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1,3-HYDRON TRANSFER IN SOME 5- AND 7-SUBSTITUTED 1-METHYLINDENES. ENANTIOSELECTIVITIES AND ENANTIOMER-DEPENDENT KINETIC ISOTOPE EFFECTS

MARIE AUNE, GÖRAN BERGSON AND OLLE MATSSON*
Institute of Chemistry, Uppsala University, P.O. Box 531, S-751 21 Uppsala, Sweden

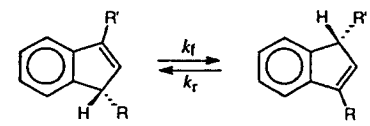
Base-catalysed substrate-enantioselective 1,3-hydron transfer (kinetic resolution) was studied in the indene system. A series of 1-methylindenes substituted in the aromatic ring [5-methoxy- (2), 5-fluoro- (3), 5-nitro- (4) and 7-nitro (5)] and 1-methylindene (1) were employed as substrates. The rate constants, the enantioselectivities and the kinetic isotope effects (KIEs) for the enantioselective reactions [$(k_H/k_D)^+$ and $(k_H/k_D)^-$] were determined at 20 °C using (+)-(8*R*,9*S*)-dihydroquinidine as chiral catalyst in the solvent *o*-dichlorobenzene. The rate constants vary according to the electronic effects of the substituents. The primary deuterium KIE, ranging from 4·73 [for (+)-(*S*)-2] to 11·3 [for (−)-(*R*)-5], is correlated with the rate constants as expected on the basis of the Melander–Westheimer postulate. The introduction of a substituent in the aromatic ring decreases the enantioselectivity. All compounds except 5 show the same sense of the enantioselectivity [$k^+/k^- > 1$; all substrates used are (+)-(*S*)/(−)-(*R*)]. The enantiomer dependence of the KIE is most pronounced for 1 [$(k_H/k_D)^+ = 5{\cdot}71$ and $(k_H/k_D)^- = 6{\cdot}46$] and vanishes for the most acidic substrates (4 and 5).

INTRODUCTION

Asymmetric synthesis is extensively utilized to obtain enantiomerically pure or enriched materials and is one of the most active areas of research in organic chemistry today.[1] However, there is a paucity of detailed quantitative information concerning the mechanism of enantioselection, i.e. how the sense and degree of enantioselection can be understood in terms of molecular structure and what structural differences between the two activated complexes may be involved in an enantioselective process.

The base-catalysed 1,3-prototropic rearrangement in the indene system (Scheme 1) has been used extensively since the early 1960s by several workers as a model reaction for investigations of, e.g., stereospecificity,[2,3] enantioselectivity,[4] competing elimination reactions,[5] kinetic methodology[2c,4a,4d,6] and different aspects of kinetic isotope effects.[7]

Using racemic 1-methylindene as substrate and the chiral base catalyst quinine, enantioselective rearrangement was observed by Ohlsson *et al.*[4b] in 1966. A more systematic investigation of enantioselectivity using a series of cinchona and ephedra alkaloids was later performed by Meurling.[4c] That investigation included



Scheme 1

the use of some different solvents and variation of the 1-alkyl group in the substrate.

The two activated complexes for the pair of the enantioselective reactions are diastereomeric and therefore afford the possibility of different kinetic isotope effects (KIEs). Such a difference in KIEs was for the first time demonstrated[7e] for the rearrangement of 1-methylindene using dihydroquinidine in *o*-dichlorobenzene at 30 °C. This difference in KIE is *a priori* dependent on the different structures of the diastereomeric activated complexes and the study of enantiomer-dependent KIEs therefore offers an interesting opportunity to obtain detailed information about the asymmetric induction (Figure 1). The variation of the enantioselectivity and primary deuterium isotope effects for this system when changing solvent has recently been studied.[8]

To aid further understanding of enantioselectivity and isotope effects for this reaction system, we decided to investigate how these phenomena are affected by

* Author for correspondence.

