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186. Steric Effects on Reaction Rates. Rate and Equilibrium Constants for Oxidation of Cyclanols

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Summary

Equilibrium constants for oxidations of cyclanols by cyclohexanone in benzene have been determined in the presence of aluminium isopropoxide. The free energies of the equilibrium (ΔG_{ox}) are correlated with equilibrium constants for dissociation of cyanohydrins, rate constants for cyclanol oxidation with chromic acid, ketone reduction with sodium borohydride and trifluoroethanolysis of tosylates.

Introduction. - The method of molecular mechanics [1] has been applied by several groups to the problem of steric effects on reaction rates [2-5]. In this field we have interpreted rates of oxidation of secondary alcohols with chromic acid in terms of strain differences between alcohols and the corresponding ketones [6], and rates of borohydride reduction of ketones with strain differences between the ketone and an empirical transition state model [7]. Although reasonable correlations were obtained they also demonstrated the need for more reliable force-fields for the molecular mechanics programs used for evaluation of energies of alcohols and ketones. There is however an unfortunate lack of thermodynamic data which could be of use for re-parametrization of the force-fields. We therefore initiated a research program with the objective of generating such data. One approach to be described later involves determination of enthalpies of formation of alcohols and ketones. The study reported here is complementary to this and deals with direct determination of the energy difference between alcohols and ketones relative to cyclohexanone/cyclohexanol by equilibration.

Equilibration experiments have been used to determine the relative stabilities of epimeric alcohols in the presence of *Raney* nickel or aluminium isopropoxide [8]. To our knowledge, no investigation has been reported where the equilibrium for transfer of hydrogen from a series of alcohols to a standard ketone is determined.

Results. - The equilibrium constants K_{ox} at 80° in benzene for oxidation of cyclanols with cyclohexanone in the presence of aluminium isopropoxide according

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Table 1. *Rate and equilibrium constants for reactions of cyclanols and cyclanones (in kcal/mol)*

Ring size	$-\Delta G_{ox}$[a])	$-\Delta G_d$[b]) Dissociation of cyanohydrins	$-\Delta\Delta H_f^0$[c])	$-\Delta\Delta G^{\ddagger}_{ox}$[e]) Cr(VI)-oxidation of alcohols	$\Delta\Delta G^{\ddagger}_{Red}$[f]) NaBH$_4$-reduction of ketones	$-\Delta\Delta G^{\ddagger}_{solv}$[g]) Trifluoroethanolysis of toluenesulfonates
C_4	1.67	-	6.5 3.7[d])	0.49	−0.25	-
C_5	2.16	1.78	3.18	0.44	1.69	1.79
C_6	0.00	0.00	0.00	0.00	0.00	0.00
C_7	2.60	2.85	5.96	0.94	2.73	2.52
C_8	3.75	3.95	10.39	0.99	4.12	4.80
C_9	4.61	4.35	10.19	0.97	4.63	4.60
C_{10}	4.84	-	11.1	0.96	5.08	4.72
C_{11}	4.26	4.11	9.16	0.89	4.77	5.35
C_{12}	3.20	3.36	3.48	0.73	3.68	1.35
C_{13}	3.03	3.25	-	0.76	3.63	-
C_{15}	2.61	2.75	-	0.71	3.12	-

[a]) From equ. 2. [b]) Relative to cyclohexanone, data from [9]. [c]) $\Delta H^0_{f(\text{ketone})}$-$\Delta H^0_{f(\text{cycloalkane})}$ [10] relative to cyclohexanone/cyclohexane. [d]) [11]. [e]) [12]. [f]) [13]. [g]) Extrapolated from [5].

to equ. 1 and 2 have been determined by GC. analysis of equilibrated mixtures starting from both sides. When the equilibrium was too strongly displaced to the right side, cycloheptanone was used as acceptor and the resulting constants converted relative to cyclohexanone by appropriate correction. Details of the procedure

