Stereochemistry and Kinetics of the Reactions of Bicyclo[3,2,1]octan-2- and -3-one with Sodium Borohydride, Methylmagnesium Iodide, and Diazomethane [1]

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Bicyclo[3,2,1]octan-2- (1) and -3-one (2) and norbornan-2-one (3) undergo reduction by sodium borohydride in isopropyl alcohol with second-order kinetics, the product distribution remaining unchanged during the course of the reaction. Relative rates for these reactions at room temperature are *ca.* 50:10:1 for (1), (3), and (2) respectively. Dissection of the rate coefficients on the basis of product distribution shows that *trans*-attack (with respect to the ethano bridge of the cyclohexanone skeleton) is *ca.* four-fold faster than *cis*-attack for (1), while the reverse order (by *ca.* 1·5-fold) is true for (2). The kinetically controlled product ratios parallel the thermodynamic values, and are very similar in the case of the norborneols. Addition of methylmagnesium iodide is only *ca.* five-fold faster for (1) than for (2) in diethyl ether at 0°. Dissection of rates on the basis of product distribution shows that *cis*-attack, which is only slightly faster than *trans*-attack for (1), is completely inhibited for (2). Crude experiments indicate that (1) reacts *ca.* 80 times faster than (2) with diazomethane in diethyl ether–methanol (1:2) at room temperature. All these observations are rationalized.

In a study of the reactions of diazomethane with norbornan-2-one (3) and its higher homologues, such as bicyclo[3,2,1]octan-2- (1) and -3-one (2),[2] we observed that (1) reacts more rapidly than (3) with diazomethane under methanol catalysis to give higher homologous ketones whereas (2) is rather inert under similar conditions. We tentatively ascribed the low reactivity of (2) to repulsive interactions between the developing alcohol oxygen atom and the ethano bridge in the transition state for nucleophilic *trans*-attack † by diazomethane on the carbonyl carbon.[2] Unfortunately, the stereochemistry of the attack of diazomethane on (2) cannot be established by any method other than isolating or observing by spectroscopy (*e.g.* n.m.r.) the intermediate(s) of diazomethane attack, and this is not feasible here.[2] This ‡ poses a severe limit on the scope of any kinetic study of these reactions because what is needed in such cases, as discussed later, are partial rates for attack at the carbonyl carbon atom from its two nonequivalent faces and not merely total rates.

Therefore, we decided to search for an order of magnitude only of the relative reactivity of (1) and (2) towards diazomethane and to investigate thoroughly the kinetics and stereochemistry of addition of hydride or methyl by, respectively, sodium borohydride or methylmagnesium iodide. In fact, when the change from the reagents to the rate-limiting transition state[2] is considered, all these reactions are similar and involve $sp^2 \longrightarrow sp^3$ hybridization at the carbonyl carbon atom to an extent depending on the position of the transition state along the reaction co-ordinate.

Previous kinetic studies of the reductions of polycyclic ketones by complex hydrides concerned bicyclo[2,2,1]-heptyl, bicyclo[2,2,2]octyl, and nortricyclyl systems.[3]

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† *cis*- and *trans*-attack by diazomethane on (1) or (2) refers to attack from the side or from the opposite side, respectively, of the ethano bridge.

‡ It is difficult to obtain accurate rates for reaction of diazomethane with ketones in general (see later) and it is practically impossible when, as in the case of (2), self-decomposition of diazomethane is a much faster process than its reaction with (2).

[1] E. Volpi, Doctoral Thesis, Pisa, 1972.

[2] G. Fachinetti, F. Pietra, and A. Marsili, *Tetrahedron Letters*, 1971, 393.

[3] H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, 1966, **88**, 2811.

The reduction of norbornan-2-one by sodium borohydride [3] has been re-examined here because information concerning product distribution was available only for the complete reaction.