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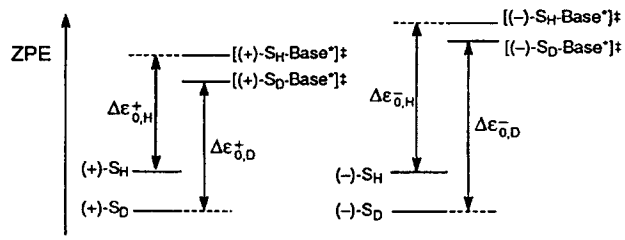
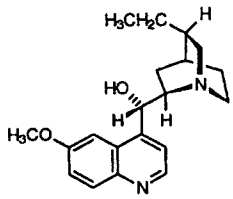
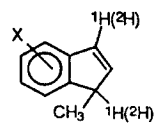


Figure 1. Zero point energy (ZPE) diagram illustrating the origin of the kinetic isotope effects in a substrate enantioselective reaction. S = substrate; $\Delta\varepsilon_0$ = difference in ZPE between the activated complex and the ground state



(+)-(8R,9S)-Dihydroquinidine



1: X = H
2: X = 5-OCH3
3: X = 5-F
4: X = 5-NO2
5: X = 7-NO2

Figure 2. The amine catalyst (+)-(8*R*,9*S*)-dihydroquinidine and the substrates 1-methylindene (**1**), 5-methoxy-1-methylindene (**2**), 5-fluoro-1-methylindene (**3**), 1-methyl-5-nitroindene (**4**) and 1-methyl-7-nitroindene (**5**)

substitution in the aromatic part of the indene molecule. The indenes used in this work were 1-methylindene (**1**), 5-methoxy-1-methylindene (**2**), 5-fluoro-1-methylindene (**3**), 1-methyl-5-nitroindene (**4**) and 1-methyl-7-nitroindene (**5**) (Figure 2). The rearrangements in this study were catalysed by the tertiary amine (+)-(8*R*,9*S*)-dihydroquinidine (Figure 2). In a parallel investigation of rates and isotope effects for these substituted indenes, we used the achiral amine DABCO.[9]

RESULTS

The kinetic experiments were run under pseudo-first-order conditions with racemic substrates (normal or isotopically labelled) at time zero. Assuming a linear relationship between optical rotation and concentration, the integrated rate equations yield equation (1) for the time dependence of the optical rotation α. Here, k^+ and k^- are the phenomenological pseudo-first-order rate constants for the enantiomers of the substrates. The pre-exponential factor a was determined from the specific optical rotation of the enantiomerically pure forms of each substrate [equation (2)]. If an isotopically impure substrate is used, due corrections have to be made. The constant term α_0, i.e. the optical rotation at time zero in equation (1), corresponds to the optical rotation of the catalysing base.

$$\alpha(t) = ae^{-k^+t} - ae^{-k^-t} + \alpha_0 \quad (1)$$

$$a = ([\alpha][A]_0)/2 \quad (2)$$

where α_0 = optical rotation of the base catalyst, $[\alpha]$ = specific optical rotation for the dextrorotatory enantiomer and $[A]_0$ = substrate concentration in g ml^{-1}.

The optical rotation of the reaction mixture as a function of time was observed by polarimetry. The parameters k^+, k^- and α_0 in equation (1) were estimated from the experimentally determined sets $\{\alpha, t\}$. This was done either by least-squares fitting or from the maximum (or minimum) of $\alpha(t)$, i.e. α_m and t_m in equations (3)–(5) (cf. Figure 3 and Refs 4a, c and d).

$$t_m = (k^+ - k^-)^{-1}(\ln S) \quad (3)$$

$$\alpha_m = aS^{S/(1-S)} + aS^{1/(1-S)} + \alpha_0 \quad (4)$$

$$S = k^+/k^- \quad (5)$$

As in the earlier investigations,[7e] the deuteriated substrate was isotopically substituted in the 3-position in addition to the reactive 1-position to avoid a contribution to the optical rotation of the reaction mixture from an isotopically chiral product. Although the reactions are practically irreversible, a small amount of reverse reaction could introduce protium in the 1-position, but this is prevented by the presence of deuterium in the 3-position. The remote secondary isotope effect from this deuterium is expected to be negligible.