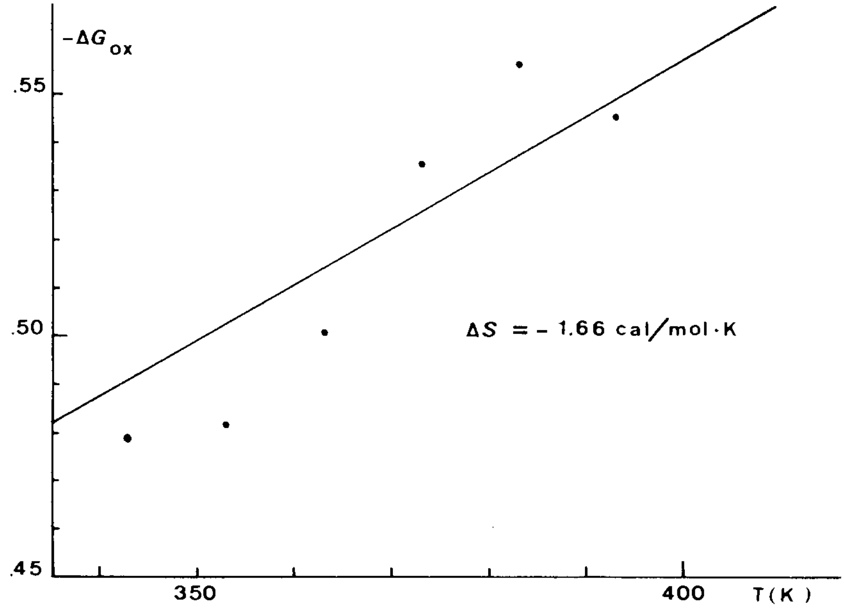

Fig. 1. *Temperature dependence of* ΔG_{ox} *for equilibration of cycloheptanol and cyclopentanone* (Data from *Table 2*)

$$R_2CHOH + C_6H_{10}O \overset{K}{\rightleftharpoons} R_2CO + C_6H_{11}OH \tag{1}$$

$$K = \frac{[R_2CO][C_6H_{11}OH]}{[R_2CHOH][C_6H_{10}O]} \tag{2}$$

are given in the experimental part. *Table 1* summarizes the results and other kinetic and thermodynamic data for reactions of cyclanols and cyclanones.

The temperature dependence of the equilibrium between cycloheptanol and cyclopentanone was investigated from 70 to 120°. Although a trend was observed ($\Delta S = -1.66$ cal/mol · K, *Fig. 1*), its significance is questionable. ΔG_{ox} varies by *ca.* 0.1 kcal over the whole range, while a fair estimate of the uncertainty in the data results in an approximate error in the range of 0.05 kcal/mol for ΔG_{ox}. Thus for the time being no attempt will be made to discuss enthalpy and entropy effects separately.

Discussion. - a) *Comparison of* ΔG_{ox} *with thermochemical and thermodynamic data.* Since our approach is new, the significance of the results must be examined.

