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STERIC EFFECTS ON REACTION RATES

II: RATE AND EQUILIBRIUM CONSTANTS FOR OXIDATION OF BICYCLIC ALCOHOLS

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Summary. Equilibrium constants for oxidation of a series of bicyclic alcohols with cyclohexanone have been determined under Meerwein-Ponndorf conditions. The data provide the thermodynamic background for interpretation of the mechanism of alcohol oxidation and ketone reductions. Free energies of the equilibrium (ΔG_{ox}) are compared with values calculated by molecular mechanics.

The importance of steric effects on rates of oxidation of alcohols with chromic acid has been widely discussed over the recent years, and various hypotheses concerning transition state structure have been advanced.[1] Similarly, the reverse reaction, ketone reduction with $NaBH_4$ and other complex hydrides is still subject of much controversy.[2] Surprisingly, the thermodynamics f these reactions have not been investigated in the past, although a precise knowledge of the strain changes occurring during these $sp^3 \rightleftarrows sp^2$ interconversions are expected to facilitate the understanding of the steric effects determining reaction rates.

We have recently found that equilibrium constants for alcohol oxidation by a ketone can be conveniently measured by GC analysis of mixtures equilibrated under Meerwein-Ponndorf conditions using $Al(O\text{-}iPr)_3$ or Raney-nickel in catalytic amounts.[3] Data for equilibration of cyclanols from C_4 to C_{15} with cyclohexanone have been reported. This communication deals with bicyclic and related alcohols. For reasons of simplicity in the analysis the compounds were selected such that no epimeric alcohols could be formed. Reactions were carried out in benzene with $Al(O\text{-}iPr)_3$ as catalyst,[3] unless otherwise indicated. Table I summarizes the experimental results. ΔG_r is the experimentally determined free energy for the oxidation of the alcohol (entry 2) by the respective ketone (entry 3).

$$K_r = \frac{[\text{ketone 1}][\text{alcohol 2}]}{[\text{alcohol 1}][\text{ketone 2}]} \quad \text{and} \quad G_r = -RT \ln K_r$$

ΔG_{ox} represents the energy relative to cyclohexanone as oxidant. The values given are averages for 6 equilibrations, starting from both sides. The error in ΔG_{ox} is estimated at ± 0.05 kcal/mol,[3] except for 7-norbornanol, where it is 0.23 kcal/mol.

Alcohol oxidation and ketone reduction. It has been proprosed that the transition state for chromic acid oxidation of alcohols should be late, *i.e.* product-like. Accordingly, ΔG_{ox} should be related to $\Delta\Delta G^{\ddagger}$ of the oxidation. Fig. 1 (stars, displaced by -3 units on y-axis) shows a plot of $\Delta\Delta G^{\ddagger}_{ox}$ *vs.* $-\Delta G_{ox}$. The poor fit as well as the slope of the regression of 0.32 (intercept 0.37, r = 0.672) indicate that alcohol reactivity is only in part reflected by ΔG_{ox}. In particular, alcohols leading to strained ketones such as 7-norbornanone or 2-adamantanone are more reactive than expected on the grounds of ΔG_{ox}. It follows, as was pointed out elsewhere,[1] that the carbonyl group can only be partially developed in the transition state. The determination of ΔG_{ox} provides the experimental background to this conclusion which previously had been derived from force-field calculations.[1]

$\Delta G^{\ddagger}$ for reduction of cyclanones with NaBH correlates with $-\Delta G_{ox}$ with a slope of 1.1 (r = 0.9785). This finding represents an illustration of Brown's I-strain hypothesis. It is indicative for a "late" transition state (product development control). The straight line in Fig. 1

Table I. Equilibrium Constants for Oxidation of Alcohols (kcal/mol)[a]

