Observation of Different Primary Kinetic Isotope Effects in a Pair of Enantioselective Reactions

Olle Matsson,*[a] Lennart Meurling,[b] Ulf Obenius,[a] and Göran Bergson[a]

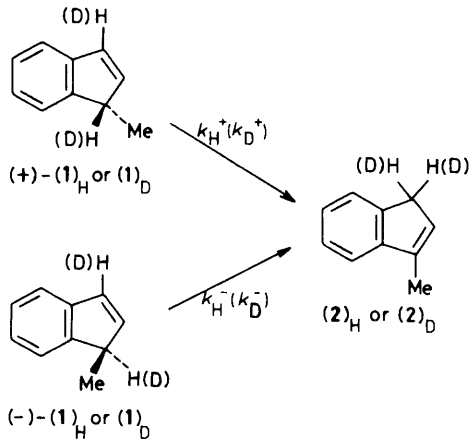
[a] *Department of Organic Chemistry, University of Uppsala, P.O. Box 531, S-751 21 Uppsala, Sweden*
[b] *National Drug Administration, P.O. Box 607, S-751 25 Uppsala, Sweden.*

The primary deuterium kinetic isotope effect has been determined to be 5.31 and 6.19 for (+)- and (−)-1-methylindene, respectively, in the enantioselective prototropic rearrangement of these compounds to 3-methylindene under the catalytic effect of the chiral base (+)-(8*R*,9*S*)-dihydroquinidine in the solvent *o*-dichlorobenzene at 30 °C.

According to previous studies, the prototropic base-catalysed rearrangement of 1-methylindene (**1**) to 3-methylindene (**2**), using chiral bases, shows fair enantioselectivity.[1] Using achiral bases, primary and secondary isotope effects in this reaction have been investigated;[2] the kinetics, mechanism, and isotope effects of this class of reaction have also been extensively studied by Cram and co-workers[3] and Ahlberg and co-workers.[4]

Isotope effects on asymmetric induction have been reported for some carbonyl reduction reactions,[5] and tunnelling has been suggested as an explanation.[5b] The validity of some of the experimental results has, however, been questioned.[5b] The asymmetric reduction of benzaldehyde by a $LiAlH_4$–quinine reagent[5b] has been shown to be rather complex, and the isotope effect on the asymmetric induction is strongly dependent on the experimental conditions.[6] Since the indene system is suitable for accurate kinetic studies,[3,4,7] the reactions in Scheme 1 might serve as a model system in the search for such effects. Information of this kind is valuable for the understanding of the factors underlying asymmetric induction.

In the present study, dihydroquinidine was selected as a catalyst since, among those chiral amines previously used, it afforded relatively large enantioselectivity and a convenient rate of reaction.[1b] For the same reasons, the inert and relatively polar solvent *o*-dichlorobenzene was used. Indene rearrangements catalysed by uncharged amine bases in non-polar or moderately polar solvents have long been known



Scheme 1

to show very high *stereospecificity*.[7a] Cram *et al.*[8] found prototropic indene rearrangements catalysed by uncharged tertiary amines to be highly *stereospecific*, even in such a polar solvent as Me_2SO. This was assumed in our previous studies[1a,1b] of enantioselectivity, using cinchona alkaloids as catalysts. We have now shown that *racemization* of the substrate (+)-$(\mathbf{1})_H$ is, in fact, less than 1% when dihydroquinidine in *o*-dichlorobenzene is used as catalyst.

Table 1. Stereoselectivities, $S_{H(D)}$, and second-order rate constants, $k^{+}_{H(D)}/[B]$ and $k^{-}_{H(D)}/[B]$ ([B] = concentration of base),[a] obtained from polarimetric kinetic experiments, starting with $(\mathbf{1})_H$ and $(\mathbf{1})_D$, *respectively*.[b]

Substrate	$S_{H(D)}$	$k^{+}_{H(D)}/[B]$ /10^{-3} dm^3 mol^{-1} s^{-1}	$k^{-}_{H(D)}/[B]$ /10^{-3} dm^3 mol^{-1} s^{-1}
$(\mathbf{1})_H$	3.26	4.76	1.46
$(\mathbf{1})_D$	3.80	0.897	0.236

[a] The values, averages from three kinetic runs, are calculated by least-squares fitting (ref. 10) of the model two-exponential function to the experimental data corrected for protium content. [b] The concentration of substrate was *ca.* 0.4 M and of base *ca.* 0.05 M. Solvent: *o*-dichlorobenzene. Temperature: 30 ± 0.04 °C