RESULTS

As solvent for the reductions of (1)—(3) by sodium borohydride we chose isopropyl alcohol for its known advantages over other alcohols [3] and because previous detailed kinetic studies on both bicyclic [3] and cyclic [3,4] ketones, with which we could compare our data, have been carried out in this solvent. There was generally a 1 : 4 mole ratio of hydride to ketone. A study of the dependence of the rate on the concentrations showed that these reactions were, as expected,[3] second order (first order with respect to each reagent). The reactions were monitored by the disappearance of the ketone and the appearance of alcohols (g.l.c.). In the case of both (1) and (3) reaction rates were also obtained (not reported here) by following the disappearance of the ketone by u.v. spectroscopy at the long wavelength band of the carbonyl group. They substantially agreed with those obtained by g.l.c.

Rate data and activation parameters for these sodium borohydride reductions are in Table 1 together with previous data for the analogous reductions of cyclohexanone (4),[3,4] cyclopentanone (5),[3] and 4-methylcyclohexanone (6).[4]

TABLE 1

Second-order rate coefficient k [a] for the reactions of sodium borohydride with cyclic or bicyclic ketones in isopropyl alcohol

Ketone	$\nu_{C=O}$/cm^{-1}	t/°C	10^4k/l mol^{-1} s^{-1}	Rel. rate at 0 °C	Rel. rate at 25 °C	ΔH^*/kcal mol^{-1}	$-\Delta S^*$/cal mol^{-1} K^{-1}
(1)	1727 [b]	0 [c]	65	77	44	5·4	53
		21 [d]	131				
(2)	1715 [e]—1721 [f]	21 [g]	2·7	1	1	8·9	46
		35 [h]	5·3				
(3)	1751 [i]	25	24·0 [i]		7·0	9·3	39·5
(4)	1716 [i]	0	161 [j]—235 [k]	280 [l]	166 [m]	5·1 [i]	48·1 [i]
		25	565 [i]				
(5)	1748 [i]	25	31·8 [j]		9·4	9·3 [n]	38·8 [n]
(6)		0 [k]	294	350			

[a] See text. [b] Ref. 15. [c] Initial concentrations; ketone 0·052, hydride 0·014M. [d] Initial concentrations; ketone 0·118, hydride 0·030M. [e] S. A. Monti, D. J. Bucheck, and J. C. Shepard, *J. Org. Chem.*, 1969, **34**, 3080. [f] Ref. 5. [g] Initial concentrations; ketone 0·120, hydride 0·030M. [h] Initial concentrations; ketone 0·110, hydride 0·026M. [i] Ref. 3. [j] Data from H. C. Brown and K. Ichikawa, *Tetrahedron*, 1957, **1**, 1221. [k] Data from ref. 4. [l] Calculated from data of ref. 4. [m] Calculated from ref. 3. [n] Calculated from data of ref. *j* above.

TABLE 2

Product distributions and partial (second-order) rate coefficients for reactions of sodium borohydride with cyclic or bicyclic ketones in isopropyl alcohol

Ketone	t/°C	Isomeric alcohols *trans* [a]	Isomeric alcohols *cis* [a]	Rate coefficients 10^4k/l mol^{-1} s^{-1} Total	*cis*-Attack [b]	*trans*-Attack [b]
(1)	0	21	79	65	14	51
	21	20	80	131	26	105
(2)	21	63	37	2·7	1·7	1·0
	35	59	41	5·3	3·1	2·2
(6)	0 [c]	88·8 [d]	11·2 [d]	294		
		76·1 [e]	23·9 [e]			
(4)	0					
	25					
(5)	0					
	25					
		exo	*endo*		*endo*-Attack	*exo*-Attack
(3)	0 [f]	14	86	5·29	0·74	4·55
	25	17	83			

[a] Viewing these alcohols as cyclohexanols with an ethano bridge, *trans* or *cis* refers to the relationship between the OH group and the ethano bridge. [b] With respect to the ethano bridge. [c] Data from ref. 4. [d] At 0% reaction. [e] At 100% reaction. [f] Data from ref. 3; partial rate coefficients are for *endo*- or *exo*-attack where *exo*- or *endo*-isomers are obtained, respectively.

Product analyses and rate coefficients for attack at the two faces of the carbonyl group are in Table 2. The ratio of stereoisomeric alcohols remained constant during the reduction of ketones (1)—(3) from 10 to 100% reaction.

