Steric Effects in Five-membered Rings. Part VI.[1] Kinetics of Oxidation of β-Substituted Cyclopentanols by Chromium(VI) Oxide

By **Pablo S. Wechsler** and **Benzion Fuchs**,* Department of Chemistry, Tel-Aviv University, Tel-Aviv, Israel

A study is presented on the Cr^{VI} oxidation rates of 3,3- and 3,3,4,4-substituted cyclopentanols at four temperatures. The activation parameters were evaluated. Kinetic isotope effects were also measured at all temperatures. Mechanistic and conformational implications are discussed, and it is concluded that, in contrast to analogous six-membered ring compounds, the behaviour of cyclopentanols indicates lack of appreciable non-bonded interactions and the operation of torsional strain relief.

THE stereochemistry and conformation of cyclopentanes has been the subject of sustained interest in recent years.[1-3] One of its peculiar and rather disconcerting aspects is the virtual lack of stereospecificity and conformational control in many reactions.[3c,4] A typical reaction known to be governed *inter alia* by conformational

---

[1] Part V, A. Warshawsky and B. Fuchs, *Tetrahedron*, 1969, **25**, 2633.

[2] Taken in part from the Ph.D. Thesis of P. S. Wechsler, Tel-Aviv University, 1974.

[3] (*a*) E. L. Eliel, N. S. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Wiley, New York, 1966, p. 200; (*b*) C. Altona in 'Conformational Analysis, Scope and Present Limitations,' ed. G. Chiurdoglu, Academic Press, New York, 1971, p. 1; (*c*) B. Fuchs, 'Conformation of Five-membered Rings,' *Topics Stereochem.*, 1976, **10**, in the press.

[4] (*a*) W. Hückel and R. Bross, *Annalen*, 1963, **664**, 1; (*b*) I. Lillien and K. Khaleeluddin, *Chem. and Ind.*, 1964, 1028; (*c*) A. P. Krapcho and D. E. Horn, *Tetrahedron Letters*, 1966, 6107; (*d*) R. G. Haber and B. Fuchs, *ibid.*, p. 1447.

factors is the oxidation of secondary alcohols by chromium(VI) oxide.[5] This reaction has been extensively studied[6-14] and has found application in stereochemical and conformational investigations of alicyclic alcohols, mainly six-membered ones.[7,9-12,15,16] Notably, axial hydroxy-groups have been found to be oxidized more rapidly than equatorial ones by a factor of >50.[7,15,16] This has been interpreted in terms of 'steric acceleration' of the rate-determining step.[7] The latter has been shown[6,10] to consist of the decomposition of a chromate ester intermediate concomitantly with the dissociation of the carbinol C–H bond, probably in a cyclic mechanism.[9]

Other alicyclic alcohols have also been investigated, including various bicyclic systems[17-19] and small[1,20-22] as well as large[20] rings.

A useful linear free energy relation has been shown to exist between the free energy of formation of epimeric secondary alcohols (as obtained from equilibration studies with aluminium isopropoxide in isopropyl alcohol) and their free energy of activation in the CrO_2 oxidation.[11,12,15-18] There have been attempts also to assert another, isokinetic linear relation,[23] *i.e.* between the enthalpies and entropies of activation for oxidation.[16,17]

Recently, a number of substituted cyclopentanols were subjected to Cr^{VI} oxidation in various laboratories[2,21,24-26] and surprisingly similar rates were found for different alcohols in each study and evidently also for pairs of *cis*- and *trans*-epimers.

We thought it worthwhile to undertake a more detailed investigation of the CrO_3 oxidation of a number of β-substituted cyclopentanols available in our laboratory as a result of our activities in this field.[4d,24,27] Hence, rate measurements at four temperatures of some 3,3- and 3,4-substituted cyclopentanols and of their 1-deuteriated analogues were performed in order to obtain entropies and enthalpies of activation as well as to evaluate the kinetic isotope effect. The results are presented in Tables 1—3.

TABLE 1

The second-order rate constants k_2 of chromic acid oxidation reactions at four different temperatures

Cyclopentanol	10^2k_2/l mol^{-1} s^{-1} * 25 °C	32 °C	39 °C	45 °C
Parent	2.5	3.9	6.2	9.6
3,3-Dimethyl	7.51	12.5	19.5	29.0
3,3,4,4-Tetramethyl	20.3	34.7	52	74
1-Deuterio	0.30	0.55	0.88	1.40
1-Deuterio-3,3-dimethyl	0.98	1.6	2.8	4.44
1-Deuterio-3,3,4,4-tetramethyl	2.82	4.7	7.9	12.1
Cyclohexanol	1.4			6.3

* Average error 0.1×10^{-2}.

