Solvent Dependence of Enantioselectivity for a Base-Catalyzed 1,3-Hydron Transfer Reaction. A Kinetic Isotope Effect and NMR Spectroscopic Study

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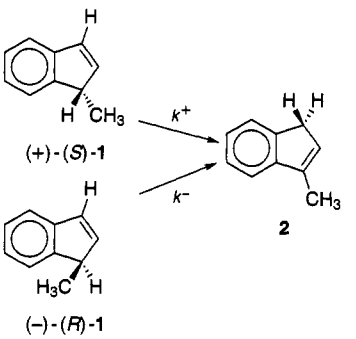
The base-catalyzed rearrangement of 1-methylindene (**1**) to 3-methylindene (**2**) has been studied. The reaction proceeds with substrate enantioselectivity (kinetic resolution) when chiral tertiary amines are used as catalysts. When dihydroquinidine (DHQD) (**3**) is used to accomplish the 1,3-hydron shift, the enantioselectivity shows a change of sense when the solvent is changed from *o*-dichlorobenzene (*o*-DCB) ($k^+/k^- = 3.70$) to dimethyl sulfoxide (DMSO) ($k^+/k^- = 0.579$). The enantiomer-dependent primary deuterium kinetic isotope effects (KIEs) have been determined to $(k_H/k_D)^+ = 5.30$ and $(k_H/k_D)^- = 5.86$ in *o*-DCB and $(k_H/k_D)^+ = 7.76$ and $(k_H/k_D)^- = 8.26$ in DMSO, respectively. The enantioselectivity was found to decrease slightly with increasing concentration of the catalyst. Using (*p*-chlorobenzoyl)dihydroquinidine (*p*-ClBzDHQD) (**4**) as catalyst in *o*-DCB yields the same sense of the enantioselectivity ($k^+/k^- = 0.502$) as dihydroquinidine (**3**) in DMSO. The conformational properties of the alkaloid DHQD (**3**) in the solvents acetone, chloroform, DMSO, dioxane, *o*-DCB, and tetrahydrofuran and of *p*-ClBzDHQD (**4**) in *o*-DCB and chloroform were investigated by means of ^{1}H NMR spectroscopy. The observed solvent dependence of the enantioselectivity is rationalized in terms of the conformational composition of the cinchona alkaloid catalyst.

Asymmetric catalysis is an important part of the armamentarium used for the preparation of enantiomerically pure or enriched compounds.[1] However, quantitative kinetic and mechanistic investigations are sparse in this field.

Among the catalysts used to accomplish asymmetric induction, the cinchona alkaloids occupy a central position.[2] For example, Obenius and Bergson used quinine in the first example of the use of a chiral catalyst in an asymmetric aldol reaction.[3] A detailed mechanistic investigation of cinchona alkaloid-catalyzed addition of aromatic thiols to conjugated cycloalkenones was performed by Hiemstra and Wynberg.[4] More recently, Sharpless has used osmium tetroxide with cinchona ligands for the enantioselective dihydroxylation of alkenes.[5]

Stereoselective proton transfer in the indene system using quinine as the catalyst was reported by Bergson *et al.*[6] as early as 1966, and a more systematic study was later published by Meurling.[7] This work included the use of a variety of cinchona and ephedra alkaloids as well as differently substituted indenes. Interestingly, it was also observed that the sense of the enantioselectivity could be reversed by changing the solvent. The cinchona alkaloid-catalyzed prototropic rearrangement in the indene system has also been used as a model reaction system for the detailed kinetic analysis of kinetic resolution.[8]

Scheme 1



We have earlier introduced the enantiomer-dependent kinetic isotope effect as a new instrument for the study of enantioselection.[9] Quite recently this methodology has been applied to the proton transfer reactions of a series of methylindenes substituted in the aromatic ring.[10]

In the present work we have determined the enantioselectivity (k^+/k^-) for the base catalyzed prototropic rearrangement of 1-methylindene (**1**) to 3-methylindene (**2**) in the solvents DMSO and *o*-dichlorobenzene (*o*-DCB) which show a reversal of the sense of stereoselectivity (see Scheme 1).

The primary deuterium kinetic isotope effects (KIEs) have been determined for the reactions of the enanti-

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Table 1. Enantioselectivities and Second-Order Rate Constants for the Base-Catalyzed Rearrangement of 1-Methylindene (1)[a] in *o*-DCB or DMSO at 30 °C

base	solvent	k^+_H/k^-_H[b]	k^+_H/[base] [b] / 10^{-5} M^{-1} s^{-1}	k^-_H/[base] [b] / 10^{-5} M^{-1} s^{-1}
DHQD (**3**)[c]	*o*-DCB	3.70(6)	829(11)	224(4)
p-ClBzDHQD (**4**)[d]	*o*-DCB	0.502(4)	1.51(2)	3.01(3)
DHQD (**3**)[e]	DMSO	0.579(3)	341(4)	590(6)

[a] The substrate concentration was 0.3−0.5 M. [b] Error limits were obtained by estimation of the maximal experimental errors involved. [c] [**3**] = 9 × 10^{-3} M. [d] [**4**] = 0.4 M. [e] [**3**] = 0.01−0.04 M.

Table 2. Enantioselectivities and Second-Order Rate Constants for the Base-Catalyzed Rearrangement of 1-Methyl(1,3-$^2H_2$)indene [(1,3-$^2H_2$)-1][a] in *o*-DCB or DMSO at 30 °C

base	solvent	k^+_D/k^-_D[b]	k^+_D/[base] [b] / 10^{-5} M^{-1} s^{-1}	k^-_D/[base] [b] / 10^{-5} M^{-1} s^{-1}
DHQD(**3**)[c]	*o*-DCB	4.09(9)	156(3)	38.2(8)
p-ClBzDHQD(**4**)[d]	*o*-DCB	0.592(5)	0.337(4)	0.569(6)
DHQD(**3**)[e]	DMSO	0.613(5)	44.0(5)	71.8(8)

[a] The substrate concentration was 0.3−0.5 M. Correction for the protium content was made in the calculation of rate constants (and ratios). [b] Error limits were obtained by estimation of the maximal experimental errors involved. [c] [**3**] = 9 × 10^{-3} M. [d] [**4**] = 0.4 M. [e] [**3**] = 0.01−0.04 M.

omers in both solvents. Dihydroquinidine (DHQD) (**3**) and its chlorobenzoate ester (*p*-ClBzDHQD) (**4**) were employed as chiral catalysts. To aid the interpretation of the kinetic data, we have also performed a detailed NMR investigation of the conformational behavior of DHQD (**3**) and its derivative *p*-ClBzDHQD (**4**) in a number of solvents including those used in the kinetic work.

