192. Steric Effects in the Reduction of Ketones with Sodium Borohydride

by **Paul Müller** and **Jean-Claude Perlberger**

Département de Chimie Organique, Université de Genève,
1211 Geneva 4, Switzerland

(3. V. 76)

Summary. The rates for the reduction of ketones with sodium borohydride are interpreted in terms of two parameters, both derived from force-field calculations; *i.e.* the strain difference between alcohol and ketone (Δ strain) and the steric hindrance towards approach of the hydride R. Models for the evaluation of R are discussed. With this approach reduction rates over a range of 10^8 can be rationalized within a factor of 6–10.

The reduction of ketones with complexed hydrides such as sodium borohydride or lithium aluminium hydride is subject to steric effects determining stereo- and regioselectivity of the reaction. These effects are still not fully understood. The stereochemistry of the reduction is usually explained in terms of thermodynamic considerations (product development control [1] [2]) and of steric hindrance of the attacking hydride (steric approach control [1] [3]) however, so far no quantitative relationship between structure and reactivity could be established. In this communication we propose an approach towards the rationalization of the ketone reduction rates with sodium borohydride, taking into account both product development and steric approach control.

It is assumed that the maximum rate of reduction, in the absence of steric hindrance of the attacking nucleophile, is proportional to the strain difference (Δ strain) between alcohol and ketone:

$$\log k_{\mathbf{max}} = A_1 \cdot \Delta \text{ strain}$$

This factor represents 'product development control'. If the approach of the hydride is hindered $k_{\mathbf{max}}$ will be reduced, and we may write:

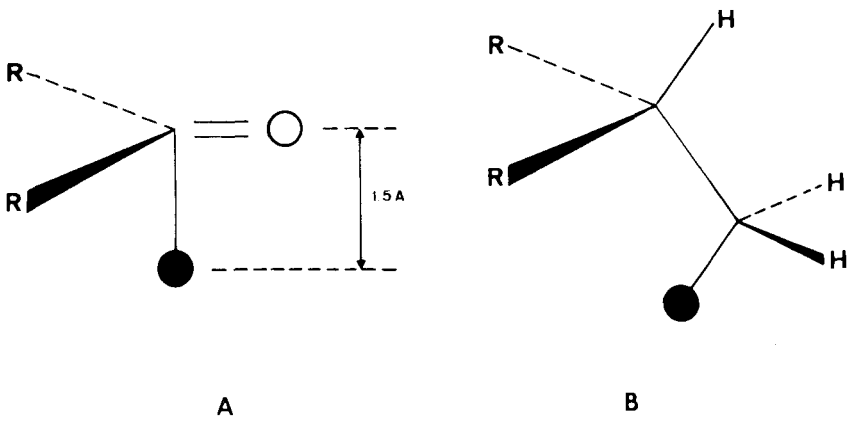
$$\log k = A_1 \cdot \Delta \text{ strain} - A_2 \cdot R$$

where R represents the steric hindrance of the carbonyl group towards approach of a nucleophile from one side. A_1 and A_2 are proportionality constants. Force field calculations allow the evaluation of strain in ketones [4]. The strain in alcohols may be approximated by that of the corresponding hydrocarbons [5]. The strain difference between ketones and alcohols obtained in this way determines the rates of alcohol oxidation with chromic acid [5a]. If the carbonyl reduction is controlled by

thermodynamic factors (transition state resembling the alcohol), Δ strain will also determine the reduction rates. The problem then is to obtain values for R.

One method to handle 'steric approach control' has recently been published [6]. *Wipke*'s congestion function describes the 'bulk' at a reacting centre in the direction of preferred approach of an attacking reagent. In our own approach we probe the steric environment on the respective sides of the carbonyl group by placing a hydrogen atom perpendicular to the carbonyl carbon atom at arbitrary distances (Model A). The energy of the ketone is minimized beforehand by means of the BIGSTRN-program of *Schleyer* & *Mislow*, using the *Allinger* force-field [4]. In a second step the

Scheme



non-bonded interactions of the extra hydrogen atom with all the other atoms are calculated and added up. For these interactions the parametrization of *Schleyer* is used [5b]. In an alternative procedure the energy of the appropriate methyl compound (Model B) is minimized, and the non-bonded interactions of the methyl hydrogen atom, pointing towards the 'inside' of the molecule, with the other atoms are added up. Table 1 contains values for R of 21 ketones calculated with the model A with the hydrogen probe at 1.5, 1.75 and 2.25 Å and with model B. The table also contains the relevant reduction rates from the literature and the Δ strain values published previously [5a]. For clarity the name of the alcohol formed is given instead of that of the reacting ketone.

