution (0.050 mL) of 0.0300 M ammonium chromate (acetic acid–water, 4:1 v/v). All runs were followed at 1 s intervals for a minimum of three half-lives.

We thank Dr Peter M. Wege II for a summer stipend to E.H.S. and Dr Edward W. Lipkin for financial support. Additional funding was provided by the Williams College Faculty Research Fund.

Received, 27th October 1998; Accepted, 18th November 1998
Paper E/8/08311H

References

1 R. Stewart, *Oxidation Mechanisms*, W. A. Benjamin, New York, 1964, pp. 33–48.
2 K. B. Wiberg, *Oxidation in Organic Chemistry, Part A*, ed. K. B. Wiberg, Academic Press, New York, 1965, pp. 142–170.
3 D. G. Lee, *Oxidation*, ed. R. L. Augustine, Marcel Dekker, New York, 1969, pp. 56–63.
4 M. Hudlický, *Oxidation in Organic Chemistry*, American Chemical Society, Washington, 1990, pp. 133–138.
5 F. H. Westheimer and N. Nicolaides, *J. Am. Chem. Soc.*, 1949, **71**, 25; M. Cohen and F. H. Westheimer, *J. Am. Chem. Soc.*, 1952, **74**, 4387.
6 H. Kwart and P. S. Francis, *J. Am. Chem. Soc.*, 1959, **81**, 2116.
7 P. Müller and J.-C. Perlberger, *Helv. Chim. Acta*, 1974, **57**, 1943; *J. Am. Chem. Soc.*, 1975, **97**, 6862; 1976, **98**, 8407; P. Müller, *Chimia*, 1977, **31**, 209.
8 K. Nagarajan, S. Sundaram and N. Venkatasubramanian, *Indian J. Chem., Sect. A*, 1979, **18**, 260; J.-C. Richer and N. T. T. Hoa, *Can. J. Chem.*, 1969, **47**, 2479.
9 M. Eckert-Maksić, L. Tušek and D. E. Sunko, *Croat. Chem. Acta*, 1971, **43**, 79.
10 F. J. Kakis, M. Fetizon, N. Douchkine, M. Golfier, P. Mourges and T. Prange, *J. Org. Chem.*, 1974, **39**, 523.
11 H. C. Brown, S. C. Kim and S. Krishnamurthy, *J. Org. Chem.*, 1980, **45**, 1.
12 I. Nongkynrih and M. K. Mahanti, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1403.
13 H. B. Özgün and N. Değirmenbasi, *J. Chem. Res. (S)*, 1997, 32.
14 R. Durand, P. Geneste, G. Lamaty and J. P. Roque, *Recl. Trav. Chim. Pays-Bas*, 1975, **94**, 131.
15 P. von R. Schleyer and R. D. Nicholas, *J. Am. Chem. Soc.*, 1961, **83**, 182.
16 H. C. Brown, T. Imai, P. Perumal and B. Singaram, *J. Org. Chem.*, 1985, **50**, 4032.
17 H. L. Goering, R. W. Greiner and M. F. Sloan, *J. Am. Chem. Soc.*, 1961, **83**, 1391.
18 K. Mislow and J. G. Berger, *J. Am. Chem. Soc.*, 1962, **84**, 1956.
19 H. M. Walborsky and D. F. Loncrini, *J. Am. Chem. Soc.*, 1954, **76**, 5396.
20 T. Hashimoto, G. K. S. Prakash, J. G. Shah and G. A. Olah, *J. Org. Chem.*, 1987, **52**, 931.