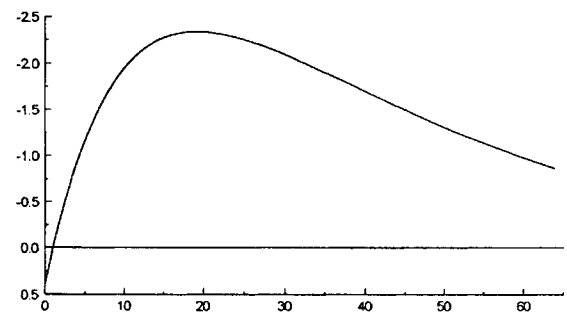


Figure 3. Optical rotation (degrees) as a function of time (h) for the rearrangement of 1-methylindene (**1**) catalysed by dihydroquinidine in *o*-dichlorobenzene at 20 °C

Table 1. Second-order rate constants for the dihydroquinidine-catalysed rearrangement of some 1-methylindenes and their deuterated analogues in *o*-dichlorobenzene at 20 °C

Substrate[a]	[Base] (10^{-3} M)	k_H^+/[base][b] (10^{-3} $M^{-1}s^{-1}$)	k_H^-/[base][b] (10^{-3} $M^{-1}s^{-1}$)	k_D^+/[base][b] (10^{-3} $M^{-1}s^{-1}$)	k_D^-/[base][b] (10^{-3} $M^{-1}s^{-1}$)
5-Methoxy-1-methylindene (**2**)	22	0·497(7)	0·151(3)	0·105(2)	0·0281(5)
5-Methoxy-1-methylindene (**2**)	6·1	0·721(11)	0·187(4)	--	--
1-Methylindene (**1**)	5·8	4·66(7)	1·13(2)	0·816(14)	0·175(4)
5-Fluoro-1-methylindene (**3**)	6·0	5·42(7)	2·05(3)	0·896(12)	0·304(5)
1-Methyl-7-nitroindene (**5**)	0·68	141(2)	196(2)	12·6(2)	17·4(2)
1-Methyl-5-nitroindene (**4**)	0·15	2100(50)	1770(40)	195(5)	164(4)

[a] The substrate concentration was 0·3–0·4 M. Correction for the protium content was made in the calculation of the rate constants (and ratios) for the deuterated substrates.
[b] Error limits, given in parentheses, were obtained by estimation of the maximum experimental errors involved. The rate constants were obtained by least-squares fitting of the kinetic model equation to the complete data set and are within error limits equal to those obtained by use of equations (3) and (4).

Table 2. Enantioselectivities and enantiomer-dependent kinetic isotope effects for the dihydroquinidine-catalysed rearrangement of some 1-methylindenes in *o*-dichlorobenzene solution at 20 °C

Substrate	[Base] (10^{-3} M)	k_H^+/k_H^-[b]	k_D^+/k_D^-[b]	$\frac{k_H^+/[\text{base}]^b}{k_D^+/[\text{base}]^b}$	$\frac{k_H^-/[\text{base}]^b}{k_D^-/[\text{base}]^b}$
5-Methoxy-1-methylindene (**2**)	22	3·28(6)	3·74(8)	4·73(16)	5·39(19)
5-Methoxy-1-methylindene (**2**)	6·1	3·83(8)	--		
1-Methylindene (**1**)	5·8	4·11(7)	4·66(11)	5·71(19)	6·46(24)
5-Fluoro-1-methylindene (**3**)	6·0	2·64(3)	2·95(5)	6·05(16)	6·74(22)
1-Methyl-7-nitroindene (**5**)	0·68	0·720(2)	0·723(3)	11·2(3)	11·3(2)
1-Methyl-5-nitroindene (**4**)	0·15	1·18(1)	1·19(1)	10·8(9)	10·8(9)

[a] The substrate concentration was 0·3–0·4 M. Correction for the protium content was made in the calculation of the constants (and ratios) for the deuterated substrates.
[b] Error limits, given in parentheses, were obtained by estimation of the maximum experimental errors involved.