Inspection of the table reveals that R may increase or decrease within the model A with increasing distance of the probe, depending from the ketone structure. In some cases (entries 6, 11, 21) extremely high energies are obtained, particularly at 2.25 Å. This is not the case in model B, where the strain can be distributed over the entire molecule. Because of the energy minimization the position of the hydrogen probe in model B is different in each molecule, contrary to A, where it is kept constant.

The relative rate constants for formation of the various alcohols are correlated with the parameters Δ strain and R by means of the equation

$$\log k_{\text{rel}} = A_1 \, \Delta \text{ strain} + A_2 R + A_3$$

Table 1. *Ketone reductions*

Alcohol formed		log k_{rel} [a]	Δ strain [b]	R Model B [kcal/mol]	R, Model A [kcal/mol] 1.5 Å	1.75 Å	2.25 Å
Cyclobutanol	(**1**)	– 0.09	1.94	0.28	4.45	3.0	0.93
Cyclopentanol	(**2**)	– 1.66	– 1.55	0.19	4.84	3.40	1.12
cis-4-Methylcyclohexanol	(**3**)	– 0.52	0.14	0.14	6.29	4.38	1.42
trans-4-Methylcyclohexanol	(**4**)	– 0.02	1.79	0.45	5.46	6.74	7.29
trans-3, 5, 5-Trimethylcyclohexanol	(**5**)	– 1.92 [c]	– 2.87	0.15	5.93	4.09	1.29
cis-3, 5, 5-Trimethylcyclohexanol	(**6**)	– 2.10 [c]	1.09	0.92	28.03	49.99	241.09
2-Propanol	(**7**)	– 1.33	0.08	0.12	4.62	3.04	0.84
2-*endo*-Norbornanol	(**8**)	– 1.55	0.24	0.42	8.31	8.33	6.48
2-*exo*-Norbornanol	(**9**)	– 2.34	1.07	0.62	12.00	15.75	18.86
7-Norbornanol	(**10**)	1.67	5.65	0.71	8.38	11.05	12.96
Borneol	(**11**)	– 5.66	– 1.56	1.00	58.54	224.53	725.24
Isoborneol	(**12**)	– 4.86	– 3.51	0.93	15.72	21.01	25.14
2-*endo*-Bicyclo[3.2.1]octanol	(**13**)	– 0.66	1.53	0.50	7.78	10.11	11.81
2-*exo*-Bicyclo[3.2.1]octanol	(**14**)	– 1.24	0.53	0.33	11.16	12.02	10.87
3-*endo*-Bicyclo[3.2.1]octanol	(**15**)	– 2.89 [c]	– 4.19	0.21	7.26	5.21	1.81
3-*exo*-Bicyclo[3.2.1]octanol	(**16**)	– 2.64 [c]	0.49	0.85	10.33	17.40	36.39
9-Bicyclo[3.2.1]nonanol	(**17**)	– 0.66 [c]	1.27	0.70	10.32	13.55	15.77
8-*endo*-Bicyclo[3.2.1]octanol	(**18**)	– 1.56 [c] [d]	3.69	0.93	16.58	22.03	25.31
8-*exo*-Bicyclo[3.2.1]octanol	(**19**)	0.44 [c]	2.12	0.42	3.49	3.97	3.93
3-*endo*-Bicyclo[3.2.1]nonanol	(**20**)	– 5.29 [c]	– 11.56	0.33	7.96	5.70	1.98
3-*exo*-Bicyclo[3.3.1]nonanol	(**21**)	– 6.16 [c]	– 3.34	1.06	165.39	418.21	2446.53

[a] Partial rate constants relative to cyclohexanone; solvent 2-propanol, 0° [1a].
[b] Δ strain = strain $R_2C{=}O$ – strain $RCHCH_3$, in kcal/mol [5a].
[c] Solvent 0.025 *M* NaOH/dioxane 1:1, 25° [2c].
[d] Estimated from [7].

using a double regression procedure. The best fit was obtained with model A at a 1.5 Å hydrogen distance and with model B. Fig. 1 and 2 show plots of the experimental rate constants as a function of the values calculated from the double regression. The characteristic constants of the regression and of Fig. 1 and 2 are summarized in Table 2.