Equilibration of the two isomeric bicyclo[3,2,1]octan-3-ols was carried out with aluminium isopropoxide in isopropyl alcohol containing some acetone at 100 °C starting from either a 34 : 66 [as obtained from the lithium aluminium hydride reduction of (2) in ether] or a 0·6 : 99·4 mixture of *cis*- to *trans*-alcohol [as obtained by sodium–ethanol reduction [5] of (2)]. Both these results and the corresponding ones for bicyclo[3,2,1]octan-2-ols [6] and norbornan-2-ols [7] are collected in Table 3.

TABLE 3

Equilibrium composition for the couples of isomeric bicyclo[3,2,1]octan-2- or -3-ols and norbornan-2-ols in isopropyl alcohol, aluminium isopropoxide, and acetone

Alcohols	t/°C	Equilibrium composition (%) *trans*	*cis*
Bicyclo[3,2,1]octan-2 ols	88—89	5—6 [a]	96—95 [a]
Bicyclo[3,2,1]octan-3-ols	100	96·6	3·3
		exo	*endo*
Norbornan-2-ols	100	80 [b]	20 [b]
	131	77 [b]	23 [b]

[a] Data (g.l.c.) from ref. 6. [b] Data from ref. 7.

Because of very high rates [8] and complications expected from enolization phenomena, we only measured competitive

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[4] B. Rickborn and M. T. Wuesthoff, *J. Amer. Chem. Soc.*, 1970, **92**, 6894.

[5] W. Kraus, *Chem. Ber.*, 1964, **97**, 2719.

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

[7] A. A. Youssef, M. E. Baum, and H. M. Walborsky, *J. Amer. Chem. Soc.*, 1959, **81**, 4709.

[8] S. G. Smith, *Tetrahedron Letters*, 1966, 6075.

rates for the reactions of (1) or (2) with methylmagnesium iodide in ether. The usual competitive conditions,[9] *i.e.* a large deficiency of the competing ketones *vs.* the organomagnesium compound, were used. Data are reported in Table 4.

For reactions of diazomethane with (1) or (2) no competitive experiment of the type already carried out for several other bicyclic ketones [2] were possible because the reactivities of (1) and (2) differ too much. A crude indication of the relative rates was obtained by running two parallel reactions of the ketones (1) or (2) (0·08M) with diazomethane in 3·5-fold excess in diethyl ether–methanol (1 : 2) at room temperature. Samples were withdrawn at intervals and poured into dilute hydrochloric acid. The homogeneous solutions obtained were examined by g.l.c. for residual starting ketone and formation of higher homologous ketones. Before the yellow colour due to diazomethane had completely disappeared, *ca.* 10% of ketone (2) had reacted. Further addition of diazomethane [3·5-fold excess with respect to (2)] led to 30% disappearance of (2) [we used solvent mixtures containing a higher percentage of methanol than in the previous study [2] to speed up the reaction of (2)]. It was thus possible to estimate that (1) is *ca.* 80 times more reactive than (2) towards diazomethane in the presence of a high proportion of methanol.

TABLE 4

Product distributions and relative rates [a] for reactions of methylmagnesium iodide [b] with bicyclic ketones in diethyl ether at 0°

Ketone	Relative total rates	Isomeric alcohols (%) *trans* [c]	*cis* [c]	Relative partial rate *cis*-Attack [d]	*trans*-Attack [d]	Ketone recovered (%) after work-up
(1) [e]	5	53	47	2·65	2·35	2
(2) [e]	1	100		*ca.* 0	1	10

[a] Obtained from competitive experiments. The ratio reported here represents an upper limit (see text). [b] Initial concentration 0·19M. [c] See footnote *a* of Table 2. [d] See footnote *b* of Table 2. [e] Initial concentration 0·040M.

