

## The Effective Concentration of a Hydride Transfer Reaction

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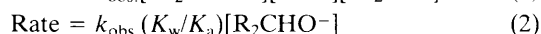
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The effective concentration of intramolecular hydride transfer in a rigid hydroxy-ketone is  $6.5 \times 10^6$  M compared with a model intermolecular process; this contrasts with low values normally observed for proton transfer and is compatible with a tighter transition state for hydride transfer.

The effectiveness of an intramolecular reaction is quantified by its effective concentration, and, even for a given type of ring closure, these can range from  $10^{-2}$  to  $10^{16}$  M.<sup>1</sup> The spread is greatest for ring closures involving nucleophiles, with values of  $10^4$ – $10^8$  M common for formation of five-membered rings from conformationally mobile precursors, although higher values have been found in special cases. It has been suggested that entropic contributions can account for effective concentrations up to  $10^8$  M,<sup>1,2</sup> and that for nucleophilic ring closures, variations can be accounted for by changes in entropy associated with loss of internal rotation and in strain accompanying ring closure.<sup>1</sup>

For intramolecular reactions involving proton transfer, *i.e.* general acid or base catalysis, effective concentrations are small, with most being less than 10 M.<sup>1,3</sup> This relative ineffectiveness has been attributed to the loose transition states involved.<sup>1,2,4</sup> Although the same nucleus is in motion, hydride transfers are expected to show fundamental differences. In the gas phase, for example, hydride transfers show behaviour consistent with large negative entropy changes indicative of tight transition states.<sup>5</sup> Accordingly, it has been suggested that intramolecular hydride transfers should show large effective concentrations.<sup>6</sup> Hitherto, data to test this claim have not been available, and we now report results which allow the effective concentration of a hydride transfer reaction to be calculated.



Reductions of ketones by alcohols in basic aqueous dioxane (Scheme 1) were followed by g.l.c., monitoring the appearance of the product alcohol. The reactions were very slow and were followed to only about 15% completion. Under conditions of excess of reductant alcohol, first-order rate constants were shown to be independent of ketone, and first order in alcohol and base concentration. The rate law, equation (1), is kinetically equivalent to (2), consistent with rate-limiting hydride transfer from alkoxide anion to ketone (1). The  $pK_a$  values of the alcohols in 50% v/v aqueous dioxane were obtained by extrapolation of a linear plot of  $pK_a$  values

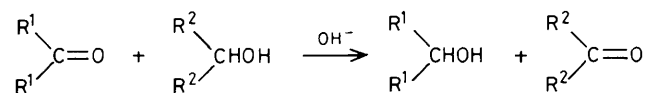
of more acidic alcohols measured in this medium against known  $pK_a$  values in water. The second-order rate constants for the reactions thus obtained are given in Table 1. Addition of cryptand, or use of potassium, rather than sodium hydroxide as base did not affect the rates, showing that counter-ion effects are not important under the conditions used.

The analogous intramolecular process is the base-catalysed interconversion of the hydroxy-ketones (2) and (3).<sup>7</sup> In the same solvent mixture, this reaction is first order in hydroxy-ketone and base, and independent of both buffer concentration and cation. From the observed pseudo-first-order rate constant for the equilibration and from the equilibrium constant of 1.75 at 50 °C, the forward second-order rate constant  $k$  is  $4.8 \times 10^{-1} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ . Assuming a  $pK_a$  of 17.6 for (2), *i.e.* similar to that for propan-2-ol, the first-order rate constant for the hydride transfer within its alkoxide anion is  $7.6 \text{ s}^{-1}$ . Comparing with the intermolecular reduction of cyclopentanone by alkoxide, the effective concentration of the intramolecular process is  $6.5 \times 10^6$  M.

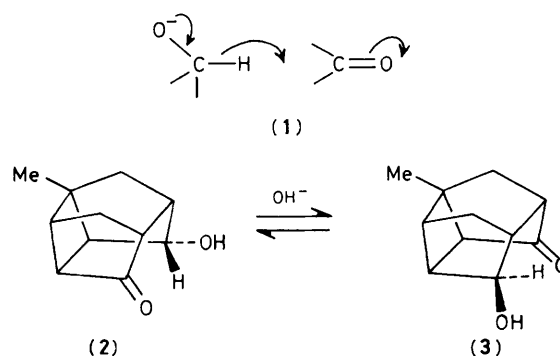
The near unity of the equilibrium constant shows that little strain is released in the intramolecular process. However, an X-ray crystal structure of (2) shows that there may be some compression between the functional groups, most evident in a short non-bonded distance (2.35 Å) between the hydridic hydrogen and carbonyl carbon. An empirical force field calculation shows that (2) is only 1.7 kcal mol<sup>-1</sup> (1 cal = 4.184 J) more strained than the corresponding dione where the hydridic hydrogen is absent.

It is therefore difficult to envisage that there is any significant release of strain in the transition state which would enhance the rate and so give an effective concentration which is higher than in a completely strain-free system.

Effective molarities reported for intramolecular proton transfer involve the freezing out of at least one internal



Scheme 1



**Table 1.** Summary of the second-order rate constants for the reduction of cyclohexanone to cyclohexanol and cyclopentanone to cyclopentanol by alcohols in the presence of sodium hydroxide at 50 °C in 50:50 v/v water–dioxane.

Alcohol	$pK_a$	$k/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$
Cyclohexanone:		
PrOH	17.6	$2.55 \times 10^{-5}$
MeOH	16.7	$1.16 \times 10^{-7}$
EtOH	17.1	$9.54 \times 10^{-6}$
Cyclopentanol	17.6	$2.06 \times 10^{-5}$
Cyclopentanone:		
PrOH	17.6	$1.16 \times 10^{-6}$

rotation in the transition state.<sup>1,3</sup> However, in view of the relatively small decrease in rate that this produces<sup>2</sup> the low effective molarities observed for intramolecular proton transfer cannot be due to the unfavourable freezing of internal rotations.

We conclude that the high effective concentration in hydride transfer is the result of differences in the entropy changes of the two reactions and reflects the 'tighter' transition states of hydride compared with proton transfers.

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