TABLE 2

Thermodynamic activation parameters of chromic acid oxidations

Cyclopentanol	$\Delta H^{\ddagger}$ [a]	$\Delta S^{\ddagger}$ [b]	$\Delta F^{\ddagger}_{303}$ [a]	r
Parent	12.2	−25	19.8	0.999
3,3-Dimethyl	12.2	−23	19.2	1.000
3,3,4,4-Tetramethyl	11.5	−23	18.5	0.997
1-Deuterio	13.9	−23	20.9	0.999
1-Deuterio-3,3-dimethyl	13.4	−23	20.4	1.000
1-Deuterio-3,3,4,4-tetramethyl	13.3	−21	19.7	1.000

[a] In kcal mol^{-1}; average error ($\pm\sigma$) 0.4 kcal mol^{-1}. [b] In cal mol^{-1} K^{-1}; average error 1 cal mol^{-1} K^{-1}.

TABLE 3

The kinetic isotope effect k_H/k_D of chromic acid oxidation reactions

Cyclopentanol	k_H/k_D 25 °C	32 °C	39 °C	45 °C
Parent	8.3	7.1	7.0	6.8
3,3-Dimethyl	7.7	7.8	7.0	6.5
3,3,4,4-Tetamethyl	7.2	7.3	6.5	6.1

EXPERIMENTAL

Analytical samples of alcohols[4d,24,27] were used, after repeated crystallizations and/or preparative g.l.c. Solutions *ca.* 10^{-2}M in alcohol and *ca.* 10^{-3}M in CrO_3 were used and measurements performed at 25, 32, 39 and 45 °C. The oxidations were followed spectrophotometrically at 350 nm.

The Cr^{VI} stock solution in acetic acid (90% v/v, distilled once over $KMnO_4$ and once over CrO_3 prior to use) was

[5] (*a*) K. Wiberg, 'Oxidations in Organic Chemistry,' Academic Press, New York, 1965; (*b*) R. Stewart, 'Oxidation Mechanisms,' Benjamin, New York, 1964.

[6] (*a*) F. H. Westheimer, *Chem. Rev.*, 1949, **45**, 419; (*b*) F. Holloway, M. Cohen, and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1951, **73**, 65; (*c*) M. Cohen and F. H. Westheimer, *ibid.*, 1952, **74**, 4383; (*d*) J. Hampton, A. Leo, and F. H. Westheimer, *ibid.*, 1956, **78**, 306.

[7] (*a*) J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, 1955, **38**, 1529; (*b*) G. Grimmer, *Annalen*, 1960, **636**, 42.

[8] (*a*) J. Rocek and J. Krupicka, *Coll. Czech. Chem. Comm.*, 1958, **23**, 2068; (*b*) J. Rocek, *ibid.*, 1962, **25**, 1052.

[9] H. Kwart, *Suomen Kem.*, 1961, **A34**, 173 and references therein.

[10] J. Rocek, F. H. Westheimer, A. Eschenmoser, L. Moldovany, and J. Schreiber, *Helv. Chim. Acta*, 1962, **45**, 2554.

[11] F. Sipos, J. Krupicka, M. Tichy, and J. Sicher, *Coll. Czech. Chem. Comm.*, 1962, **27**, 2079.

[12] C. F. Wilcox, M. Sexton, and M. R. Wilcox, *J. Org. Chem.*, 1963, **28**, 1079.

[13] K. B. Wiberg and H. Schafer, *J. Amer. Chem. Soc.*, 1969, **91**, 927, 933.

[14] P. M. Nave and W. S. Trahanowsky, *J. Amer. Chem. Soc.*, 1970, **92**, 1120.

[15] (*a*) E. L. Eliel, S. H. Schroeter, T. J. Brett, F. J. Biros, and J. C. Richer, *J. Amer. Chem. Soc.*, 1966, **88**, 3327; (*b*) J. C. Richer, L. A. Pilato, and E. L. Eliel, *Chem. and Ind.*, 1961, 2007.

[16] J. C. Richer and C. Gilardeau, *Canad. J. Chem.*, 1963, **43**, 538.

