Primary and Secondary β-Deuterium Kinetic Isotope Effects in the 1,3-Prototropic Rearrangement of 1-Methylindene using Tertiary Amines as Catalysts in the Solvents Toluene and Dimethyl Sulphoxide

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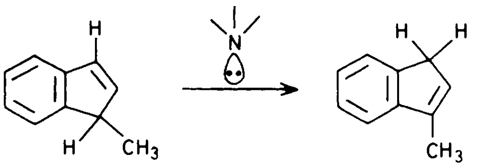
Rate constants, primary deuterium kinetic isotope effects (k.i.e.s), and secondary β-deuterium k.i.e.s have been determined for the base-catalysed 1,3-prototropic rearrangement reaction of 1-methylindene (**1**) to 3-methylindene (**2**) in the solvents toluene and Me_2SO at 20 °C. The structurally similar tertiary amines quinuclidine (**3**), 1,4-diazabicyclo[2.2.2]octane (**4**), 1,3,5-triaza-adamantane (**5**), and 1,3,5,7-tetra-aza-adamantane (**6**), were used as catalysts. The primary k.i.e.s obtained for amines (**3**), (**5**), and (**6**) are rather strong; 5.75—6.06 in toluene and 7.62—7.83 in Me_2SO, *i.e.* almost constant over the p*K* range of *ca.* 4 (in Me_2SO). Amine (**4**), despite its intermediary basicity, showed a significantly lower primary k.i.e.: 5.03 in toluene and 7.29 in Me_2SO. The secondary β-deuterium k.i.e.s of *ca.* 10% were found to correlate inversely with the primary k.i.e.s. The variation of primary and secondary k.i.e.s for the amines (**3**)—(**5**) is similar in the two solvents, but the absolute values of the primary k.i.e.s are lower and the secondary k.i.e.s are higher in toluene. The k.i.e. data are related to the degree of proton transfer and anionic hyperconjugation in the TS of the rate-determining proton abstraction step. The possible importance of internal return is discussed.

In connection with the development of a new method[1] for the simultaneous determination of kinetic isotope effects (k.i.e.s) and rate constants in one kinetic experiment we have reported the primary deuterium k.i.e. and the secondary β-deuterium k.i.e. in the prototropic rearrangement of 1-methylindene (1) to 3-methylindene (2) using 1,4-diazabicyclo[2.2.2]octane (DABCO) as catalyst in the solvent toluene.[1]

Since this polarimetric differential method permits relatively accurate measurements to be made, it was thought worthwhile to extend the study of both primary and secondary k.i.e.s in this system. Such measurements should provide an experimental basis for comparison with model calculations of the k.i.e.s with a view to obtaining more detailed knowledge of the structure of the transition state (TS). The indene system is also suitable for further studies of this type, since it is well characterized in many respects through the extensive investigations performed during the past 20 years, particularly by Bergson,[2] Cram,[3] and Ahlberg[4] and their respective co-workers. Studies of primary k.i.e.s in this system have also been made earlier,[5] but no systematic investigations of the connection between reaction rates and primary and secondary deuterium k.i.e.s have been reported.

The amines used as catalysts in the present work were quinuclidine (3), which is a stronger base than DABCO (4), 1,3,5-triaza-adamantane (5), and 1,3,5,7-tetra-aza-adamantane (6), which are both weaker; all are conformationally rigid and bear strong structural resemblance to DABCO. The relatively nonpolar solvent toluene† was thought to have fairly little interaction with TS as well as reactant molecules, and should thus be well suited for comparison with model calculations of k.i.e.s. Since a rate–equilibrium study in the polar aprotic solvent Me_2SO has been performed earlier for this particular system,[6] this solvent was also included in the present work.