Results

Kinetics. The reactions were run under pseudo-first-order conditions. The deuteriated indene was substituted in the 3-position as well as in the reactive 1-position to avoid a contribution to the optical rotation of the reaction mixture from an isotopically chiral reaction 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 kinetics were followed by polarimetry using a method described earlier.[9,10] The rate constants and enantioselectivities were calculated from the kinetic data from the value of the maximum (or minimum) optical rotation and the corresponding reaction time, or by nonlinear regression of eq 1 to the whole set of data. The fitting procedure is described in detail elsewhere.[10]

$$\alpha = a_1 e^{-k^+ t} - a_2 e^{-k^- t} - a_3 \quad (1)$$

$$a_1 = a_2 = ([\alpha][A]_0)/2 \quad (2)$$

a_3 = contribution to the optical rotation from the base catalyst

$[\alpha]$ = specific optical rotation

$[A]_0$ = substrate concentration (g/mL)

Rate constants and enantioselectivities (k^+/k^-) for the proton transfer in 1-methylindene using DHQD (**3**) or its *p*-chlorobenzoate **4** in the two solvents are displayed in Table 1. The corresponding data for the deuteriated system are shown in Table 2. From these data the primary KIEs for the enantiomeric 1-methylindenes were calculated, and they are given in Table 3.

Table 3. Primary Enantiomer-Dependent KIEs for the Base-Catalyzed Rearrangement of 1-Methylindene (1)[a] in *o*-DCB or DMSO at 30 °C

base	solvent	$\left(\frac{k_H/[base]}{k_D/[base]}\right)^{+}$ [b]	$\left(\frac{k_H/[base]}{k_D/[base]}\right)^{-}$ [b]
DHQD(**3**)[c]	*o*-DCB	5.30(17)	5.86(23)
p-ClBzDHQD(**4**)[d]	*o*-DCB	4.48(11)	5.29(11)
DHQD(**3**)[e]	DMSO	7.76(18)	8.26(18)

[a] The substrate concentration was 0.3−0.5 M. Correction for the protium content in (1,3-$^2H_2$)-**1** was made in the calculations of the KIEs. [b] Error limits were obtained by estimation of the maximal experimental errors involved. [c] [**3**] = 9 × 10^{-3} M. [d] [**4**] = 0.4 M. [e] [**3**] = 0.01−0.04 M.

As can be seen in Table 1, the (+)-enantiomer reacts faster than the (−)-enantiomer in *o*-DCB when DHQD (**3**) is used as catalyst, whereas the opposite is the case in DMSO. The magnitude of the enantioselectivity is larger in *o*-DCB. When *p*-ClBzDHQD (**4**) is used as catalyst in *o*-DCB, the (−)-enantiomer reacts faster than the (+)-enantiomer. Looking at absolute rate constants, one finds that the reaction rate is much smaller for the ester derivative (**4**) than for the amino alcohol (**3**). Further, it is interesting to note that the change to DMSO as the solvent not only increases the observed rate constant for the reaction of the enantiomers of the substrate to a different degree but also affects them in different directions: k^+ decreases and k^- increases. The kinetic isotope effects are all fairly large, the smallest value being 4.48, and the values in the solvent DMSO are larger than those determined in *o*-DCB. The KIEs are larger for the (−)-enantiomer in all cases, even when the enantioselectivity is reversed.

Experiments with different concentrations of DHQD (**3**) were performed in the solvent *o*-DCB to investigate the concentration dependence of the enantioselectivity. The investigation was augmented by two measurements in chloroform because of the low solubility of the base in *o*-DCB. The results are given in Table 4. The enantioselectivity was found to be slightly dependent on the concentration of catalyst, *e.g.*, the value of k^+/k^- in chloroform decreases from 4.52 at 5.8 mM to 3.16 at 0.173 M.

NMR Spectroscopy. Solvent dependent changes of conformational equilibria appear to be a likely source of the observed variations in enantioselectivities. It is

Table 4. Concentration-Dependent Enantioselectivities for the Rearrangement of 1-Methylindene (1)[a] Using DHQD (3) as Catalyst in *o*-DCB or Chloroform at 20 °C

[DHQD] 10^{-3} M	solvent	k^+_H/k^-_H[b]	k^+_H/[DHQD][b] 10^{-3} M^{-1} s^{-1}	k^-_H/[DHQD][b] 10^{-3} M^{-1} s^{-1}
14	*o*-DCB	3.87(6)	3.84(5)	0.993(17)
8.5	*o*-DCB	3.95(9)	4.29(7)	1.09(2)
5.8	*o*-DCB	4.12(7)	4.67(7)	1.13(2)
2.5	*o*-DCB	4.22(7)	4.81(8)	1.14(2)
1.2	*o*-DCB	4.28(7)	5.75(12)	1.34(3)
173	chloroform	3.16(5)	0.441(9)	0.140(3)
5.8	chloroform	4.52(9)	0.765(13)	0.169(4)

[a] The substrate concentration was 0.3–0.5 M. [b] Error limits were obtained by estimation of the maximal experimental errors involved.

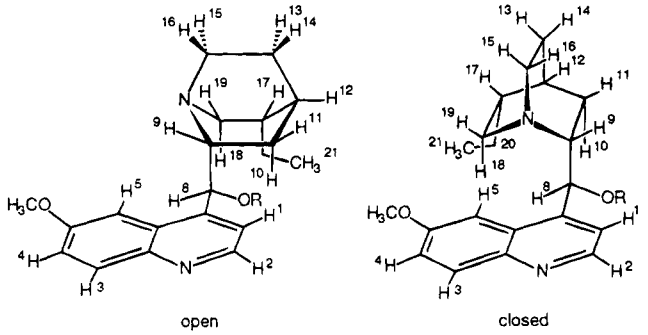

Figure 1. The open and closed conformation of dihydroquinidine (**3**) (R = H) and (*p*-chlorobenzoyl)dihydroquinidine (**4**) (R = *p*-ClBzO).

known that cinchona alkaloids may adopt two major conformations in solution, open or closed, which differ in the relative orientations of the quinoline and the quinuclidine units (Figure 1). A detailed investigation of the solvent-dependent conformational equilibria of these compounds was published a few years ago.[11] The open conformation dominated (≥90%) for dihydroquinidine (**3**) in all solvents investigated.[12] Ester derivatives, on the other hand, mainly adopted the closed conformation (≈70%). These findings were inferred from NOEs between specific sets of quinoline protons and quinuclidine protons and supported by MO (molecular orbital) calculations as well as molecular modeling studies. Since the solvents used in the kinetic work were not examined before, we found it important to examine the solution behavior of the two bases DHQD (**3**) and *p*-ClBzDHQD (**4**) used in the present kinetic investigation in more detail. At room temperature, NOEs for both the open and the closed conformers were detected under all conditions investigated.