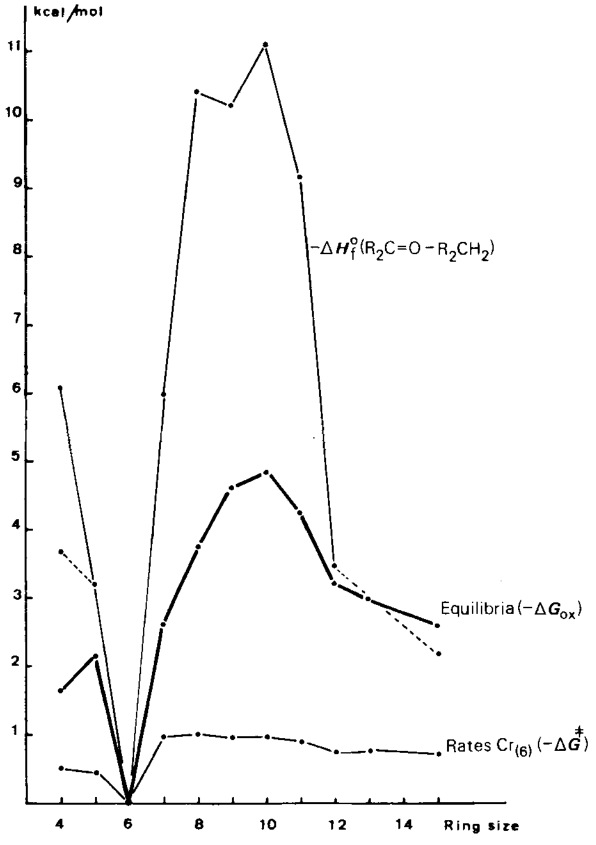

Fig. 2. *Variation of* ΔG_{ox} *as a function of ring size* (Data from *Table 1*)

ΔG_{ox} measures the energy difference between an alcohol and the corresponding ketone relative to the energy difference between cyclohexanol and cyclohexanone. It should also be characteristic for the energetics of other $sp^3 \rightleftarrows sp^2$ interconversions. Data for such reactions are available from *Brown*'s fundamental paper on the *I*-strain hypothesis [13] and from enthalpies of formation [14].

The variation of ΔG_{ox} as a function of ring size *(Fig. 2)* shows the expected shape with regard to the *I*-strain hypothesis. The curve reproduces the well known preference for a sp^2-hybridized center in the medium-sized rings. Comparison of the curve with that for differences in enthalpies of formation between cycloalkanes and cyclanones (upper curve) reveals, two significant discrepancies, although their shapes are very similar. ΔG_{ox} covers only about half the range of $\Delta\Delta H_f^0$ and, furthermore, the results for the cyclobutane ring are inconsistent, *i.e.* the cyclobutane ring is below the cyclopentane ring for ΔG_{ox}, but above for $\Delta\Delta H_f^0$. The former discrepancy implies that there should be less strain change in going from a substituted cycloalkane to the ketone than from the unsubstituted one, while the latter must in part be due to unreliability of the thermochemical data. Two values are available for ΔH_f^0 of cyclobutanone; *Wolf* [10] reports -24.20, and *Roček* [11] -21.9 kcal/mol. There is no reason to prefer one value over the other, but although *Roček*'s value is in better agreement with ΔG_{ox}, the discrepancy still remains. On the other hand, the calculated gas-phase heats of hydrogenation are -12.7 (*Roček*'s value), -11.41 and -13.08 kcal/mol for cyclobutanone, cyclopentanone and cycloheptanone, which is in agreement with the sequence predicted by ΔG_{ox}. The case of cyclobutanone is complex and not yet entirely explicable.

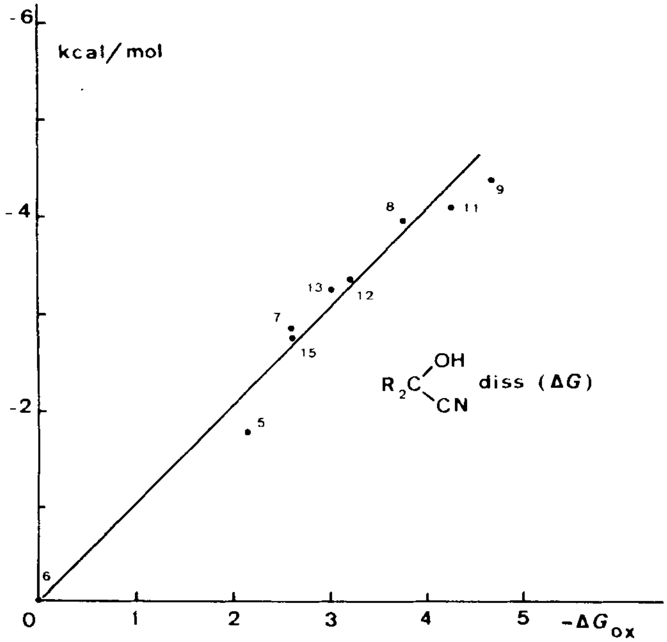

Fig. 3. *Dissociation of cyanohydrins* (ΔG) *relative to cyclohexanone* vs. ΔG_{ox}. Slope: 0.99, correlation coefficient 0.9857. (Data from *Table 1*)