DISCUSSION

Second-order kinetics and the invariance of the stereochemical distribution of products as the reduction by sodium borohydride of the ketones (1)—(3) proceeds clearly show that the rate-limiting step in these reactions is the transfer of the first hydride ion from sodium borohydride to the ketone.* Consequently, as all four hydrogens of sodium borohydride are active, any stereochemical observation of these reactions must reflect the combined result of the transfer of one hydride ion from BH$_4^-$ and of three further hydride ions from intermediate alkoxyborohydride species.

For the reactions of (1) or (2) with methylmagnesium iodide, the reliability of the rate ratio reported in Table 4 depends primarily on the assumption that the mechanism is the same for the two reactions. Moreover, we are dealing here with enolizable ketones and, notwithstanding the extremely high rates, some of the ketone is recovered in the work-up after complete reaction, the quantity being appreciably larger for (2) than (1) probably for statistical reasons. Therefore, the ratio 5 : 1 we have measured (Table 4) is an upper limit to the reactivity difference between ketones (1) and (2) towards methylmagnesium iodide.† This is an intrinsic limitation with these systems and detailed mechanistic studies of the reaction of organomagnesium compounds with ketones have always been carried out with non-enolizable ketones.[8,10]

Finally, the reaction of diazomethane with (3) proved to be too slow for kinetic investigation, side decomposition of diazomethane prevailing over reaction with the ketone.‡

The discussion is simplified by considering partial rate coefficients for reactions by sodium borohydride (Scheme 1) § and partial relative rates for reactions by methylmagnesium iodide (Scheme 2). The first observation from Scheme 1 is that, in parallel with the cyclopentanone character of (3) (when the rate for *exo*-attack is considered),[3] compound (1) approaches the

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* With some cyclic ketones, like 4-methylcyclohexanone (6), the stereochemistry of the reduction by sodium borohydride in isopropyl alcohol does indeed depend, albeit only slightly, on the extent of the reaction,[4] indicating that some reagent bulkier than BH$_4^-$ builds up during the course of the reaction.[4]

† We have no indication that similar factors are involved in our reductions by sodium borohydride. It is a fact, however, that enolization may intervene to such an extent in reduction of ketones by sodium borohydride in dry solvents that certain ketones, such as menthone, undergo epimerization faster than reduction (V. Hach, E. C. Fryberg, and E. McDonald, *Tetrahedron Letters*, 1971, 2629).

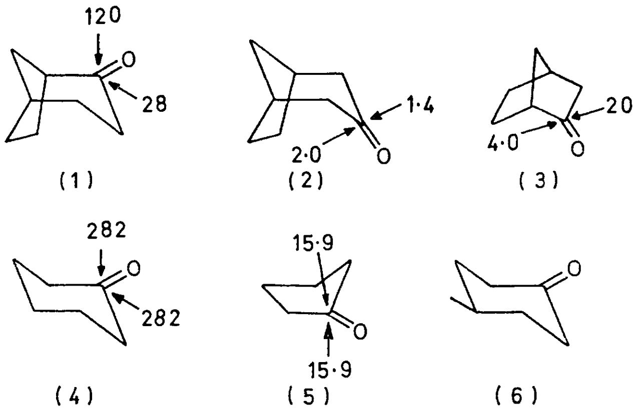
‡ It seems legitimate to ask whether the low reactivity of (2) *vs.* (1) with diazomethane may reflect to some extent enolization phenomena which, by analogy with the reaction with methylmagnesium iodide, are expected to be more important for (2) than (1). We are aware of a report on enolization of a (mono)-ketone by diazomethane. This concerns 2-isopropyl-4,7-dimethylhydrindan-5-one which, with diazomethane generated either *ex situ* or *in situ* in alcohol, only undergoes enolization giving the isomeric ketone (R. R. Coats and J. W. Cook, *J. Chem. Soc.*, 1942, 55). In our case, however, enolization cannot be a major competing path because the yield of the products of ring enlargement steadily increases on the addition of further diazomethane to the reaction mixture (see earlier).