Signal Assignment. Proton signals were assigned by homonuclear correlations derived from P.E.COSY[13] spectra, in combination with distance information from NOESY[14] or ROESY[15] spectra. Pairs of methylene protons were also identified from HSQC[16] spectra. The assignment was verified for all combinations of solvent, concentration, and temperature (Table 5). As an example, we describe the assignment for DHQD (**3**) dissolved in $CDCl_3$ (0.02 M). In the quinoline residue, two protons show an NOE with the methoxy protons. One of these is a doublet of 2.6 Hz and is thus identified as H-5 (7.21 ppm), while the other one is H-4 (dd, J = 2.6, 9.2 Hz, 7.33 ppm).[17] H-4 also couples to H-3 at 8.00 ppm. The two remaining quinoline protons (H-1 and H-2) might be distinguished by their chemical shifts (8.70 vs 7.52 ppm), and furthermore, only one of them, *i.e.*, H-1 at 7.52 ppm, shows NOEs to the quinuclidine protons. A broad doublet at 5.54 ppm (J = 5.0 Hz) with an unresolved coupling to the OH proton (at 3.19 ppm) belongs to H-8. It is coupled to H-9 (at 3.08 ppm, ddd, J = 5.0, 9.0, 9.0 Hz), which in turn couples to a pair of geminal protons at 1.90 (dddd, J = 2.0, 2.0, 9.0, 13.2 Hz) and 1.18 ppm (ddd, J = 4.8, 9.0, 13.2 Hz), H-10 and H-11. The signal at 1.18 ppm is revealed as H-11 by its large NOE with H-9. It couples to H-12, which has a broad featureless signal at 1.68 ppm due to many small couplings. On the other hand, the signal at 1.90 ppm shows an NOE to H-20 (1.39 ppm), identified as the methylene protons coupled to the methyl group (0.86 ppm). Returning to H-9, we detect NOEs with three different quinuclidine protons, one of which is already identified as H-11. The other two signals must belong to H-16 at 2.84 ppm (strong NOE with H-9) and H-14 at 1.45–1.55 ppm (much weaker NOE). Of these two signals, only H-14 shows an NOE with H-11. With the help of H-16, we find H-15 (NOESY and P.E.COSY cross peaks, and HSQC experiment) at 2.74 ppm. H-13 is located at almost the same chemical shift as H-14 *via* the HSQC cross peak. Of the three remaining proton signals, one is located at 1.39 ppm and revealed as H-17 by its correlation to a methine carbon (HSQC). The remaining two protons, H-18 and H-19, have the same chemical shift at 2.90 ppm. At higher concentration (0.2 M in $CDCl_3$) or at lower temperature, H-18 has a higher chemical shift. It can then be distinguished from H-19 by NOEs with H-20 and H-10 (weak). In $CDCl_3$ solution (0.2 M), an NOE between H-18 and the methyl protons (H-21) was also found.

Room-Temperature NOEs. NOE measurements at room temperature were performed using the NOESY pulse sequence. Under the conditions described in ref 11, cross peaks were observed for both possible conformers.[18,19] The reason could have been an improperly adjusted mixing time.[20] However, this source of error could be excluded by running a series of separate experiments with mixing times varied over a range from 0.1 to 1.5 s. The relative sizes of the cross peaks remained

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(12) Solvents were $CDCl_3$, CD_2Cl_2, CD_3COCD_3, C_6D_6, and CD_3OD.

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(17) An NOE between the methoxy protons and both H-4 and H-5 was observed in all solvents except tetrahydrofuran and acetone, where the NOE with H-4 was not detected.

Table 5. Proton Chemical Shifts and Values of J_{H8-H9} for DHQD (3) and *p*-ClBzDHQD (4)[a]

H	**3** in $CDCl_3$ 0.2 M, 25 °C	**3** in $CDCl_3$ 0.02 M, 25 °C	**3** in $CDCl_3$ 0.006 M, 25 °C	**3** in $CDCl_3$ 0.02 M, rt[b]	**3** in $CDCl_3$ 0.02 M, −35 °C	**3** in $CDCl_3$ 0.02 M, −55 °C	**4** in $CDCl_3$ 0.02 M, 25 °C
1	7.46	7.52	7.54	7.26	7.52	7.50	7.41
2	8.46	8.70	8.74	8.50	8.45	8.30	8.73
3	7.87	8.00	8.02	7.90	7.86	7.77	8.01
4	7.23	7.33	7.36	7.26	7.19	7.13	7.38
5	7.16	7.21	7.24	7.17	6.97	6.91	7.50
8	5.51	5.54	5.55	5.52	5.63	5.65	6.73
9	2.96	3.08	3.11	3.04	2.88	2.85	3.42
10	1.93	1.90	1.89	1.96	1.92	1.92	1.84
11	1.04	1.18	1.22	1.06	0.88	0.78	1.56
12	1.64	1.68	1.69	1.66	1.65	1.63	1.74
13	1.3−1.45	1.45−1.55	1.45−1.55	1.3−1.55	1.33−1.50	1.32−1.52	1.44−1.60
14	1.3−1.45	1.45−1.55	1.45−1.55	1.3−1.55	1.33−1.50	1.32−1.52	1.44−1.60
15	2.68	2.74	2.76	2.65−3.05	2.72[c]	2.65−2.90	2.68
16	2.79	2.84	2.83−2.91	2.65−3.05	2.83[c]	2.65−2.90	2.80
17	1.35−1.5	1.39	1.35−1.41	1.3−1.55	1.33−1.50	1.32−1.52	1.66
18	3.02	2.90	2.83−2.91	2.65−3.05	3.21	3.29	2.68
19	2.84	2.90	2.83−2.91	2.65−3.05	2.91	2.95	2.92
20	1.38−1.48	1.39	1.35−1.41	1.43	1.33−1.50	1.32−1.52	1.48
21	0.84	0.86	0.86	0.85	0.85	0.84	0.90
OCH_3	3.82	3.89	3.92	3.81	3.75	3.73	3.96
OH	5.31	3.19	2.68	5.15	6.26	4.65	
R-							7.44
R-							8.02
J_{H8-H9}	4.2	5.0	5.0	3.5			7.4

H	**4** in $CDCl_3$ 0.02 M, −45 °C	**4** in $CDCl_3$ 0.02 M, rt[b]	**4** in *o*-DCB 0.02 M, 25 °C	**3** in *o*-DCB 0.02 M, 25 °C	**3** in *o*-DCB 0.005 M, 25 °C	**3** in DMSO 0.02 M, 25 °C	**3** in dioxane 0.02 M, 25 °C
1	7.44	7.40	7.65	7.67	7.68	7.46	7.46
2	8.74	8.75	8.94	8.83	8.94	8.66	8.65
3	8.02	8.02	8.21	8.18	8.23	7.90	7.96
4	7.40	7.39	7.44	7.40	7.43	7.36	7.33
5	7.40	7.45	7.79	7.49	7.45	7.46	7.37
8	6.70	6.72	7.05	5.71	5.70	5.23	5.38
9	3.40	3.38	3.60	3.19	3.21	2.93	3.00
10	1.86	1.85	2.03	2.12	2.08	1.83	1.98
11	1.58	1.55	1.73	1.32	1.36	1.37	1.23
12	1.79	1.75	1.77	1.71	1.72	1.62	1.64
13	1.44−1.66	1.46	1.52	1.46	1.46	1.32	1.38
14	1.44−1.66	1.56	1.64	1.52	1.55	1.45	1.52
15	2.70−3.00	2.70	2.70	2.75	2.75	2.48	2.57−2.67
16	2.70−3.00	2.79	2.84	2.87	2.88	2.54	2.74
17	1.44−1.66	1.45	1.45	1.40	1.38	1.32	1.25
18	2.75	2.68	2.87	3.11	3.04	2.73	2.91
19	2.70−3.00	2.85	2.98	2.97	2.98	2.67	2.80
20	1.44−1.66	1.45	1.56	1.52	1.50	1.46	1.48
21	0.90	0.92	0.99	0.98	0.97	0.86	0.90
OCH_3	3.99	3.95	4.00	3.94	3.95	3.89	3.90
OH				4.24	1.60	5.56	4.27
R-	8.05	7.46	7.43				
R-	7.48	8.05	8.17				
J_{H8-H9}		7.5−8.3	7.8	5.0	4.8	7.2	5.0