No	Alcohol	Ketone	ΔG_r	ΔG_{ox}	$-\Delta\Delta G^{\ddagger b}_{ox}$ Cr(6)-ox	$\Delta\Delta G^{\ddagger c}$ NaBH$_4$ Red	ΔΔ Strain[d] R=O-RCH$_3$	ΔΔ Strain[e] R=O-ROH
1	Cyclohexanol	Cyclohexanone	-	0	0	0	1.74[h]	-
2	3-Pentanol	"	-	-1.99[g]	0.0[k]	-	-1.07[i]	-
3	3,3,5,5-Tetramethylcyclohexanol	"	-	-1.35	0.53	-	-0.46	-0.37
4	2-Bicyclo[2.1.1]hexanol	2-Adamantanone	-1.09	-0.77	0.0	-	1.84	1.83
5	7-Norbornanol	"	3.35[f]	3.70	-1.16	-2.09	5.65[h]	3.47
6	2-Bicyclo[2.2.2]octanol	Cycloheptanone	0.61	-1.99	1.15	2.77	-0.57	-0.48
		Cyclopentanone	0.19	-1.97				
7	9-Bicyclo[3.3.1]nonanol	Cycloheptanone	2.96	0.35	1.18	0.83	1.27[h]	0.67
		Cyclohexanone	-	0.34				
8	2-Adamantanol	"	-	0.32	1.13	0.76	1.68[h]	0.90
9	4-Homoadamantanol	"	-	-2.88	1.95	-	-3.21	-2.22

[a] Conditions: 0.1 mmol of alcohol and ketone in 0.25 ml of benzene, 80°, 0.02 mmol of catalyst. [b] Chromic acid oxidation of alcohols, relative to cyclohexanol, Ref. 1b. [c] Ketone reduction with NaBH$_4$, relative to cyclhexanone, Ref. 4. [d] Strain difference calculated by MMI,[5] (Allinger 1976 force-field).[6] [e] Parameters according to Ref. 6. [f] Al(O^{t}Bu)$_3$ as catalyst. [g] Raney-nickel as catalyst. [h] Ref. 1b. [i] Ref. 7. [k] Extrapolated from Ref. 1b and 8.

represents this correlation. If the points relating to reduction of bicyclic ketones are added it is found that the latter are decelerated with respect to the cyclanones. Thus the transition state for reduction of 2-adamantanone (8), 9-bicyclo 3.3.1 nonanone (7) and 7-norbornanone (5) are destabilized by *ca.* 1.1, 1.3 and 2.1 kcal/mol relative to the average TS of the cyclanones.

Obviously ΔG_{ox} does not adequately express the reactivity of hindered ketones *vs.* $NaBH_4$. Since the stereoselectivity for reduction of hindered ketones is usually interpreted in terms of an "early" transition state[2] (steric approach control), it appears justified to invoke the same reason in connection with their reactivity. These considerations are qualitatively corroborated by force-field calculations with our previously published TS model for ketone reduction which accounts for both "steric approach" and "product development" control.[4] The TS model for reduction of unhindered ketones is *ca.* 6.5 kcal/mol more strained than the products. For hindered ketones this additional strain increases to 7.7 for 2-adamantanone and 10.0 for 7-norbornanone

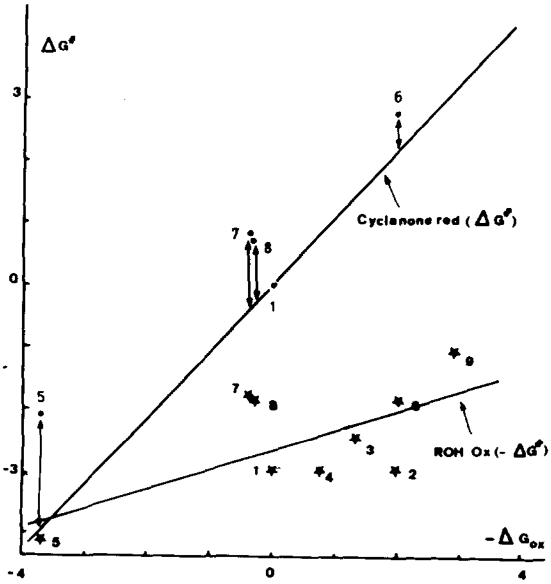

Fig. 1 Ketone reduction (circles) and alcohol oxidation (stars, displaced by -3 units on y-axis) *vs.* ΔG_{ox}