Table 2. *Regression constants and statistical parameters*

Model	Double regression			Plot log $k_{(exp)}$ *vs.* log $k_{(calc)}$			
	A_1	A_2	A_3	Slope	Intercept	Correlation coefficient	Standard deviation
A_1 1.5 Å	0.407	– 0.0275	– 1.226	0.9999	$-1.11 \cdot 10^{-4}$	0.8965	0.96
B	0.495	– 3.61	0.155	1.0000	$-3.02 \cdot 10^{-4}$	0.93	0.79

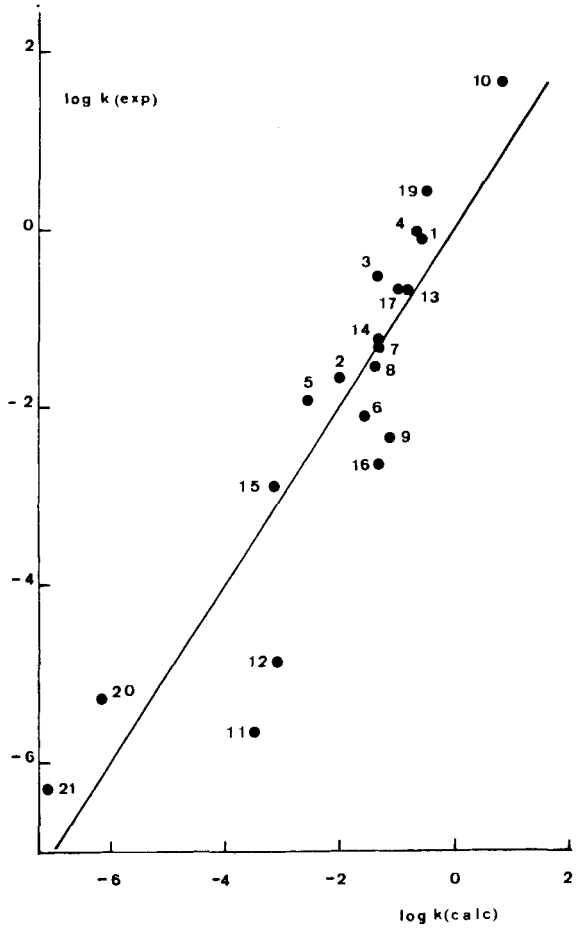


Fig. 1. *Plot of experimental* vs. *calculated rate constants. Model A* (1.5 Å C–H distance)

With model B the standard deviation of the rate constants corresponds to a factor of *ca.* 6. The correlation coefficient is higher than with A. On the other hand, the standard deviation in model A is to a considerable degree determined by the two points related to the reduction of camphor. This ketone is handled very poorly indeed, while all the others come out rather better in model A than in B. Both approaches are however far from perfect.

For practical purposes it is often of interest to know the stereoselectivity of the reduction, that is the relative rates for *exo/endo* attack. Table 3 shows the experimental and calculated relative rate constants for *exo/endo* reduction. From a total of eight epimeric alcohol pairs the best model predicts in six cases the experimental preference for *exo/endo* attack (model A), the other only in four, a very poor agreement. If one considers only the repulsions R for the prediction the failures are one with A and three with B. Although the calculations seem to give reasonable values