§ We recognize the difficulty [3] of dealing with partial rate factors for a reaction in which three hydride ions are transferred from some reagents in fast processes. However, and this also applies to the validity of the definition below of sodium borohydride as a 'small' reagent, data discussed later show that sodium borohydride behaves as a small reagent towards (1) and (2) when compared to methylmagnesium iodide. If one admits that, owing to rapid disproportionation, dialkoxyborohydrides are the bulkiest effective reducing species,[4] molecular models indicate that the transfer of hyride to the ketone may still be attended by moderate steric effects. Dissection of the rate coefficient for (4) in Scheme 1 is only a rough indication. Studies for (6) showed [4] that the stereochemistry depends on the percentage of reaction completed, so that, strictly speaking, the dissection should refer to a certain reaction percentage.

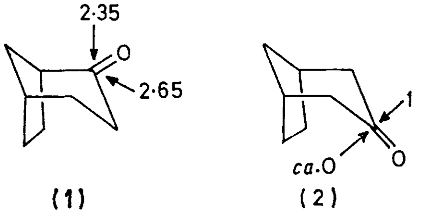
[9] G. A. Russell, in 'Investigation of Rates and Mechanism of Reactions, Part I,' ed. A. Weissberger, Interscience, New York, 1961, pp. 343—388.

[10] E. C. Ashby, *Quart. Rev.*, 1967, **21**, 259.

behaviour of cyclohexanone when the rate for *trans*-attack is considered. The isomeric ketone (2) shows a greatly reduced rate with respect to cyclohexanone as standard and, moreover, *cis*-attack is faster than *trans*-attack, contrary to that found for (1). Also, a rate depression of the same order of magnitude (*ca.* 80) for (2) *vs.* (1) was observed for the reaction with diazomethane. These findings are discussed in terms of a cyclohexanone structure carrying a 2,4-ethano bridge for (1) and of a cyclohexanone carrying a 3,5-ethano bridge for (2).



SCHEME 1 Partial rate coefficients for reactions of sodium borohydride with cyclic or bicyclic ketones in isopropyl alcohol at 25 °C



SCHEME 2 Partial relative rates for reactions of methylmangesium iodide with bicyclic ketones in diethyl ether at 0 °C (these values represent an upper limit, see text)

It may be suggested that, for reactions with sodium borohydride, *trans*-attack on (1) and *cis*-attack on (2) are favoured with respect to attack from the respective reverse directions because they represent axial attack on a cyclohexanone carbonyl carbon in both cases. For a small reagent,[11] torsional effects,[12] hindering equatorial attack, are more important that steric compression by the two 3,5-diaxial hydrogen atoms or methylene group for axial attack.* Steric compression by the 3,5-ethano bridge [reaction of (2)] must be substantially larger than that by 3,5-diaxial hydrogens [reaction of (1)] to account for the much slower axial attack on (2) than (1). Moreover, to rationalize the fact that equatorial attack on (2) is slower than on (1) it can be assumed that, on going to the transition state, steric compression between the developing $\mathrm{OB}\leqslant$ group and the 3,5-diaxial ethano bridge comes into play to some extent.

For a ' large '[11] reagent such as methylmagnesium iodide steric compression by 3,5-diaxial groups is expected to play a major role (while torsional effects are postulated not to be much different from the case of a small reagent[12]). In fact, contrary to the case of the small reagent (sodium borohydride), equatorial attack is favoured here. When steric compression involves the 3,5-diaxial ethano bridge (2) axial attack is completely inhibited (within the limits of the analytical method, flame ionization–g.l.c., used to detect products).

The effect on the rates here, with respect to the analogous reactions by sodium borohydride, may reflect an earlier transition state for organomagnesium reactions than sodium borohydride reactions. It has been in fact shown that typical Hammett ρ values are nearly one order of magnitude larger for the former (ρ 3·06) than the latter (ρ 0·36) reactions.[13]

Finally, for the reactions of diazomethane, it is more difficult than for the other cases to rationalize the rate data [*i.e.* the much lower reactivity of (2) with respect to (1)] in the absence of direct information concerning the stereochemistry of these reactions. Assuming that diazomethane behaves as a ' large ' reagent, axial attack on (2) should also be inhibited. Therefore, these data seem to imply a transition state far along the reaction co-ordinate for diazomethane, the low reactivity of (2) being largely due to steric compression between the 3,5-diaxial groups and the developing alcohol oxygen atom in agreement with our tentative ideas.[2]