H	**3** in acetone 0.02 M, 25 °C	**3** in acetone 0.02 M, −45 °C	**3** in acetone 0.02 M, −80 °C	**3** in THF 0.02 M, 25 °C	**3** in THF 0.02 M, −55 °C	**3** in THF 0.02 M, −80 °C
1	7.54	7.60	7.65	7.49	7.59	7.61
2	8.67	8.69	8.62	8.60	8.63	8.64
3	7.94	7.92	7.85	7.89	7.89	7.90
4	7.34	7.36	7.28	7.25	7.26	7.27
5	7.52	7.46	7.24	7.41	7.39	7.38
8	5.47	5.56	5.73	5.48	5.74	5.77
9	3.08	2.95−3.05	2.87	2.94	2.84	2.82
10	2.01	1.95	1.94	2.08	2.13	2.13
11	1.39	1.25	0.94	1.09	0.76	0.68
12	1.68	1.61	1.56	1.62	1.59	1.58
13	1.40	1.31−1.54	1.25−1.50	1.30−1.50	1.32−1.44	1.30−1.55
14	1.54	1.31−1.54	1.25−1.50	1.30−1.50	1.32−1.44	1.30−1.55
15	2.59	2.51	2.50[c]	2.63	2. 66[c]	2.60−2.90
16	2.70	2.62−2.76	2.65−2.80[c]	2.76	2.82[c]	2.60−2.90
17	1.41	1.31−1.54	1.25−1.50	1.36	1.32−1.44	1.30−1.55
18	2.93	2.95−3.05	3.21	3.10	3.36	3.45
19	2.78	2.62−2.76	2.72	2.81	2.81	2.80
20	1.50	1.31−1.54	1.25−1.50	1.51	1.50	1.30−1.55
21	0.90	0.85	0.80	0.89	0.87	0.86
OCH_3	3.94	3.91	3.76	3.89	3.89	3.88
OH	4.72	5.56	6.63	4.90	5.89	6.32
J_{H8-H9}	6.3			4.2		

[a] All solvents were deuteriated. [b] Taken from Ref. 11. [c] Assignments may be reversed.

unchanged and, furthermore, the NOE buildup rates were of similar magnitude for all cross peaks.[21]

Effect of Concentration. It is known that the conformations of the cinchona alkaloids are to some extent concentration dependent,[22a] and substantial chemical shift changes were observed for several protons of DHQD (**3**) (Table 5).[22b] Thus, the chemical shifts of H-9 and H-11, as well as of H-2 and H-3, showed the largest changes when comparing a 0.006 M with a 0.2 M $CDCl_3$ solution. Changes were less pronounced in *o*-DCB solution. In any case, the NOEs were only little affected. Our chemical shifts do not match the reported set.[11b,23] It was also important to exclude the presence of acidic impurities.[24] Protonation on the quinuclidine nitrogen in *p*-ClBzDHQD (**4**) has been reported to result in line broadening of the signals from the α protons, as well as a reduced chemical shift of H-11 (by ca. 0.47 ppm) and disappearance of the coupling between H-8 and H-9.[11b]

Effect of Solvent. Chemical shifts of DHQD (**3**) and *p*-ClBzDHQD (**4**) are changed specifically in different solvents. Thus, comparing a $CDCl_3$ with a DMSO-d_6 solution of DHQD (**3**), the chemical shifts of the quinuclidine protons ($\Delta_{solvent} = \delta_{DMSO} - \delta_{CDCl_3}$) H-9 ($\Delta_{solvent}$ = −0.15 ppm), H-11 ($\Delta_{solvent}$ = +0.19 ppm), H-18 ($\Delta_{solvent}$ = −0.17 ppm) and H-19 ($\Delta_{solvent}$ = −0.23 ppm) show the most characteristic changes (*cf.* Table 6). These protons also have very different spatial positions relative to the quinoline rings in the open and the closed conformer (Figure 1). Notably, similar chemical shift changes are induced when a small amount of DMSO-d_6 is added to a $CDCl_3$ solution of DHQD (**3**). Probably the DMSO induces a transition from the open to the closed conformer by binding to the OH group. This is also supported by further observations (*vide infra*).

Coupling Constants. Since the main difference between the open and the closed conformer of DHQD (**3**) and *p*-ClBzDHQD (**4**) is the dihedral angle between H-8 and H-9, the coupling constant J_{H8-H9} should be indicative of changes in the conformational equilibrium. From AM1 calculations, this dihedral angle is obtained as 62° for the open conformation and 159° for the closed conformation.[18b] The corresponding coupling constants are calculated as 2.6 and 8.3 Hz, respectively (Table 7).[25] From the observed values (Table 5), relative conformer populations are estimated, which indeed show a solvent dependent preference of DHQD (**3**) for either the open conformation (around 70% in $CDCl_3$ and THF-d_8) or the closed conformation (70−80% in DMSO-d_6) (Table 7).[26] The closed conformer seems to predominate in solutions of DHQD (**3**) in acetone-d_6 (J_{H8-H9} = 6.3 Hz) and for a solution of the ester **4** in $CDCl_3$ (J_{H8-H9} = 7.4 Hz) and *o*-DCB-d_4 (J_{H8-H9} = 7.8 Hz). The situation is less clear for a solution of DHQD (**3**) in *o*-DCB-d_4 (J_{H8-H9} = 5.0 Hz). Conformational changes are also indicated by the observed variation of this coupling constant with concentration and temperature. Obviously, this parameter is a more suitable indicator than the NOEs.

Low-Temperature Spectra. If NOEs at room temperature indicate the presence of both conformers (*i.e.*, open and closed) it might be possible to increase the population of the energetically more favorable conformer

Table 6. Temperature- and Solvent-Dependent Chemical Shift Variations of Selected Protons in DHQD (3) and *p*-ClBzDHQD (4)[a]

base	solvent	*T*/°C	H-9	H-10	H-11	H-18	H-19	H-12
3	acetone-d_6	25	3.08	2.01	1.41			1.68
		−45	2.99	1.95	1.26			1.62
		Δ	−0.09	−0.06	−0.15	0	0	−0.06
3	$CDCl_3$	25	3.08	1.9	1.18	2.9	2.9	1.68
		−55	2.85	1.92	0.78	3.3	2.94	1.63
		Δ	−0.23	0.02	−0.4	0.4	0.04	−0.05
3	THF-d_8	25	2.94	2.08	1.09	3.1	2.8	1.62
		−55	2.86	2.13	0.76	3.38	2.79	1.59
		Δ	−0.08	0.05	−0.33	0.28	−0.01	−0.03
4	$CDCl_3$	25	3.38	1.85	1.55	2.68	2.85	1.75
		−45	3.41	1.87	1.6	2.73	2.95	1.79
		Δ	0.03	0.02	0.05	0.05	0.1	0.04
3	$CDCl_3$	25	3.08	1.9	1.18	2.9	2.9	1.68
3	DMSO-d_6	25	2.93	1.83	1.39	2.73	2.67	1.62
		Δ	−0.15	−0.07	0.21	−0.17	−0.23	−0.06

[a] For 0.02M solutions, $\Delta = \delta_{low\ temp} - \delta_{25}$.