In *Figure 3* ΔG_{ox} is correlated with the free energies for dissociation of the cyanohydrins of the cyclanones [9]. The regression line has a slope of 0.99 and a correlation coefficient of 0.9857. This excellent agreement is a consequence of the small steric requirements of the cyano substituent. The latter may be illustrated by the conformational energy of 0.15-0.25 [15] kcal/mol of cyclohexyl bound cyano groups. Unfortunately, the value for the cyanohydrin of cyclobutanone is not available.

b) *Comparison of* ΔG_{ox} *with reactivities for* $sp^3 \rightleftarrows sp^2$ *interconversions.* The reactions studied in this context are ketone reduction with $NaBH_4$ [13], alcohol oxidation with chromic acid [12] and solvolysis of *p*-toluenesulfonates in 97% trifluoroethanol [5]. Ketone reduction is particularly interesting, because the rate profile for the cyclanones has been used in support of the hypothesis of a late transition state for $NaBH_4$-reduction [16]. In *Figure 4* ΔG_{ox} is plotted against the free energies of ketone reduction with $NaBH_4$. Again an excellent correlation is obtained. The slope of -1.1 ($r=0.9785$) is in agreement with complete sp^3 hybridization in the transition state of reduction. This in no way invalidates our previously proposed models for the transition state of reduction [7]; it rather implies the same degree of steric hindrance to attack of borohydride for all the ketones of this particular series.

For unknown reasons however, cyclobutanone falls out of the correlation, reacting faster than all other cyclanones, while ΔG_{ox} suggests it to be less reactive

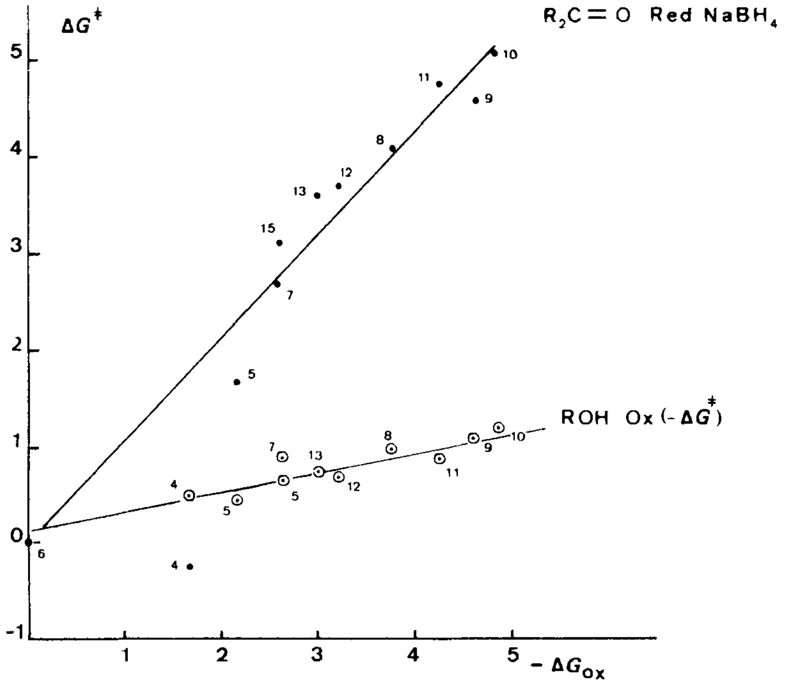

Fig. 4. *Plot of* $-\Delta G_{ox}$ vs. $\Delta G^{\ddagger}$ *for reduction of ketones with* $NaBH_4$ (slope -1.1, $r=0.9785$) *and* $-\Delta G^{\ddagger}$ *for oxidation of alcohols with chromic acid* (slope 0.19, $r=0.905$). (Data from *Table 1*)

than cyclohexanone. This observation requires further investigation. It is of interest in this context that in the enzymatic reduction of cyclanones with horse liver alcohol dehydrogenase (HLAD [17]) cyclobutanone is reduced at a slower rate than cyclohexanone; the free energies of the reaction from C_4 to C_9 correlates with ΔG_{ox} with a slope of 0.99 (r = 0.96).