The kinetic data were obtained by measuring the optical rotation as a function of time for reaction mixtures initially containing racemic $(\mathbf{1})_H$ or $(\mathbf{1})_D$. The reactions are pseudo first order and the rate constants (k^+ and k^-) were calculated by least-squares fitting of the appropriate two-exponential function to the complete set of kinetic data (α; t). The enantioselectivity ($S = k^+/k^-$) may also be accurately calculated directly from the maximum induced optical rotation (α_{max}),[1a,2d] and the individual rate constants can be calculated using α_{max} and the corresponding reaction time (t_{max}). The ratio S_H/S_D is, by definition, equal to the ratio of the observed isotope effects $[(k^+_H/k^+_D)/(k^-_H/k^-_D)]$.

The substrates, racemic $(\mathbf{1})_H$ and $(\mathbf{1})_D$, were prepared from the corresponding racemic 3-phenylbutanoic acids.[2d] For the determinations of the specific rotations of enantiomerically pure (+)-$(\mathbf{1})_H$ and (+)-$(\mathbf{1})_D$, the corresponding enantiomerically pure 3-phenylbutanoic acids were used.[2d] No racemization of significance occurs during the synthesis of the indenes.[2d,9] The isotopic purity of racemic $(\mathbf{1})_D$ and (+)-$(\mathbf{1})_D$ was determined by ^{1}H n.m.r. spectroscopy. Correction for the protium content in $(\mathbf{1})_D$ (1.6%) was made in the calculation of the rate constants (and ratios). The 3-position of $(\mathbf{1})_D$ was also labelled with deuterium in order to avoid a possible contribution to the optical rotation from chiral 3-methyl(1-^{2}H)indene, which would have been formed by stereospecific rearrangement of 1-methyl(1-^{2}H)indene. The results of the experiments are shown in Table 1.

The kinetic isotope effects calculated from these data are 5.31 ± 0.10 and 6.19 ± 0.15 for (+)-(**1**) and (−)-(**1**), respectively.

There are several possibilities for the mechanistic interpretation of these results. In our first detailed analysis of the relation between observed and mechanistic enantioselectivities,[1a] we pointed out the importance of a knowledge of the collapse ratios for the diastereoisomeric ion pairs postulated as intermediates. There, it was suggested by analogy that the ratio is less than 0.05 for collapse back to (**1**), compared with collapse to the 3-substituted product (**2**). If this assumption is correct, the main part of the enantioselectivity difference between $(\mathbf{1})_H$ and $(\mathbf{1})_D$ and the kinetic isotope effect (K.I.E.) difference between (+)-(**1**) and (−)-(**1**) (Table 1) can be attributed to effects in a rate-determining proton-abstraction step. In such a case, the following considerations are relevant.

Steric hindrance between the reactants in proton-transfer reactions is generally[11] believed to increase the tunnel correction and hence the K.I.E. by a sharpening of the potential barrier. Model calculations by McLennan,[12] employing transition states in which the sum of bond orders to the transferring proton is less than 1, also yield an increase in the primary K.I.E. Such loose transition states are suggested to be a consequence of steric repulsion, and thus offer an alternative explanation to the tunnelling model. Theoretical calculations[13] based on the quantum-statistical theory for proton-transfer reactions by Dogonadze and co-workers[14] also suggest that increased steric repulsion between the reactants leads to a diminished rate of reaction and an increased K.I.E. Obviously, the higher isotope effect for the slower, more sterically hindered process, with substrate (−)-(**1**), is in agreement with any of these theoretical models. Further experiments, such as an investigation of the temperature dependence of the K.I.E., must be performed in order to reveal the detailed physical mechanism.

Further investigations of the ion-pair collapse ratios in all four reactions involved in the present study are necessary before final conclusions can be drawn. On the basis of calculations, we have found that assumptions of at least some sets of collapse ratios, differing within the sets and larger than those previously assumed,[1a] can account for the observed results.

However, our results indicate that measurements of the K.I.E. in carefully designed experiments on simple stereoselective reactions may provide insight into the factors governing asymmetric induction, especially if the measurements are combined with model calculations. The present investigation may also offer an opportunity to study, *ceteris paribus*, the influence of steric hindrance on K.I.E.

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