Asymmetric Induction. An Anisotropic Inductive Effect as an Important Factor in the Hydride Reduction of 3-Alkyl Bicyclo[2.2.2]octan-2-ones

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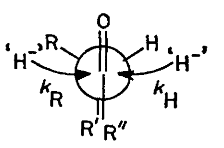
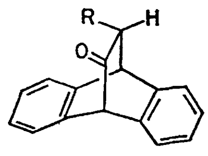
Summary The unexpectedly large proportions of *trans* alcohols (**5**) formed in the title reaction, especially when R = Pr^i, and the trends in the rate constants, are attributed to an anisotropic inductive effect of the alkyl groups, which leads to an anomalously high rate of attack from the alkyl side of the carbonyl group.

BOTH chemical intuition[1] and STO-3G *ab initio* calculations[2] lead to the prediction that the hydride reduction of carbonyl compounds should occur preferentially from the less hindered side of the molecule (*i.e.*, $k_R/k_H < 1$) when the conformation of the carbonyl group is such that it is symmetrically flanked by R (=alkyl) and H, as in (**1**). This apparently reasonable prediction is, however, not always borne out in practice: a number of bicyclic ketones (**2**) and (**3**), in which conformation (**1**) is built in, have recently been found to undergo reduction by LiAlH$_4$ preferentially from the *more* hindered side (*i.e.*, $k_R/k_H > 1$).[3] As shown in Figure 1, not only do the ketones with R = Et and Pr^i lead predominantly to the *trans* alcohols, but the *trans/cis* ratio (= k_R/k_H) actually *increases* along the series R = Me, Et, Pr^i.[3] This cannot only be due to the carbon skeleton of the bicyclo-octanones (**3**) not having perfect D_{3h} symmetry[4] [corresponding to a slight clockwise rotation of R′, R, and H in (**1**), which would relieve torsional strain between the eclipsed hydrogen atoms on the two ethylene bridges], since (a) exactly the same trend is observed with the dibenzoketones (**2**), which are much more rigid and devoid of eclipsed hydrogen atoms on the two benzo bridges, and (b) the ketones (**2**) and (**3**) with R = Ph both behave quite differently from the alkyl ketones, giving, as expected, the *cis* alcohols almost exclusively.[3]



(1)



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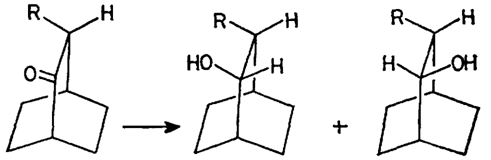
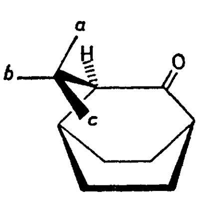


(3) (4) (5)



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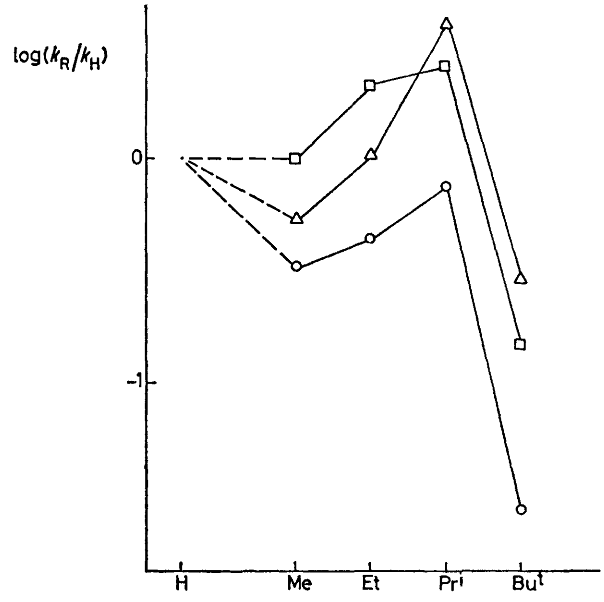

FIGURE 1. log k_R/k_H as a function of R in the reduction of the ketones (**2**) and (**3**): (**2**) (△) and (**3**) (□) with LiAlH$_4$ (in Et$_2$O at 20 °C) (ref. 3); (**3**) (○) with LiAl(OBu^t)$_3$H (in tetrahydrofuran at 30 °C).