Table 7. Populations of Open (A) and Closed (B) Conformers of DHQD (3) and *p*-ClBzDHQD (4) Calculated from J_{H8-H9}[a]

base	solution (25 °C)	*J*(**A**)[a]	*J*(**B**)[a]	*J*(obs)	*P*(**A**)[b]	*P*(**B**)[b]
3	$CDCl_3$, 0.2 M	2.6	8.29	4.2	0.72	0.28
3	$CDCl_3$, 0.02 M	2.6	8.29	5.0	0.58	0.42
3	THF-d_8, 0.02 M	2.6	8.29	4.2	0.72	0.28
3	*o*-DCB-d_4, 0.005 M	2.6	8.29	4.8	0.61	0.39
3	*o*-DCB-d_4, 0.02 M	2.6	8.29	5.0	0.58	0.42
3	dioxane-d_8, 0.02 M	2.6	8.29	5.0	0.58	0.42
3	acetone-d_6, 0.02 M	2.6	8.29	6.3	0.35	0.65
3	DMSO-d_6, 0.02 M	2.6	8.29	7.2	0.19	0.81
4	$CDCl_3$, 0.02 M	2.5	8.73	7.4	0.21	0.79
4	*o*-DCB-d_4, 0.02 M	2.5	8.73	7.8	0.15	0.85

[a] Based on AM1 structures, *J* values calculated with substituent corrections by Gandour et al.[25] [b] Populations of open (**A**) and closed (**B**) conformer.

(18) (a) See Experimental Section for concentrations and temperatures. Cross peaks indicative of the conformational equilibrium are those between protons which are close in space in only one of the two conformers (Table S1, supplementary material), *i.e.*, for the open conformer H-1 ↔ H-10 (2.31 *vs* 4.39 Å), H-5 ↔ H-9 (2.36 *vs* 3.85 Å) and H-8 ↔ H-9 (2.45 *vs* 3.09 Å), for the closed conformer H-1 ↔ H-9 (2.90 *vs* 4.14 Å), H-5 ↔ H-18 (2.18 *vs* 5.06 Å), H-8 ↔ H-10 (2.84 *vs* 3.70 Å) and H-8 ↔ H-18 (2.05 *vs* 3.07 Å). (b) Structural parameters for the open and closed conformers were derived by energy minimization with the AM1 module in MOPAC 6.0 (QCPE nr. 455).

(19) This refers to open conformer **3** and closed conformer **2** in ref 11b. An additional small amount of closed conformer **1** was observed for DHQD (**3**) in $CDCl_3$ and *o*-DCB-d_4 at 25 °C (Figure 3), but not in the other solvents. In conformer **1** the quinoline ring system is rotated by 180° as compared to conformer **2**, which results in a NOE between H-1 and H-18 (Figure 3).

(20) (a) Since ref 11 provides no values for the mixing times, these were initially set to the usual value of $\approx T_1$.[20b] Spin diffusion, which in principle can produce cross peaks between remote protons as well, can be excluded since at 25 °C both DHQD (**3**) and *p*-ClBzDHQD (**4**) should be in the extreme narrowing regime.[20b] Further, spin diffusion would produce even more cross peaks at low temperatures, which was not observed (*vide infra*). (b) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: Weinheim, Germany, 1989.

(21) Buildup rates were typically between 0.2 and 0.5 s^{-1} (*cf.* Table S2, supplementary material).

(22) (a) *Cf.*: ref 11. (b) Concentration-dependent interactions between enantiomeric dihydroquinidine molecules affect the chemical shifts of particularly H-1, H-2, H-3, and H-8: Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwiller, J.; Uskoković, M. *J. Am. Chem. Soc.* **1969**, *91*, 1871.

(23) By mistake, ref 11b reports chemical shifts for **3** in $CDCl_3$, 0.02 M, which are those for a concentration of 0.1 M. This has been verified by one of the authors (personal communication).

(24) The solvent quality, *i.e.*, different batches of commercial $CDCl_3$, with or without drying or removal of acidic impurities (filtering through neutral aluminum oxide), had no substantial effect on the chemical shifts.

(25) A modified Karplus equation with substituent corrections was used: (a) Colucci, W. J.; Jungk, S. J.; Gandour, R. D. *Magn. Reson. Chem.* **1985**, *23*, 335. (b) Colucci, W. J.; Gandour, R. D.; Mooberry, E. A. *J. Am. Chem. Soc.* **1986**, *108*, 7141. (c) Similar results are obtained using the relation proposed by Altona and coworkers: Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

(26) J_{H8-H9} increases from 4.2 to 5.6 Hz upon addition of 70 μL of DMSO to a 0.02 M solution of DHQD (**3**) in $CDCl_3$.

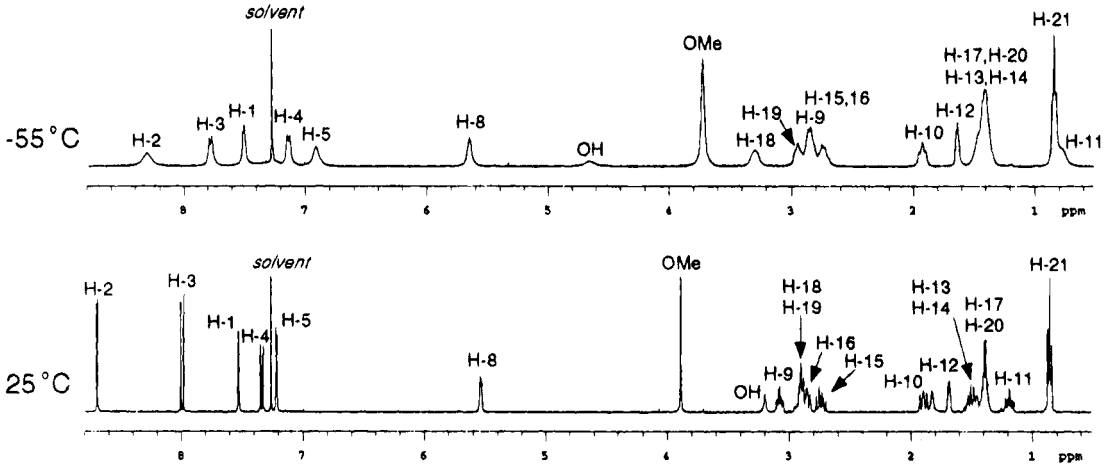


Figure 2. ^{1}H NMR spectrum (400 MHz) of dihydroquinidine (**3**) (0.02 M in $CDCl_3$) at +25 °C and −55 °C.