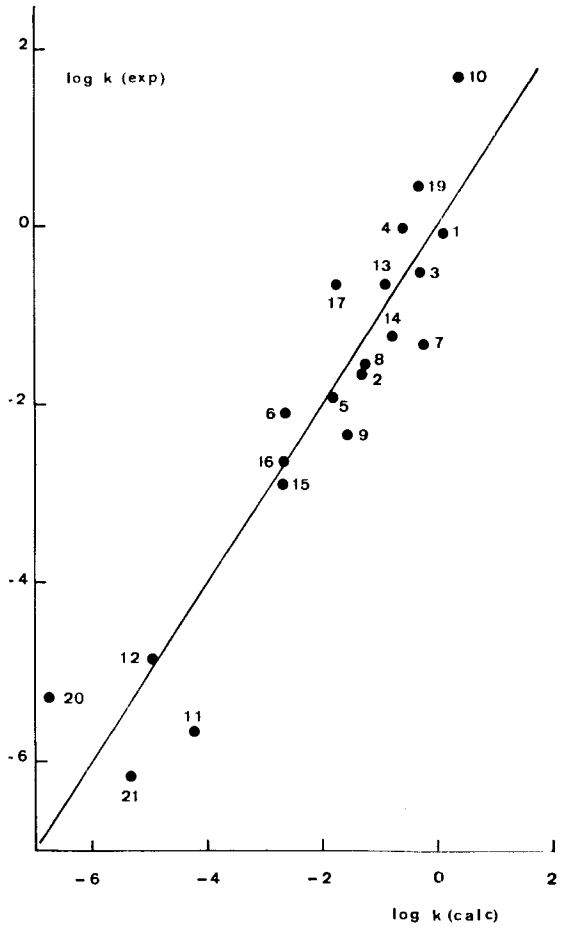


Fig. 2. *Plot of experimental* vs. *calculated rate constants. Model B*

Table 3. *Experimental and calculated* exo/endo *preference of attack for ketone reduction*

Ketone	log (k_{exo}/k_{endo}) experimental[a]	log (k_{exo}/k_{endo}) calc. model A 1.5 Å	log (k_{exo}/k_{endo}) calc. Model B
4-Methylcyclohexanone	−0.50	−0.69	−0.30
3,3,5-Trimethylcyclohexanone	0.18	−1.01	0.82
2-Norbornanol	0.79	−0.24	0.31
Camphor	−0.80	−0.38	0.71
Bicyclo[3.2.1]octanone-2	0.58	0.50	−0.12
Bicyclo[3.2.1]octanone-3	−0.25	−1.82	−0.01
Bicyclo[3.2.1]octanone-8	< -2.0[b]	−0.31	−0.96
Bicyclo[3.2.1]nonanone-3	0.87	0.98	−1.43

[a] k_{exo} = rate constant for attack from exo side. Data from Table 1.
[b] Estimated from [7].

for R, the regression procedure tends to put 'too much' weight on the A strain term, so that the trends predicted from R may in part be overcompensated. The advantage of this approach over that of *Wipke* is that it allows to correlate rate constants. However, when it comes to predict *exo/endo* preferences the uncertainties in the procedure become too high as to allow predictions, at least when small reactivity differences are involved. In terms of energy, A strain and R are in the same order of magnitude and to achieve a balance is a delicate matter.

The approach proposed here for the calculation of steric effects on reduction rates is based on ground state properties of the molecules. Although it allows predictions of rate constants within the appreciable rate range of 8 powers of 10 it needs further refinement. One possible approach which is currently under investigation consists in deriving models for the transition state in such a way, that the contribution from steric approach control and product development control can be obtained from one and the same structure.

This work was supported by the *Fonds National Suisse de la Recherche Scientifique* (project No 2.1280.74) by the *Société Académique de Genève* (*Fonds Frédéric Firmenich*), and by the *Fonds Xavier Givaudan*. The authors are indebted to Professor *K. Mislow* for the BIGSTRN program.

REFERENCES

[1] a) *H. C. Brown & J. Muzzio*, J. Amer. chem. Soc. *88*, 2811 (1966); b) *H. C. Brown & K. Ichikawa*, Tetrahedron Letters *1957*, 221; c) *W. G. Dauben, E. J. Blanz, J. Ziu & R. A. Micheli*, J. Amer. chem. Soc. *78*, 3752 (1956); d) *D. J. Pasto & B. Lepeska*, J. Amer. chem. Soc. *98*, 1091 (1976).

[2] *P. Geneste & G. Lamaty*, Bull. Soc. chim. France *1968*, 669; *CC. Moreau*, Thèse de doctorat, Université des Sciences et Techniques du Languedoc, Montpellier 1972.

[3] *M. Cherest & H. Felkin*, Tetrahedron Letters *1968*, 2205.

[4] *N. L. Allinger, M. T. Tribble & M. A. Miller*, Tetrahedron *28*, 1173 (1972).

[5] a) *P. Müller & J. C. Perlberger*, J. Amer. chem. Soc. *97*, 6862 (1975); b) *E. M. Engler, J. D. Andose & P. v. R. Schleyer*, ibid. *95*, 8005 (1973); c) *J. D. Andose & K. Mislow*, ibid. *96*, 2168 (1974).

[6] *W. T. Wipke & P. Gund*, J. Amer. chem. Soc. *96*, 299 (1974).

[7] *C. S. Foote & R. B. Woodward*, Tetrahedron *20*, 687 (1964).