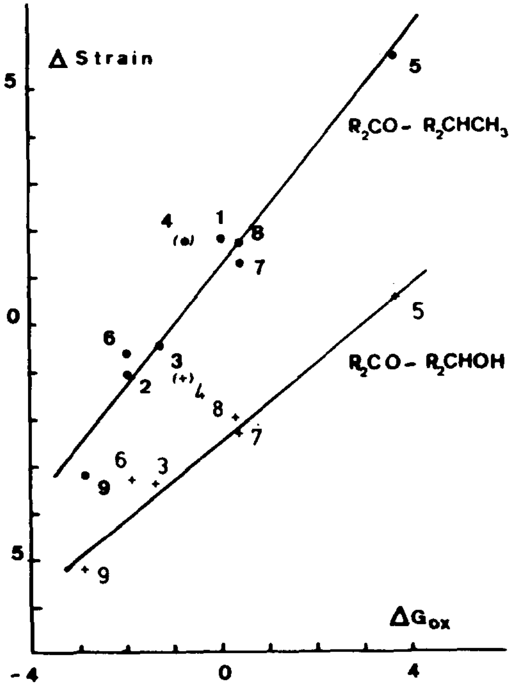

Fig. 2 Δ Strain (R_2CO-$RCHCH_3$, circles) and (R_2CO-R_2CHOH, stars, displaced by -3 units on y-axis) *vs.* ΔG_{ox}

Force-field calculations. Over the recent years force-field calculations have become popular for interpretation of reaction rates. Since the computer programs available at the early stages were only parametrized for hydrocarbons, the steric requirements of other functional groups had to be simulated by use of alkane models. Fig. 2 (upper line) shows how the calculated strain difference between ketone and methyl-substituted alkane correlates with ΔG_{ox}. The slope of the regression of 1.25 (intercept 1.22, r = 0.9838) is in agreement with the well-known fact that methyl groups are "bulkier" than OH substituents. The lower line, which is displaced by 3 units, represents the calculated strain difference between ketones and alcohols, using Allinger's parametrization for OH groups incorporated in the MMI program.[6] This correlation line has a slope of 0.80 (intercept 0.48, r = 0.97129). It appears that while the alkane model overestimates the strain for OH groups, the alcohol force-field underestimates it by about the same amount. The significance of this trend is not yet clear and will require further investigations using more recent force-field methods for alcohols.[9]

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REFERENCES

1) (a) P. Müller, Chimia 31, 209 (1977); (b) P. Müller & J.C. Perlberger, J. Am. Chem. Soc. 98, 8407 (1976).

2) J.R. Boone & E.C. Ashby, Topics in Stereochemistry 11, 53 (1979).

3) P. Müller & J. Blanc, Helv. Chim. Acta 63, 0000 (1980).

4) J.C. Perlberger & P. Müller, J. Am. Chem. Soc. 99, 6316 (1977).

5) N.L. Allinger, Adv. Phys. Org. Chem. 13, 1 (1976).

6) N.L. Allinger & D.Y. Chung, J. Am. Chem. Soc. 98, 6798 (1976).

7) E.M. Engler, J.D. Andose & P.v.R. Schleyer, J. Am. Chem. Soc. 95, 8005 (1973); N.L. Allinger, M.T. Tribble & M.A. Miller, Tetrahedron 28, 1173 (1972).

8) J. Rocek, Coll. Czech. Chem. Comm. 25, 1052 (1960).

9) U. Burkert, Tetrahedron 35, 209 (1979).

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