Table 3. Concentration-dependent enantioselectivities for the dihydroquinidine-catalysed rearrangement of 1-methylindene (**1**) and 5-fluoro-1-methylindene (**3**) in *o*-dichlorobenzene at 20 °C

Substrate[a]	[Base](10^{-3} M)	k_H^+/[base][b] (10^{-3} $M^{-1}s^{-1}$)	k_H^+/k_H^-[b]
1-Methylindene (**1**)	14	3·85(5)	3·88(6)
	8·5	4·35(7)	3·96(9)
	5·8	4·66(7)	4·11(7)
	2·5	4·82(8)	4·22(7)
	1·2	5·84(12)	4·26(7)
5-Fluoro-1-methylindene (**3**)	52	2·18(3)	2·04(2)
	29	3·27(4)	2·22(3)
	14	4·24(5)	2·45(3)
	8·3	5·02(6)	2·60(3)
	6·0	5·42(7)	2·64(3)

[a] The substrate concentration was 0·3–0·4 M.
[b] Error limits, given in parentheses, were obtained by estimation of the maximum experimental errors involved. The rate constants were obtained by least-squares fitting of the kinetic model equation to the complete data set and are within error limits equal to those obtained by use of equations (3) and (4).

For all substrates used, the *S*-configuration is dextrorotatory at the wavelength (546 nm) used in the kinetic measurements.

According to ^{1}H NMR spectra of the equilibrated kinetic solutions, the only product formed in the kinetic experiments was the 3-isomer of the substrates, and no remaining reactant isomer was detected. Further details concerning the kinetic experiments and the syntheses are reported elsewhere.[9]

Table 1 shows the second-order rate constants (calculated by dividing the measured pseudo-first-order rate constants by the base concentration) for the base-catalysed rearrangement of the different 1-methylindenes and their deuteriated analogues. The enantioselectivities and the primary enantiomer-dependent KIEs, calculated from the second-order rate constants in Table 1, are given in Table 2. [Note that we have the mathematical identity $(k_H^+/k_D^+)/(k_H^-/k_D^-) \equiv (k_H^+/k_H^-)/(k_D^+/k_D^-)$.] The second-order rate constants and enantioselectivities are, to some extent, dependent on the catalyst concentration. Table 3 shows this concentration dependence for the substrates 1-methylindene (**1**) and 5-fluoro-1-methylindene (**3**). Both **1** and **3** show a slightly increasing enantioselectivity with decreasing catalyst concentration. The concentration dependence is further discussed in Ref. 8. With the exception of the reactive nitro substrates **4** and **5**, the results presented in Tables 1 and 2 were obtained from experiments run at comparable concentrations.

DISCUSSION

According to the current mechanistic view[7b,10] (Scheme 2), the 1,3-proton transfer in indene and its alkyl-substituted analogues is believed to occur via ion-pair intermediates. The suggested intermediates are tightly hydrogen-bonded complexes between the protonated amine and the carbanion.[11,12] The rearrangement of 1-isomer to 3-isomer may be regarded as irreversible.[13]

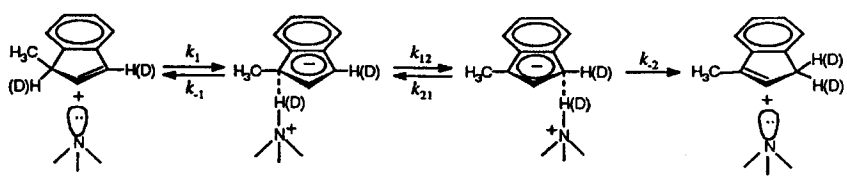
The observed KIE (k^H/k^D) is related to the KIE for the rate-determining ionization step k_1^H/k_1^D and the ion-pair collapse ratios $\sigma^L = k_{-1}^L/k_2^L$, L = H or D according to equation (6) (derived under the assumption of fast ion-pair equilibration, i.e. $k_{21} \gg k_{-2}$).[7c] This equation also contains the ion-pair equilibrium constant $\chi^L = k_{21}/k_{12}$.