[17] N. Venkatrasubramanian, *J. Sci. Res. India*, 1961, **20B**, 385.

[18] (*a*) R. Baker and T. J. Mason, *J. Chem. Soc. (B)*, 1971, 988; (*b*) I. Rothberg and R. W. Musso, *J. Org. Chem.*, 1967, **32**, 2003.

[19] K. B. Wiberg and S. K. Mukherjee, *J. Amer. Chem. Soc.*, 1971, **93**, 2543.

[20] J. C. Richer and N. T. T. Hoa, *Canad. J. Chem.*, 1969, **47**, 2479.

[21] J. C. Richer and C. Gilardeau, *Canad. J. Chem.*, 1965, **43**, 3418.

[22] H. G. Kuivila and W. J. Becker, *J. Amer. Chem. Soc.*, 1952, **74**, 5329.

[23] (*a*) L. P. Hammett, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1970, 2nd edn.; (*b*) J. E. Leffler, *J. Org. Chem.*, 1965, **31**, 533.

[24] B. Fuchs and R. G. Haber, *Tetrahedron Letters*, 1966, 1323.

[25] A. K. Awasthy, J. Rocek, and R. M. Moriarty, *J. Amer. Chem. Soc.*, 1967, **89**, 5400.

[26] A. Warshawsky, M.Sc. Thesis, Israel Institute of Technology, Haifa, 1967.

[27] (*a*) B. Fuchs and R. Haber, *Bull. Res. Council Israel*, 1962, **11A**, 30; (*b*) B. Fuchs, *Israel J. Chem.*, 1965, **3**, 52.

checked before and after an experiment, using calibration curves obtained from titrations with standard sodium thiosulphate solution.

In a typical run chromic acid solution (3 ml; 0.8×10^{-3}M) was introduced into a 1 cm optical path quartz cell by means of a 5 ml microburette. Sample and reference cells were introduced in the spectrophotometer (Varian Techtron model 635, equipped with a thermostatted bath with circulation system adjusted to the desired temperature, and attached to a Sargent SRLG recorder). A 0.1 ml sample of a 0.7M solution of the alcohol in the same solvent (preheated at the desired temperature in the bath) was added, by means of 250 μl microsyringe (previously kept in a test-tube immersed in the bath) to the sample cell (time zero) upon which the recorder was started. In calculations of initial concentrations all dilutions as well as their changes with temperature (through changes in specific gravity of the solvent [28]) were considered.

The data obtained from the recording charts (averages of three runs) were fed into a CDC 6600 computer using a program based on the second-order reaction relationship (1)

$$k_{\mathrm{ox}}t = \frac{1}{3a - 2b} \ln \frac{b(a - 2x)}{a(b - 3x)} \qquad (1)^*$$

where a = initial concentration of $\mathrm{Cr^{VI}}$, b = initial concentration of alcohol, $a - 2x$ = momentary concentration of $\mathrm{Cr^{VI}}$ as measured spectrophotometrically.

Excellent second-order behaviour was observed in most cases with 0.5—2% standard deviation. This is noteworthy since data for up to *ca.* 90% reaction were fed into the computer and no other limitations were imposed. The resulting rate constants are given in Table 1. The kinetic isotope effect ratios, $k_{\mathrm{H}}/k_{\mathrm{D}}$ are displayed in Table 3. The enthalpies and entropies of activation were obtained from the slope and intercept, respectively, of plots of the left-hand side of the rearranged Eyring equation (2) *versus* $1/T$.

$$\ln k - \ln\left(\frac{k_{\mathrm{B}}}{h}\right) + \ln\left(\frac{1}{T}\right) = -\frac{\Delta H^{\ddagger}}{R}\left(\frac{1}{T}\right) + \frac{\Delta S^{\ddagger}}{R} \qquad (2)$$

The thermodynamic activation parameters are given in Table 2 together with the correlation coefficients (r) of the best straight line fits in the above plots.

DISCUSSION

First a caveat concerning the appraisal of $\mathrm{Cr^{VI}}$ oxidation results from different laboratories, particularly since the reaction is very sensitive to solvent, acidity, temperature, and, of course, impurities. Even for relative rates, surprising differences can be found in reports from different groups. Thus, the ratios $k^{\mathrm{ox}}_{\mathrm{cyclopentanol}}/k^{\mathrm{ox}}_{\mathrm{cyclohexanol}}$ recorded are 1.22,[17] 1.4,[9] 1.5,[22,26] 1.8—1.9,[16,18,20] and 1.78 (this work). Another striking example is the norbornan-2-ol pair for which the k_{endo}/k_{exo} ratio is quoted as 7.8,[18a] 6.47,[18b] and 2.5.[9] It appears therefore that one should apply caution even when using relative rate constants for comparison, and absolute values should actually never be compared or extrapolated from different investigations.