The situation is much less satisfactory for alcohol oxidation with chromic acid. As *Figure 2* (bottom curve) shows, the rates vary very little with ring size from C_4 to C_7 and, in addition, the medium and large-size rings show almost no rate variations at all. The corresponding correlation of $\Delta G^{\ddagger}$ with ΔG_{ox} *(Fig. 4)* has a small slope of 0.19 (r = 0.90). This demonstrates again [6] that the strain changes between alcohol and ketone are only partly reflected in the free energy of activation for chromic acid oxidation. Furthermore, an additional complication might arise due to the flexible nature of the molecules used. They are partly conformationally heterogeneous and it is uncertain whether the different conformers pass through a common transition state [5]. Finally, since transition states are very short-lived entities, it is uncertain that they reach the conformation of minimum energy, since complete relaxation could require more than their life-time.

The solvolysis of cycloalkyl *p*-toluenesulfonates in acetic acid has been investigated by *Brown* [13] in relation to his work on the *I*-strain hypothesis. The reaction correlates reasonably well with ΔG_{ox} from C_4 to C_{10}, but breaks down for the higher homologues. Recently *Schneider & Thomas* [5] have reinvestigated the solvolysis of cycloalkyl *p*-toluenesulfonates in 97% trifluoroethanol. This solvent was selected because of its low nucleophilic character which should unify the reaction mechanism for toluenesulfonate solvolysis by suppression of solvent-

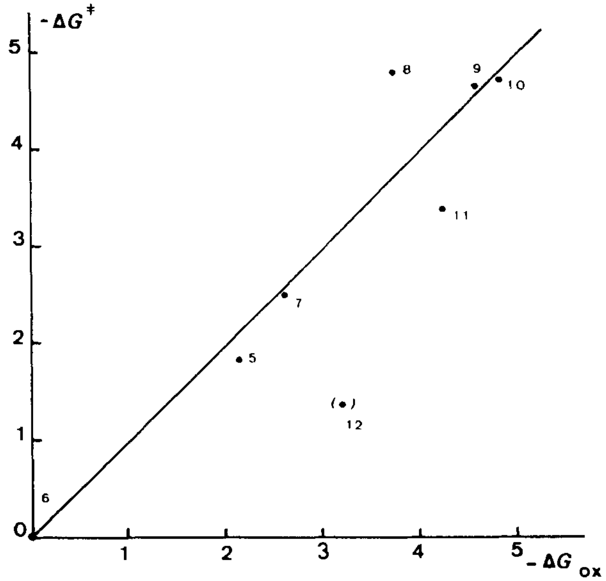

Fig. 5. *Plot of* $-\Delta G_{ox}$ vs. $-\Delta G^{\ddagger}$ *for solvolysis of cycloalkyl* p-*toluenesulfonate in 97% trifluoroethanol* (slope 0.99, r = 0.9458) (C_{12} excluded). (Data from *Table 1*)

assisted pathways [18]. *Figure 5* shows a plot of the data of [5] *vs.* ΔG_{ox}. From the slope of 0.99 (r = 0.95) we conclude that the carbonyl group simulates the steric requirements of the transition state for solvolysis very well. For reasons explained by *Schneider & Thomas* [5] we have not included the value for C_{12}. One might be tempted to speculate why cyclooctyl toluenesulfonates solvolyzes faster than predicted by ΔG_{ox}. *Parker* [19], on the ground of ε-deuterium isotope effects has estimated that the rate of acetolysis of cyclooctyl *p*-bromobenzenesulfonate could be anchimerically assisted by *ca.* 22%; although this effect has never been demonstrated [20], anchimeric assistance of this order of magnitude would account for the deviation of cyclooctyl toluenesulfonate from our plot. The possibility of simulating the steric requirements of the solvolysis transition state by a carbonyl group was recognized very early by *Foote & Schleyer* [21]. Their approach, like ours, is however limited because steric hindrance of the leaving group is not considered [22]. We hope that the latter problem can eventually be overcome by force-field calculations.