$$\frac{k^H}{k^D} = \frac{k_1^H}{k_1^D}\,\frac{1+\sigma^D\chi^D}{1+\sigma^H\chi^H} \qquad (6)$$

The magnitude of the observed primary deuterium KIEs strongly suggest rate-determining hydron abstraction and the following discussion is based on the assumption $k^H/k^D = k_1^H/k_1^H$. This is true in two situations: (i) when internal ion-pair return is negligible, i.e. $\sigma \ll 1$ and $\chi \leqslant 1$, and (ii) when σ and χ are isotopically insensitive.[7c,12] Experiments intended to shed light on the rate of ion-pair equilibration compared with ion-pair collapse are in progress.[10,14]

The conformational behaviour of a number of cinchona alkaloids has been the subject of investigations using NMR spectroscopy.[8,15] These studies have demonstrated the existence of two dominating conformers in solution, open or closed, which differ in the relative orientations of the quinoline and the quinuclidine units. Studies of dihydroquinidine in *o*-dichlorobenzene[8] show a predominance of the open conformer (60:40 open:closed). This implies that the observed rate constants k^+ and k^- for the enantiomeric substrate molecules may in fact be sums of rate constants for the reactions catalysed by the two conformers of the base. The following discussion, however, is based on the variation of the observed rate constants, since the intrinsic rate constants corresponding to catalysis by the respective conformers are not experimentally known.

The reaction rates vary qualitatively as predicted on the basis of the electronic effect exerted by the substituents, i.e. a large increase in reaction rate is observed for the nitro-substituted indenes (**4** and **5**) as compared with the unsubstituted compound (**1**). The fluoroindene (**3**) shows a small increase of rate whereas the methoxyindene (**2**) reacts slower than the unsubstituted 1-methylindene (**1**). The main effect of a nitro substituent should be the resonance stabilization of the carbanion moiety of the ion-pair intermediate formed in the rate-determining step. According to the Hammond postulate, a corresponding stabilization of the intermediate-like activated complex occurs. The resulting increased acidity of the substrate is illustrated by the increase in reaction rate for **4** and **5** as compared with the unsubstituted compound. In Table 1 it is thus seen that for, e.g., the reaction of (+)-(*S*)-**4** a 450-fold increase of the second-order rate constant is observed. For (+)-(*S*)-**5** only a 30-fold increase in rate constant was observed, which might be attributed to a larger amount of steric hindrance to approach of the catalysing base for this compound. Further, the nitro group in the 7-position is fairly close to the 1-methyl



Scheme 2

substituent, which could force the nitro group to be twisted out of the indene ring plane. This would to some extent prevent delocalization of the negative charge into the nitro group in the transition state (TS) of the proton abstraction step causing a less pronounced rate increase. For the 5-substituted substrates, including 1-methylindene (**1**), the logarithmic rate constant ratios, $\log(k_X/k_H)$, were found to correlate with the Hammett σ-values[16] for the substituents (correlation coefficient = 0·998; for the nitro substituent the tabulated σ^- value was used). The magnitude of the Hammett reaction parameter, $\rho = 2{\cdot}18$, supports the idea of a late ion-pair-like TS for the rate-limiting step. A value of $\rho = 2{\cdot}84$ was recently determined for the DABCO-catalysed reaction of these 5-substituted substrates.[9]