In a forthcoming paper[7] we will describe a new radiochemical method for the experimental determination of a secondary carbon k.i.e. ($^{11}C/^{14}C$-methyl) for the methylindene system. Model calculations of the k.i.e.s are in progress and will be reported subsequently. Some preliminary results of this work have been reported as a conference contribution.[8]



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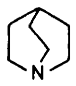

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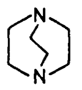

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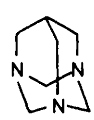

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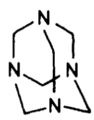

(6)

Fundamental Characteristics of the Indene Rearrangement and the Method Used.—Experiments with optically active and isotopically labelled indenes demonstrated that intramolecular[9] and stereospecific[2a,b] 1,3-hydrogen migration can take place when uncharged amines are used as catalysts. Cram and co-workers[10] showed that the tertiary amine DABCO gave almost complete stereospecificity even in such a polar solvent as Me_2SO. Limited stereospecificity was obtained when primary or secondary amines were used.[2d] The current view is that the proton shift proceeds *via* one (or more) tight ion pair(s), where the hydrogen-bonded substituted ammonium ion slides over one surface of the carbanion. Stereospecificity and intramolecularity are determined by the relative rates of collapse of the ion pair (to product or starting material) and dissociation of, or rotation within, the ion pair.

For 1-methylindene, the rearrangement to 3-methylindene may be regarded as irreversible (*cf.* Scheme 1).[11]

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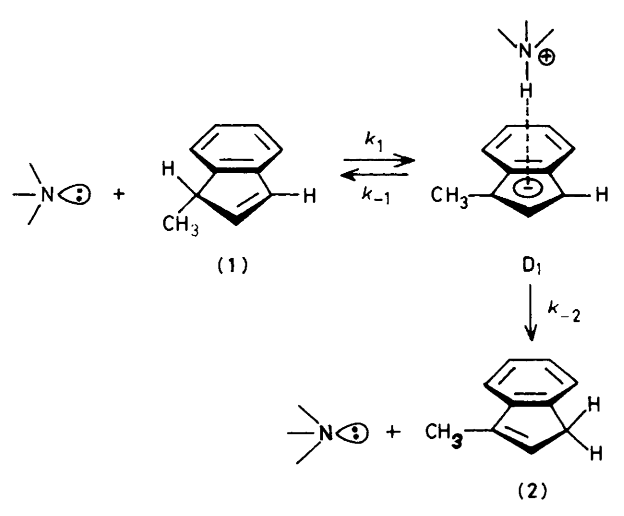
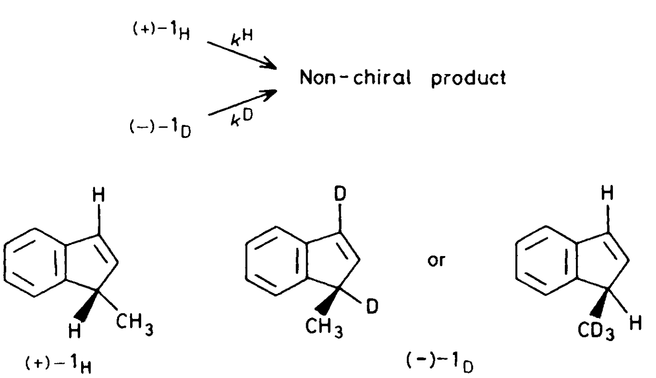
† Amine (6) was not used in toluene because of its low solubility.



Scheme 1. Simplified mechanistic scheme for the amine-catalysed rearrangement of 1-methylindene (**1**) to 3-methylindene (**2**)



Scheme 2. The principle of the polarimetric differential method for determination of k.i.e., *i.e.* the rate-constant ratio k^H/k^D. The experiment starts from a 'quasi-racemic' mixture of (+)-1_H and (−)-1_D [or (−)-1_H and (+)-1_D]. The rate constants and their ratio are determined from the observed optical rotation of the reaction mixture as a function of time