Conclusion. - The equilibration of alcohols and ketones permits the determination of relative energies with higher precision than other methods. These energies correlate well with equilibrium for dissociation of cyanohydrins of cyclic ketones. They are useful within certain limitations for interpretation of reaction rates involving $sp^2 \rightleftarrows sp^3$ interconversions and confirm *Brown*'s *I*-strain hypothesis. They should provide the background for improved force-fields for alcohols and ketones.

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Experimental Part

Materials. The ketones were all from commercial sources except cyclononanone which was a gift of Prof. *A. Fischli*. The alcohols not available commercially were prepared by $LiAlH_4$-reduction of

Table 2. *Equilibration of alcohols and ketone with aluminium isopropoxide in benzene* (80°)

Alcohol	Ketone	*K*	$-\Delta G$ reaction	$-\Delta G_{ox}$ rel. cyclohexanone	Comments
Cyclobutanol	Cyclohexanone	10.85		1.67 ± 0.05	
Cyclopentanol	Cyclohexanone	21.65		2.15 ± 0.02	*Raney* Ni
Cycloheptanol	Cyclohexanone	40.87		2.60 ± 0.02	*Raney* Ni
Cyclooctanol	Cycloheptanone	5.10	1.14	3.74 ± 0.01	
Cyclononanol	Cycloheptanone	17.44	2.00	4.61 ± 0.03	
Cyclodecanol	Cycloheptanone	24.16	2.23	4.84 ± 0.01	
Cycloundecanol	Cycloheptanone	10.58	1.65	4.26 ± 0.02	
Cyclododecanol	Cycloheptanone	2.36	0.66	3.20 ± 0.05	
Cyclotridecanol	Cycloheptanone	1.84	0.43	3.03 ± 0.01	
Cyclopentadecanol	Cycloheptanone	1.01	0.007	2.61 ± 0.02	
Cycloheptanol	Cyclopentanone	2.02	0.48		$Al(O\textit{i}Pr)_3$ T = 70°
Cycloheptanol	Cyclopentanone	1.99	0.48	2.63 ± 0.04	T = 80°
Cycloheptanol	Cyclopentanone	2.02	0.51		T = 90°
Cycloheptanol	Cyclopentanone	2.06	0.54		T = 100°
Cycloheptanol	Cyclopentanone	2.07	0.56		T = 110°
Cycloheptanol	Cyclopentanone	2.01	0.55		T = 120°

the ketones. All compounds were purified by preparative GC. up to 99% minimum purity before equilibration. Aluminium isopropoxide *(Fluka)* was sublimed.

Equilibration. Weighed equimolar quantities (*ca.* 0.10 to 0.15 mmol) of alcohol (or ketone) and cyclohexanone (or cyclohexanol) were dissolved in 0.25 ml of dry benzene containing 0.02 mmol of aluminium isopropoxide. The solutions were heated in sealed ampoules to 80±0.5° until equilibrium (3 to 10 days). For each run 3 ampoules were equilibrated from both sides and the reaction was stopped when the equilibrium constants from both sides were within 2%. GC. analysis was carried out by direct injection of the samples on an FFAP column and electronic integration (*Hewlett-Packard* Model 5831A). The detector response was calibrated for each run with samples of known composition. If the reaction mixture was hydrolyzed before injection, no measurable change in the composition could be detected. The equilibrium constants reported in *Table 2* refer to average values for the 6 samples equilibrated, with the average experimental error.

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