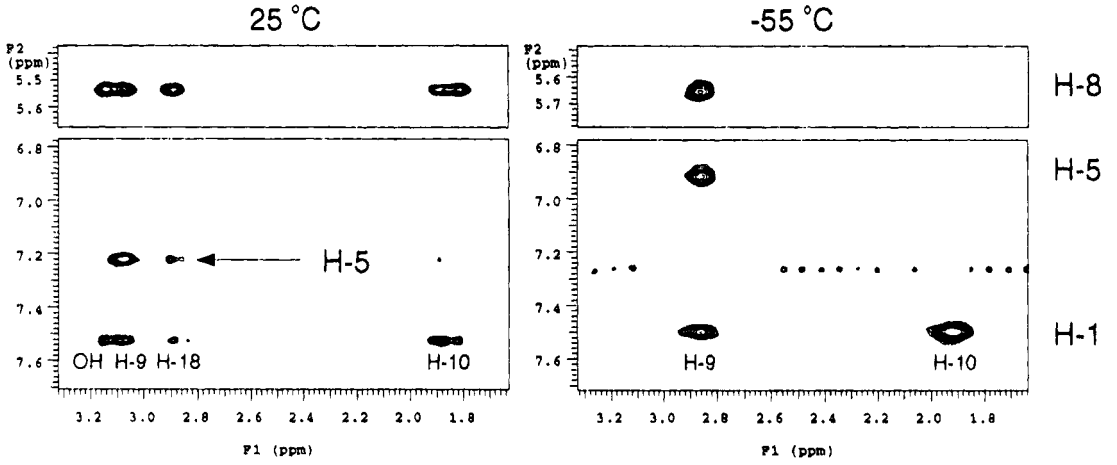


Figure 3. Part of the 2D NOE spectra of dihydroquinidine (**3**) (0.02 M in $CDCl_3$): left, NOESY (at +25 °C, mixing time 0.7 s); right ROESY (at −55 °C, mixing time 0.2 s).

and then observe NOEs for this main conformer at low temperatures. Further, if chemical shifts and J_{H8-H9} are conformation-dependent, these should also change with temperature. This is, in contrast to previous reports,[11] exactly what we observe. Decreasing the temperature results in chemical shift changes for several protons (Table 5 and 6), as well as pronounced broadening of several other signals (Figure 2). Chemical shift changes occur particularly for those quinuclidine protons which are very close to the aromatic ring system in one of the two main conformers but remote in the other. Particularly large changes are detected for H-9, H-11, and H-18, the same protons which also experience the largest chemical shift effect by solvent change (*vide supra*), although the chemical shift of H-9 is affected in the reverse sense.[27] The chemical shift of H-11 decreases upon lowering the temperature, which is what would be expected if the population of the open conformer increases, since here H-11 is situated almost directly above the aromatic ring system. The situation is reversed for H-18, which is nearer to the aromatic rings in the closed conformer. Thus, temperature-dependent chemical shift variations support the conclusions drawn from the behavior of J_{H8-H9}.

The signals for the aromatic protons which are nearest to the quinuclidine ring, *i.e.*, H-1, H-2, and H-5 are broadened at lower temperature (Figure 2).[28] In addition, the coupling between H-8 and OH becomes unresolved. This is in line with a slower conformational mobility at lower temperature.[29]

Lowering the temperature has also a notable effect on the NOEs (Figure 3). In both THF and $CDCl_3$ at low temperature, the NOEs which are indicative of the open conformer dominate (Table S1 in the supplementary material). The situation is less clear for acetone solutions.

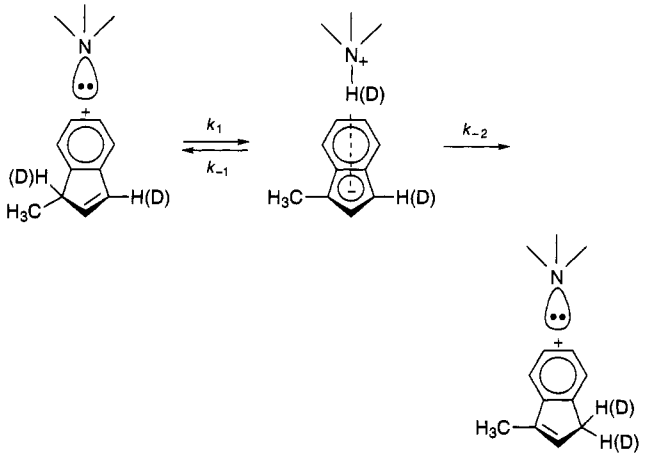
Addition of Substrate. NMR spectra were also recorded in the presence of a 6-fold excess of 1-methylindene at 25 °C. No substantial changes of chemical shifts or NOEs were found, the only visible effect being a slight broadening of some of the quinuclidine signals.

(27) If it is assumed that the transition from $CDCl_3$ to DMSO-d_4 ($\Delta_{solvent} = \delta_{DMSO} - \delta_{CDCl_3}$) affects the conformational equilibrium in the same way as a temperature increase, *i.e.*, by increasing the population of the closed conformer, the corresponding chemical shift changes, $\Delta_{temp} = \delta_{-55\,°C} - \delta_{+25\,°C}$, for $CDCl_3$ solutions are H-11, $\Delta_{solvent} = -0.19$, $\Delta_{temp} = -0.40$; H-18, $\Delta_{solvent} = +0.17$, $\Delta_{temp} = +0.40$; H-9, $\Delta_{solvent} = +0.11$, $\Delta_{temp} = -0.23$; H-19, $\Delta_{solvent} = -0.23$, $\Delta_{temp} = -0.04$. The reverse effect for H-9 may be explained by additional interaction with DMSO molecules hydrogen-bonded to the OH group.

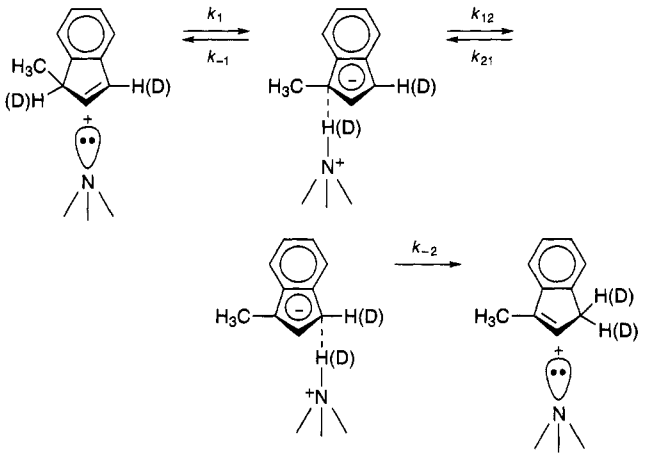
(28) The absence of any such effect was emphasized in ref 11. In addition, the signals of H-1 and H-5 are considerably broadened by lowering the temperature to −55 °C ($CDCl_3$ or THF solution).

(29) The H-8−OH coupling constant ($J \approx 6$ Hz) becomes unresolved at $T \approx -55$ °C, whereas the chemical shift differences in the two conformers obviously are so small that the signals are only broadened, but do not separate even at −80 °C in THF. Below that temperature, low solubility set a limit for our experiments.

Scheme 2



Scheme 3



Discussion

The mechanistic picture of the indene rearrangement that has emerged on the basis of work by the groups of Bergson,[30] Cram,[31] and Ahlberg[32] is shown in Scheme 2.