EXPERIMENTAL

Materials.—*cis*-Bicyclo[3,2,1]octan-2-ol[7] was prepared by sodium–ethanol reduction of bicyclo[3,2,1]octan-2-one by analogy with the method[5] used to prepare *trans*-bicyclo[3,2,1]octan-3-ol from bicyclo[3,2,1]octan-3-one. *trans*-Bicyclo[3,2,1]octan-2-ol,[5] *cis*-bicyclo[3,2,1]octan-3-ol,[5] the two isomeric norborneols,[14] and bicyclo[3,2,1]octan-3-one[2] were prepared by known methods. Bicyclo[3,2,1]-octan-2-one was a commercial product (Fluka). Bicyclo-[4,2,1]nonan-2- and -3-one were from previous work.[2] Sodium borohydride and isopropyl alcohol were purified by literature methods.[3] Products of the reactions of (1) or (2) with either methylmagnesium iodide[15] or diazomethane[2] were determined by g.l.c. (flame ionization). Determination of the composition of the mixtures of isomeric alcohols was by g.l.c. (flame ionization), generally on 15% polypropylene glycol on Chromosorb W, 80—100 mesh (6 ft × $\frac{1}{8}$ in; 120—140 °C). For the two isomeric bicyclo[3,2,1]octan-2-ols 25% diglycerol on acid washed Chromosorb CW, 80—100 mesh (3 ft × $\frac{1}{8}$ in; 90 °C; N_2 flow rate 20 ml min^{-1}) was used instead.

Equilibration of Bicyclo[3,2,1]*octan*-3-*ols*.—A mixture (see

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* Clearly, it is the rate for axial attack on (1) that must be used to evaluate (see above) to what extent (1) possesses cyclohexanone character. This is, in fact, the torsional strain free direction of attack certainly sought by the reagent for cyclohexanone itself.

[11] J. D. Morrison and H. S. Mosher, in ' Asymmetric Organic Reactions,' Prentice-Hall, New Jersey, 1971, pp. 123—125.

[12] M. Chérest and H. Felkin, *Tetrahedron Letters*, 1968, 2205.

[13] P. Geneste, G. Lamaty, and J. P. Roque, *Tetrahedron Letters*, 1970, 5007.

[14] J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.*, 1965, **30**, 2635.

[15] W. Kraus, *Annalen*, 1965, **685**, 97.

Results section) of the two alcohols (20 mg) and aluminium isopropoxide (2 mol. equiv.) was sealed in a glass ampoule together with isopropyl alcohol (2 ml) and acetone (0·02 ml) and heated at 100 °C for 7 days. The mixture was then poured into excess of dilute hydrochloric acid and analysed by g.l.c.

Kinetics.—Kinetics of the reductions of ketones (1) and (2) by sodium borohydride were determined by measuring both the disappearance of the ketones and the formation of alcohols by g.l.c. Samples of the reaction mixture were withdrawn at intervals and poured into excess of dilute hydrochloric acid in a calibrated flask. The appropriate internal standard [(1) for reaction of (2) and (2) for reaction of (1)] was then added and the mixture made up with isopropyl alcohol. The resulting solution was analysed by g.l.c. and the concentrations were obtained by reference to a calibration curve. The kinetics for reduction of ketone (1) were also followed by examination of the u.v. long wavelength absorption band of the ketone [$\lambda_{max.}$ 285 nm (ε 25·6)], good agreement being obtained with the g.l.c. method. In the case of ketone (2) the u.v. method worked well only up to 20—30% reaction, satisfactory agreement being found with the g.l.c. method. At higher reaction percentages the mixture became turbid. The rate coefficients k were calculated by the equation $dx/dt = k([R_2C{=}O] - 4x)([NaBH_4]_0 - x)$ where x is the number of moles of sodium borohydride consumed at time t. Methylmagnesium iodide or diazomethane reactions were analysed similarly.

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