Let us consider the variation of enantioselectivity (k^+/k^-) as caused by a purely electronic effect. The rate-determining step is the endoergic formation of an ion-pair intermediate. According to the Hammond postulate, this step has an ion-pair like TS. A late TS is confirmed by the Brønsted value of 0·79 determined by Meurling[17] for the rearrangement of 1-methylindene (**1**) using a series of azaadamantanes and structurally related catalysts including DABCO. The electron-withdrawing nitro group stabilizes the ion-pair intermediate, making the rate-determining step less endoergic, which is predicted to move the TS towards an earlier position along reaction coordinate. The difference in activation energy ($\delta\Delta G^{\ddagger}$) for the enantiomeric substrate molecules may be assumed to be proportional to the difference in reaction free energy ($\delta\Delta G$) for formation of the diastereomeric intermediates with a coefficient f ranging from 0 for infinitely reactant-like TS to 1 for an infinitely ion-pair-like TS ($\delta\Delta G^{\ddagger} = f \times \delta\Delta G$).[18] The conclusion based on these assumptions is that the enantioselectivity should decrease for substrates with increasing ion-pair stabilization. This is what we observe in the series **2**, **3** and **4** (Table 2). The introduction of a nitro group substantially lowers the enantioselectivity. For 1-methyl-5-nitroindene (**4**), the enantioselectivity is as small as 1·18 (Table 2). It is interesting that the sense of the enantioselectivity is reversed when the nitro substituent is moved from the 5- to the 7-position. The magnitude of the enantioselectivity is, however, very small (0·720) also for 1-methyl-7-nitroindene (**5**). It is clear from Tables 1 and 2 that the enantioselectivity for 5-substituted substrates follows a reactivity–selectivity relationship as discussed above. The unsubstituted compound **1** deviates from this behaviour, showing a larger enantioselectivity than the other substrates. Possibly this could be due to the smaller size of the 5-H as compared with the substituents. This would permit a closer interaction between the base catalyst and the enantiomeric indene moieties, thus increasing the chiral discrimination. More specific non-steric interactions between the substrate and the catalyst molecules may also take place. One possibility would be a hydrogen bonding interaction between the substituent of the substrate and the hydroxyl group of the dihydroquinidine. Such an interaction between the hydroxyl group and a solvent molecule has been invoked to explain the preference for the closed conformer of the base in the solvent dimethyl sulphoxide.[8] However, in the present case, where there is a 10–60-fold excess of substrate over base catalyst, one would not expect to see the catalyst concentration dependence for both 1-methylindene (**1**) and 5-fluoro-1-methylindene (**3**) if the hydrogen-bonding interaction between substrate and catalyst were of importance for **3**.

According to the Melander–Westheimer postulate,[19,20] the maximum primary KIE for the proton-abstraction step is expected for the most symmetric activated complex, i.e. when the proton is bound with equal strength to donor and acceptor. This should occur when the pK_a of the carbon acid equals that of the conjugate acid of the base catalyst ($\Delta pK_a = 0$).[21] For 1-methylindene [$pK_a = 19{\cdot}8$ (estimated, in DMSO[22])] and dihydroquinidine [$pK_a = 10{\cdot}8$ (estimated from the pK_a of 10·0 for quinidine)], the ΔpK_a is approximately 9, corresponding to a strongly asymmetric activated complex if this interpretation is valid. Despite this, the observed KIEs are high (Table 2). Earlier, a case of very small variation of the primary deuterium KIE over a wide range of ΔpK had been reported by Bordwell and Boyle[23] for deprotonation of nitroalkanes. The more acidic nitro and fluoro substrates are expected to display even stronger KIEs than 1-methylindene, since the ΔpK_a value is diminished. The ΔpK_a for the reaction of 1-methyl-5-nitroindene (**4**) can be estimated to be 2·6 or less (1-methyl-5-nitroindene should be more acidic than 3-methyl-6-nitroindene, for which the pK_a is 13·4[24]). The results given in Table 2 show that for both nitro compounds the KIEs are very high, e.g. 10·8 and 11·2 for the reaction of (+)-**4** and (+)-**5**, respectively. This appears to be at, or slightly above, the semi-classical limit, i.e. the highest possible value if account is taken of loss of isotropic sensitivity for both stretching and bending degrees of vibrational freedom in the activation process,[25] but without the invocation of tunnelling. It may be surprising that the much slower reacting (+)-**5** [or (−)-**5**] shows an even stronger KIE than (+)-**4** [or (−)-**4**]. However, this may be explained by a different amount of tunnelling in the reactions of the two nitro substrates. Increased steric hindrance between the reactant molecules, which is a likely cause for the lower reaction rate of (+)-**5**, has often been associated with a larger contribution of tunnelling, increasing the KIE. High primary KIEs have frequently been observed for proton abstraction from nitro compounds.[26] The fluoro compound **3** exhibits a small increase of the KIEs in accordance with the small rate increase observed. The slower reacting methoxyindene **2** shows weaker KIEs as expected on basis of the Melander–Westheimer postulate.