The acidic proton is removed by the base in a rate-limiting step, forming an intermediary contact ion pair between the substituted ammonium ion and the delocalized anion. This ion pair then collapses to the rearranged product. Thus, the 1,3-proton transfer takes place in a stepwise intramolecular suprafacial fashion. Probably, the rearrangement takes place via two ion pairs (or maybe three) where the ammonium ion is situated above the 1- or the 3-position (or the 2-position) of the anionic moiety[33] (Scheme 3). Neither the partitioning factor (k_{-2}/k_{-1}) for forward vs reverse (internal ion pair return) reaction of the ion pair(s) nor the rate of equilibration of the ion pairs are accurately known. However, the rate constants for the reactions of the ion pair(s) (k_{-1} and k_{-2}) and in particular the partition factor (k_{-1}/k_{-2}) should exhibit a much smaller solvent dependence than the rate constant for proton abstraction (k_1).[30b] A more complete discussion of these matters was published recently.[30]

The discussion below is based on the assumption of rate-limiting proton abstraction, *i.e.*, isotope effects and enantioselectivities can be interpreted in terms of the first reaction step.

Kinetic Aspects of the Conformational Equilibrium. The NMR investigation of the conformational behavior of the catalyst solutions has demonstrated that two conformers (open and closed) are dominating in each of the three systems considered.[34] The equilibration of the two conformers appears to be very fast at the temperature chosen for the kinetic measurements. Consequently, the kinetic situation is one with two catalyst species in rapid equilibrium, where both of them in principle can react under pseudo-first-order conditions with either of the two enantiomeric substrates. Hence, the observed pseudo-first-order rate constants k^+ and k^- for the enantiomeric substrate molecules will be sums of second-order rate constants multiplied by the concentration for the open and closed conformer, respectively (eq 3 and 4). Alternatively, the conformer concentrations may be expressed in terms of total concentration of base and the equilibrium constant for interconversion of the conformers. Equations 3 and 4 are always valid, irrespective of the rate of equilibration, as long as there is nothing during the kinetic experiment which perturbs the equilibrium. The total concentration of the base catalyst remains constant during each kinetic run.

$$k^+ = k^+_{\text{open}}[B_{\text{open}}] + k^+_{\text{closed}}[B_{\text{closed}}] \quad (3)$$

$$k^- = k^-_{\text{open}}[B_{\text{open}}] + k^-_{\text{closed}}[B_{\text{closed}}] \quad (4)$$

Enantioselectivity. The solvent-induced reversal of the enantioselectivity may be understood by consideration of the conformational behavior of the catalyzing bases in the solvents used. The NMR spectroscopic investigation (*vide supra*) has revealed that there is a small excess of the open conformer of DHQD (**3**) (open:closed ~60:40 at concentrations used in the determination of enantioselectivity) in *o*-DCB. In DMSO the closed conformer dominates (open:closed ~20:80). The observed enantioselectivities for DHQD in DMSO and *o*-DCB ($k^+/k^- = 0.579$ and 3.70, respectively) can be explained only by assuming that the closed conformer preferentially reacts with the (−)-enantiomer whereas the open conformer reacts more rapidly with the (+)-enantiomer of the substrate. Taking the different magnitudes of the conformational predominance in the two solvents into account, the open conformer appears to possess a larger selectivity than the closed, and we have tried to rationalize this by inspection of molecular models. Approach of the acidic hydron of the substrate molecule toward the nitrogen lone pair of the quinuclidine moiety seems to take place in a more "asymmetric" environment in the case of the open conformer of the catalyst. In the closed conformer the nitrogen lone pair is more symmetrically situated in relation to the quinoline ring system.

If the assumption that the conformational preference is determining the sense of enantioselectivity in the two solvents is correct, it might be possible to predict the sense of enantioselectivity for a change in the reacting

(30) See, for example: (a) Hussénius, A.; Matsson, O.; Bergson, G. *J. Chem. Soc., Perkin Trans. 2* **1989**, 851–857 and references therein. (b) Hussénius, A.; Matsson, O. *Acta Chem. Scand.* **1990**, *44*, 845–850.

(31) See, for example: Almy, J.; Hoffman, D. H.; Chu, K. C.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 1185 and references therein.

(32) See, for example: (a) Thibblin, A.; Ahlberg, P. *J. Am. Chem. Soc.* **1979**, *101*, 7311. (b) Ölvegård, M.; Ahlberg, P. *Acta Chem. Scand.* **1990**, *44*, 642.

(33) (a) Thibblin, A.; Bengtsson, S.; Ahlberg, P. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1569. (b) Wold, S.; Bergson, G. *Ark. Kemi* **1967**, *28*, 245. (c) Almy, J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 4445. (d) Alvarez-Idaboy, J. R.; Lunell, S.; Matsson, O.; Bergson, G. *Acta Chem. Scand.* **1994**, *48*, 423–427.

(34) As has already been mentioned in note 19, there is also a minor contribution from a third conformer (closed **1**) in the **3**/*o*-DCB system.

system, provided that the conformational composition is known. It was known from studies by Dijkstra *et al.*[11] that the *p*-chlorobenzoate ester of DHQD (**4**) adopted mainly the closed conformer in *inter alia* chloroform. A similar dominance for the closed conformer in *o*-DCB was observed in our NMR investigation (~85%). Thus, an inverse value of the enantioselectivity was predicted and verified by experiment ($k^+/k^- = 0.502$).

Concentration Dependence. There are some experimental observations reported which suggest that intermolecular hydrogen bonding may lead to dimers or larger complexes of the amino alcohol catalyst. Hiemstra and Wynberg[4] used osmometry to measure the average molecular weight for quinine. Their results indicated the presence of particles larger than monomeric quinine at 37 °C for a 16 mM solution in toluene. For concentrations <4 mM the quinine was almost completely monomeric. The ^{1}H NMR spectrum of dihydroquinine in $CDCl_3$ (0.27 M) was demonstrated by Uskoković and co-workers[22b] to exhibit diastereomerically induced anisochrony when enantiomerically impure dihydroquinine was used. At high dilution (0.01 M) the ^{1}H NMR spectra of the enantiomers, racemate and mixtures thereof became identical. These observations strongly suggest intermolecular interactions.

The observations quoted, however, do not provide any evidence for dimerization at the low catalyst concentrations used in our kinetic experiments. Neither does the present NMR investigation provide any evidence for formation of dimers. Thus, it seems likely that the variation of the enantioselectivity (see Table 4) is caused by a concentration-dependent change in the conformational composition. The enantioselectivity appears to be a very sensitive probe for these solute–solute interactions which are more delicate than dimer formation. A separate experiment at a higher concentration (0.17 M) was performed using chloroform as the solvent. At low concentration this solvent yields an enantioselectivity of approximately the same magnitude as in *o*-DCB and the conformational composition is similar. However, the solubility of DHQD (**3**) is better in chloroform than in *o*-DCB. The experiment, which was performed at a concentration where dimerization may take place, resulted in a considerable drop in enantioselectivity.