As mentioned already, anancomeric cyclohexanols exhibit marked differences in $\mathrm{Cr^{VI}}$ oxidation rates with the axial alcohol undergoing faster oxidation. Thus for the 3-t-butylcyclohexanol at 25 °C $k_{trans}/k_{cis} = 6.06$ and 4-t-butylcyclohexanol $k_{cis}/k_{trans} = 3.23$ [15] (3.88 [16]). However, larger $k^{\mathrm{ox}}_{ax}/k^{\mathrm{ox}}_{eq}$ values were recorded when additional compression by *syn*-axial group came into play, *viz.* for 3,3,5-trimethylcyclohexanol at 25 °C, $k_{trans}/k_{cis} = 33.5$.[15,16] There appears to be little doubt that a ‘ steric acceleration ’ [7] takes place indeed and that the oxidation rates ratios reflect the difference in ground states of the reacting alcohols [9,11,12,15,16] with the products playing a small, if any, role in the position of the transition states.[8]

Cyclopentanol itself is oxidized by $\mathrm{Cr^{VI}}$ only by less than a factor of two faster than cyclohexanol. In this context it is worth recalling that cyclobutanol is even somewhat faster oxidized than cyclopentanol and $k^{\mathrm{ox}}_{\mathrm{cyclobutanol}}/k^{\mathrm{ox}}_{\mathrm{cyclohexanol}} = 1.5$.[8,22,29a] Such behaviour, strengthened by the finding that $k^{\mathrm{ox}}_{\mathrm{norbornan\text{-}7\text{-}ol}}/k^{\mathrm{ox}}_{\mathrm{cyclohexanol}} = 0.5$, *i.e.* a relatively small decrease in rate yielding the strained norbornan-7-one, led Kwart [9] to reject the possibility of a product-like transition state.[8] In a recent paper, however, Rocek *et. al.*[29a] attempt to vindicate the latter point of view [8] by arguing that, based on strain-energy calculations cyclobutanone is not at all more strained than cyclobutanol and hence, a higher rate constant is not necessarily required.

We proceed now to discuss our results in a number of contexts. First, the consideration of the rate constants and the trend within the series (Table 1). We interpret the relatively small increase in the oxidation rate of cyclopentanol as compared to cyclohexanol in terms of ‘ steric acceleration ’ by the torsional strain which constitutes the dominant term in the energy scheme of small rings.[3a] This is tantamount to relief of eclipsing effects in the transition state in the respective ring system. When the latter is six-membered, such effects are known to be minimized.[3a] On the other hand, non-bonded (van der Waals) interactions prevail in the cyclohexane ring [3a] and this is indeed expressed in the *syn*-axial compression which effectively enhances the oxidation rate in, say, *trans*-3,3,5-trimethylcyclohexanol to a much larger extent.

Turning now to the trend in oxidation rates of the increasingly substituted cyclopentanols in the present investigation. Thus, 3,3-dimethyl- and 3,3,4,4-tetramethylcyclopentanol are oxidized only by factors of 3.0 and 8.1 respectively, faster than cyclopentanol as compared with a factor of *ca.* 50 of *trans*-3,3,5-trimethylcyclohexanol *versus* cyclohexanol. We take this as

---

* Although, and perhaps because, the $\mathrm{Cr^{VI}}$ oxidation of secondary alcohols has been extensively studied, many authors refrain from describing details of the exact treatment of the experimental raw data. On the other hand, in some cases, the standard integrated rate equation $kt = (a - b)^{-1}\ln[b(a - x)]/[a(b - x)]$ is used,[7b] notwithstanding the, by now, well established fact [6,11,12] that the overall stoicheiometry of the process is (i)

$$2\ \mathrm{Cr^{VI}} + 3\ \mathrm{R_2CHOH} \xrightarrow{\mathrm{H^+}} 2\ \mathrm{Cr^{III}} + 3\ \mathrm{R_2CO} \qquad \text{(i)}$$

leading to the second-order rate equation (ii) which, in turn, upon

$$\mathrm{d}x/\mathrm{d}t = k(A_0 - 2x)(B_0 - 3x) \qquad \text{(ii)}$$

integration yields expression (1).