Different isotope effects for reactions proceeding via diastereomeric transition states have been observed in a few cases where the starting material possesses diastereotopic protons. Baldwin and co-workers[27] reported diastereotopically distinct secondary KIEs for some thermal isomerization reactions. In another case a diastereotopic difference in primary deuterium KIE for a base-catalysed H–D exchange reaction was reported by Fraser and Champagne,[28] and it was interpreted as being due to intrusion of a second pathway for one of the diastereotopic hydrons. In neither of these other cases are the diastereomeric activated complexes formed in a reaction of enantiotopic atoms or groups with a chiral molecule.

The KIEs for the enantiomers do not differ significantly for any of the two nitro substrates. This is expected, since the enantioselectivities are much lower than for the unsubstituted compound, i.e. the structural difference between the diastereomeric activated complexes is much smaller for a nitro-substituted substrate than the unsubstituted substrate.

For the other substrates used, small but significant differences of the primary deuterium KIEs are observed for the reactions of the enantiomers. This enantiomer dependence of the KIEs is, however, hardly interpretable at the present stage of knowledge. One obvious complication, which prevents a more detailed analysis, is the presence of two potentially catalytically active conformers of the base. Theoretical modelling using, e.g., molecular mechanics calculations of the diastereomeric transition structures[29] might prove helpful for a better understanding of the enantioselectivity.

EXPERIMENTAL

The kinetic runs were performed with a Perkin-Elmer Model 241 photoelectric polarimeter equipped with an automatic data acquisition system consisting of a PC connected to the printer output of the polarimeter. The water-jacketed polarimetric cell (optical path length 10 cm, volume 0·9 cm^3) was connected to a HETO 02 PT 623 proportional regulating thermostat. A calibrated mercury thermometer, with an absolute accuracy of 0·02 °C, was used to measure the temperature at the outlet of the cell. The temperature did not deviate more than 0·05 °C from the average value during the runs and was thus 20 ± 0·07 °C.

^1H and ^{13}C NMR spectra were obtained with a Varian XL 300 at 20 °C or a Varian Unity 400 spectrometer at 25 °C. [^2H]Chloroform (>99·5 atom% ^2H; Dr Glaser AG, Basel, Switzerland) was used as solvent.

The substrates, racemic 1-methylindene,[7a] 1-methyl[1,3-$^2H_2$]indene[7a] and their 5- and 7-substituted derivatives[9] were prepared in the same way as the corresponding optically active compounds described elsewhere. The isotopic purities of the deuterated compounds were calculated from ^1H NMR data. The preparation and purification of dihydroquinidine and the purification of the solvent have been described elsewhere.[8] All handling of the purified amine was carried out in a glove-box, in which the atmosphere was circulated through molecular sieves (5 Å). The glove-box was flushed with nitrogen before use. The flasks containing the stock solutions of the amine were stored in larger bottles filled with dry nitrogen and containing silica gel together with KOH pellets.

The kinetic procedure has been described in detail in an earlier paper.[7b]

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