Here we report a kinetic and stereochemical study of the reduction of the ketones (**3**) (R = alkyl) using LiAl(OBu^t)$_3$H, the outcome of which suggests an explanation for these paradoxical results. The stereochemical course of the reaction [(**5**)/(**4**) = k_R/k_H; Figure 1] was determined by g.l.c.,[3a] and the overall rate constant ($k_R + k_H$) by photometry;[5] the separate rate constants (k_R and k_H; Figure 2) were derived from these data.

With LiAl(OBu^t)$_3$H, which is a bulkier reagent than LiAlH$_4$ and therefore more sensitive to steric hindrance, reduction always occurs preferentially from the less hindered side of the molecule ($k_R/k_H < 1$; Figure 1). Nonetheless, the ratio k_R/k_H varies in exactly the same way as with LiAlH$_4$, again being greater when R = Pr^i than when

R = Me. Figure 2 shows that this bizarre pattern arises from an anomalous trend in k_R. Whereas the rate of reduction from the less hindered side (k_H) decreases fairly regularly with each additional methyl group, as expected from the operation of a deactivating inductive effect,[6] the rate of reduction from the more hindered side (k_R) is the *same* for R = Me, Et, and Pr^i, and only falls (by more than two orders of magnitude) when R = Bu^t.

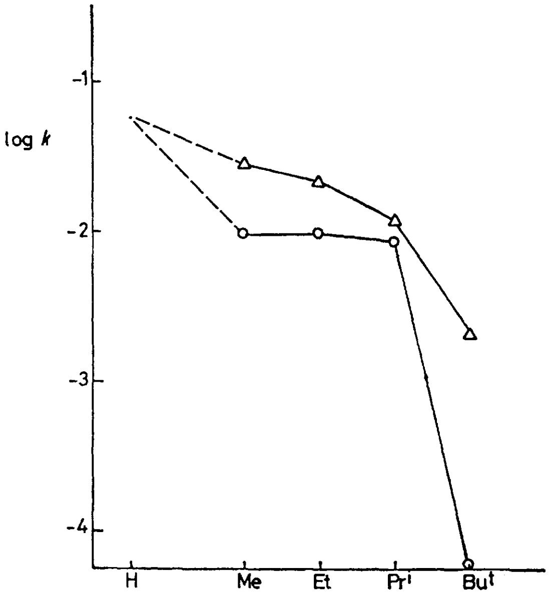

FIGURE 2. log k_R (○) and log k_H (△) as a function of R in the reduction of the bicyclo-octanones (**3**) by LiAl(OBu^t)$_3$H (in tetrahydrofuran at 30 °C; k_R and k_H in l mol^{-1} s^{-1}).

The activating inductive effect of electron-withdrawing groups (*e.g.*, Cl, Ph) upon a neighbouring carbonyl group[6] is anisotropic:[7] nucleophilic attack by anionic reagents is favoured from the side remote from the electron-withdrawing group [k_H in (**1**)], but not from the same side (k_R), probably because of electrostatic repulsion.[8] This is sufficient to explain the high stereoselectivity of the reduction of the ketones (**2**) and (**3**) (R = Ph) ($k_R/k_H < 0{\cdot}05$).[3] We suggest that the deactivating inductive effect of electron-releasing (alkyl) groups is also anisotropic, and also only operates on the side of the carbonyl group remote from the substituent (k_H).† The trend in k_R (Figure 2) is exactly as expected on the basis of this hypothesis: introduction of a methyl group on C-3 in (**3**) will lead to some steric hindrance, especially with a bulky reagent like LiAl(OBu^t)$_3$H, and k_R therefore falls on going from (**3**) (R = H) to (**3**) (R = Me); the first two 'extra' methyl groups (R = Et and Pr^i) must occupy positions *a* and *b* [see (**6**)], and they therefore have no effect on k_R; finally, the last 'extra' methyl group (R = Bu^t), being in the path of the reagent (position *c*), introduces considerable steric hindrance, and k_R drops by a factor of over 100.

In conclusion, we suggest that the electron-releasing inductive effect of alkyl groups is anisotropic, and that this is a factor which should be taken into account, among others,[2,7] in the reactions between anionic nucleophiles and carbonyl compounds.

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† This may well be what A. V. Kamernitzky and A. A. Akhrem, (*Tetrahedron*, 1962, **18**, 705) had in mind when they referred to 'a difference in the electrostatic field on the upper and lower sides of the carbonyl group connected, for example, with the uncompensated dipole moments of the carbon-hydrogen bonds' as an important factor in the stereochemical course of the hydride reduction of cyclohexanones. See also J. Klein, *Tetrahedron*, 1974, **30**, 3349.

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