[28] ‘ International Critical Tables (National Research Council U.S.A.),’ McGraw-Hill, New York, 1972, vol. III, p. 123.

[29] (*a*) J. Rocek and A. E. Radkowsky, *J. Amer. Chem. Soc.*, 1973, **95**, 7123; (*b*) J. Rocek, A. M. Martinez, and G. E. Cushmac, *ibid.*, p. 5425.

confirmation of the assertion[2,3b,c] that 1,3-nonbonded interactions are relatively unimportant in five-membered rings since they are readily relieved by the (pseudorotational) mobility of the ring system.[3] This corroborates the earlier established physical and chemical behaviour of 1,3-substituted cyclopentanes. Thus, epimeric pairs of the latter system exhibit similar physical constants (b.p.s, refractive indices, i.r. and n.m.r. spectra, g.l.c. retention times),[1,2,4,21,24,27] to the extent that they are extremely difficult to analyse and to separate. At the same time strikingly similar behaviour was recorded for such 1,3-substituted epimeric pairs in solvolytic reactions[4a,c] and oxidation rate measurements,[1,21,24,26] chemical equilibration studies,[1,2,21,24,26,30] thermodynamic parameters of formation,[31] and strain-energy calculations.[2b,32,33]

The enthalpies and free energies of activation (Table 2) show a small decline with increasing substitution as expected from the recorded rate data. The entropies of activation are nearly constant and of high negative value. This confirms the occurrence of highly organized cyclic transition states, which are not affected by even much substitution in the β-positions. Altogether, we take these results to express a similar mechanistic path for all the studied substrates in the oxidation process. We should like to point out that, from our experience, such data are truly reliable only when accompanied by high correlation coefficients (r). In our study for example, two instances exhibited r values of 0.97 and 0.98 and were found indeed to be erroneous. Rechecking led to correct results with r values of 1.000 and 0.997.

Furthermore, the criterion of an isokinetic linear relationship may also be highly misleading unless it is applied with rigorous caution in terms of its physical meaning. It so happens that, for example, in oxidation rate studies any change in slope of the ln k *versus* $1/T$, *i.e.* $-\Delta H^{\ddagger}/R$ brings about a corresponding change in the highly sensitive intercept ($\Delta S^{\ddagger}/R$) value. The result is an apparent true point on the $\Delta H^{\ddagger}$ *versus* $\Delta S^{\ddagger}$ isokinetic linear plot. Usually this can also be spotted by the r value which, when lower then 0.99 should hint that the relationship is meaningless.[23b] People tend to disregard this point and some investigators do not even quote the correlation coefficients, let alone check the physical meaning of the relationship. Moreover, such a check in our case is clearly in order, since the processes are virtually isoenergetic, clusters are obtained, and no meaningful plot can be drawn. These considerations cast, in our opinion, considerable doubt on the value and utility of such relationships in Cr^{VI} oxidation rate studies published in the past.[16,17]

Finally, the isotope effects (Table 2) were studied as an additional criterion for assessing whether heavily β-substituted cyclopentanols are sterically crowded or not. In such a case, a change in the mechanism of the reaction could occur, the chromate ester formation possibly becoming rate determining over a faster, hydrogen abstractive, extrusion step.[10] The values in Table 2 clearly indicate an identical oxidation mechanism for all three cyclopentanols. Thus additional indirect support is provided to our conclusions that the five-membered ring system, while exhibiting appreciable torsional strain, minimized non-bonded interactions.[2,3b,c]

[5/1421 *Received*, 18*th July*, 1975]

---

[30] O. A. Aref'ev, V. A. Zakharenko, and A. A. Petrov, *Neftekhimiya*, 1964, **4**, 854 (*Chem. Abs.*, 1966, **65**, 16,835e).

[31] F. D. Rossini, K. S. Pitzer, A. L. Annett, R. M. Brown, and G. C. Pimentel, 'Selected Values of Physical and Thermodynamical Properties of the Hydrocarbons and Related Compounds,' Carnegie Press, Pittsburgh, 1953.

[32] N. L. Allinger, M. A. Miller, E. A. van Catledge, and J. A. Hirsch, *J. Amer. Chem. Soc.*, 1967, **89**, 4345.

[33] R. C. Lugar, Ph.D. Dissertation, University of Pennsylvania, 1969.