Enantiomer-Dependent Primary Kinetic Isotope Effects. The fairly large magnitudes of the KIEs (Table 3) suggest rate-limiting hydron transfer in all cases. The fact that the KIEs are higher in DMSO than in *o*-DCB is consistent with results earlier reported[30b] for the solvent dependence of the primary deuterium KIE for the same reaction using quinuclidine as the base catalyst: in DMSO a value of 7.8 was determined as compared to 6.72 in *o*-DCB (both measurements at 20 °C). This solvent dependence was interpreted in terms of an earlier position along the reaction coordinate in DMSO since the charge-separated transition state is more stabilized in the more polar solvent. The results could alternatively be rationalized in terms of quantum statistical mechanical theory.[35]

The enantioselective reactions should *a priori* yield different kinetic isotope effects since they proceed *via* diastereomeric activated complexes.[9] This is equivalent to the enantioselectivities being isotope dependent. This is indeed what we observe: for all systems the primary deuterium kinetic isotope effect is somewhat larger for the (−)-enantiomer of the substrate 1-methylindene (**1**). These results are, however, difficult to interpret since the observed rate constants for the enantiomeric substrates are sums of rate constants for the active conformers of the catalyzing chiral base. Thus, each observed KIE is a weighted average of KIEs for reactions proceeding through two distinct activated complexes.

Conclusions

The cinchona alkaloids **3** and **4** exist in solution as an equilibrating mixture of two main conformers. The relative amounts of these two conformers depend on concentration as well as on solvent and temperature. Changes in the ratio between the two conformers of DHQD (**3**) can explain the observed reversal of the sense of the enantioselectivity for the indene rearrangement when the solvent is changed from *o*-DCB to DMSO. The sense of the enantioselectivity for *p*-ClBzDHQD (**4**) is consistent with the conformational composition of this base in *o*-DCB. Relative amounts of conformers can be estimated from J_{H8-H9}. Contrary to previous reports, NOE measurements at room temperature did not show any strong conformational preference of DHQD (**3**) or *p*-ClBzDHQD (**4**), because the equilibration between the two conformers was fast. At low temperature, the conversion is slower and NOEs for mainly the predominating conformer were observed. Further studies of the conformational behavior of DHQD using circular dichroism (CD) techniques are in progress.[36]

We have demonstrated that the magnitude of the primary deuterium KIE for this hydron transfer reaction is different for the two enantiomers of the substrate. The interpretation of this difference is complicated by the fact that the observed KIEs are composed of contributions from the reactions with the two major conformers of the base catalyst. The application of the concept of enantiomer-dependent KIEs is likely to be more fruitful for a less complex system where the picture is not complicated by a conformational equilibrium of the type described above.

Experimental Section

Kinetics. The kinetic runs were performed with a Perkin-Elmer 241 photoelectronic polarimeter, equipped with an automatic data-acquisition system. The water-jacketed polarimetric cell (optical path length 10 cm, volume 0.9 mL) was connected to a HETO 02 PT 623 proportional regulating thermostat. The temperature was measured with a calibrated mercury thermometer, with an absolute accuracy of 0.02 °C, at the outlet of the cell. The temperature did not deviate more than 0.04 °C from the average during the runs and was thus 20.00 ± 0.06 °C or 30.00 ± 0.06 °C.

The synthesis and purification of the substrates, 1-methylindene (**1**) and its isotopically substituted analogue, have been described earlier.[37]

Dihydroquinidine (DHQD) (**3**) was liberated from dihydroquinidine hydrochloride (Aldrich 98%) by addition of aqueous 5 M sodium hydroxide. The basic solution was extracted with chloroform, and the combined extracts were dried over calcium oxide (p.a., newly heated). Filtration and evaporation of the

(35) Sühnel, J.; Schowen, R. L. Theoretical Basis for Primary and Secondary Hydrogen Isotope Effects. In *Enzyme Mechanism from Isotope Effects*; Cook, P. F., Ed.; CRC Press: Boca Raton, FL, 1991; pp 3–72.

(36) Berg, U.; Matsson, O.; Aune, M. *Tetrahedron Lett.* Accepted.

(37) Bergson, G.; Matsson, O.; Sjöberg, S. *Chem. Scr.* **1977**, *11*, 25–31.

solvent yielded the crude dihydroquinidine, which was recrystallized twice from ethanol (99.5%) under nitrogen.

Dihydro(*p*-chlorobenzoyl)quinidine (*p*-ClBzDHQD) (**4**) was prepared according to the procedure described by Sharpless and co-workers.[38]

o-Dichlorobenzene was passed through a column of basic aluminum oxide (Fluka) before use. The purification of DMSO has been described earlier.[39] Chloroform (Riedel-de-Haën, p.a., stabilized with 1% ethanol) was used without further purification.

All handling of the purified amines was carried out in a glovebox, in which the atmosphere was circulated through molecular sieves (5 Å). The flasks containing the stock solutions of the amines were stored in larger bottles filled with dry nitrogen and containing silica gel together with KOH pellets.

NMR Spectroscopy. NMR spectra were obtained on a Varian Unity 400 instrument at 400 MHz. Chemical shifts were indirectly referenced to TMS *via* the residual ^{1}H solvent signals, δ chloroform-d_1 ($CDCl_3$) 7.26, dimethyl sulfoxide-d_6 (DMSO-d_6) 2.49, acetone-d_6 2.04, *o*-dichlorobenzene-d_4 (*o*-DCB-d_4) 7.11, tetrahydrofuran-d_4 (THF-d_4) 1.73, dioxane-d_8 3.58). Temperatures were measured with the built-in probe thermocouple. Signal assignments were obtained using P.E.COSY,[13] HSQC,[16] and NOESY[14] experiments. At low temperatures (−35 to −80 °C) NOEs were measured with the ROESY[15] pulse sequence. P.E.COSY spectra were typically acquired with a spectral width of 3400 × 3400 Hz, accumulating 200 × 2 FIDs of 16 transients each with 1.5 s acquisition time and 2 s relaxation delay. HSQC spectra were obtained for 1700 × 8250 Hz, 256 × 2 FIDs with 16 transients each, 0.15 s acquisition time, and 1.7 s relaxation delay, for a total experiment time of 4.2 h. Ambient temperature (25 °C) NOESY spectra were run for a spectral width of 3400 × 3400 Hz, 160 × 2 FIDs with 16 transients each, and 0.15 s acquisition time, a relaxation delay of 3 s was used. Different mixing times were usually employed, ranging from 0.5 to 1.5 s. For 0.02 M solutions of DHQD (**3**) in $CDCl_3$ and DMSO-d_6, mixing times were set to 0.2, 0.5, 0.7, 0.8, 1.5 s and 0.05, 0.1, 0.2, 0.5, 1.5 s, respectively. Buildup rates were obtained by fitting a first-order exponential to the cross peak volume integrals using manufacturer-supplied software. At low temperatures (−35 to −80 °C) ROESY experiments were performed, typically for a spectral width of 3400 × 3400 Hz, 160 × 2 FIDs with 16 transients each and 0.15 s acquisition time, using 1.3 s relaxation delay. A time-shared spin lock was used for mixing times between 0.2 and 0.4 s. All 2D spectra were acquired in the phase sensitive mode, and Gaussian apodization was applied in both dimensions prior to Fourier transformation.

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Supplementary Material Available: Tables containing interproton distances and normalized NOESY and ROESY cross peak volumes for **3** and **4** and NOE buildup rates from NOESY spectra for **3** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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