The principle of the polarimetric differential method is represented in Scheme 2. On the basis of the previous studies just briefly reviewed and referring to Schemes 1 and 2, we obtain relations (1) and (2) between the observed and mechanistic rate constants when using achiral tertiary amines, such as (**3**)—(**6**), as catalysts both in toluene and in Me_2SO. The k.i.e. for the rate-determining ionization step (k_1^H/k_1^D) is thus related to the observed k.i.e. (k^H/k^D) and the ion-pair collapse ratios ($\sigma^H = k_{-1}^H/k_{-2}^H$ and $\sigma^D = k_{-1}^D/k_{-2}^D$ respectively) according to equations (3). For the methylindene system, σ^H and σ^D have been assumed to be much smaller than unity.[1c,11]

$$k^H = k_1^H k_{-2}^H/(k_{-1}^H + k_{-2}^H) \qquad (1)$$

$$k^D = k_1^D k_{-2}^D/(k_{-1}^D + k_{-2}^D) \qquad (2)$$

$$\frac{k_1^H}{k_1^D} = \frac{k^H}{k^D} \times \frac{(1 + \sigma^H)}{(1 + \sigma^D)} \qquad (3)$$

Results and Discussion

Consider the generation of a carbanion or ion pair by abstraction of a proton from a carbon acid by a base. The symmetry, or degree of proton transfer, of the transition state (TS) is generally thought to be affected by the strength (p*K*) of the base used.[12] A measure of TS symmetry is the primary k.i.e., which smoothly passes a maximum for the case where the proton is bound with equal strength to substrate and base (Melander–Westheimer model).[13] This has been suggested to occur when the pK_a of the carbon acid equals the pK_a of the conjugate acid of the base catalyst.[14] Approaches for the experimental verification of the model have included measurement of the k.i.e. for a series of bases using the same substrate and solvent[15] as well as modification of the p*K* of one base by varying the solvent composition.[16] It has been reported[17] that experimental findings do not conform to the predicted behaviour. This is attributed to a variety of factors, including experimental error, contamination by secondary isotope effects, internal return, and the need for more complex TS models than the simple linear three-centre model.

Additional information about the TS structure may be obtained if one or more secondary k.i.e.s are also measured. The β-deuterium k.i.e.[18] arising from an isotopically substituted methyl group attached to the reacting carbon is determined by force-constant changes between reactant and TS molecules in the CH bonds of the methyl group. A variation in this effect, if large enough to be measured accurately, would be a probe of the development and localization of negative charge on the carbon atom undergoing bond rupture.

The second-order rate constants (calculated by division of the measured pseudo-first-order rate constants by the base concentration), primary k.i.e.s, and secondary k.i.e.s obtained in kinetic runs with the different amines in toluene and Me_2SO are presented in Tables 1 and 2, respectively.

The thermodynamic basicity of amines (**3**)—(**6**) and two other aza-adamantanes has been determined in the solvent Me_2SO (at 30 °C) by Meurling.[6] The Brønsted α-coefficient (including all six amines) was determined to be 0.79, a value consistent with an ion-pair-like TS. pK_a Values for the amines in Me_2SO are given in Table 2. The range is 3.8 p*K* units. All four amines are far from ΔG^0 0, where the maximum k.i.e. is expected; the Δp*K* values are > 10. It is reasonable to assume the same order of basicity in the solvent toluene. The rates of reaction measured in toluene correlate with k^H measured in Me_2SO, in which the rates are *ca.* 20 times faster. The faster rate in Me_2SO is expected since the TS possesses considerable charge separation and thus should be better stabilized than the reactant molecules in the highly polar solvent.

Primary K.i.e.—The substrate was substituted for deuterium in the 3-position to avoid a possible contribution to the optical rotation of the reaction mixture from the chiral product 3-methyl(1-^{2}H)indene and also to avoid introduction of protium because of the small amount of reversibility. The remote secondary isotope effect from this deuterium was neglected in the present interpretation of the results, but will be discussed in a forthcoming paper on model calculations.

The general behaviour of the k.i.e.s is the same in both solvents: primary k.i.e. is weaker for DABCO than for the other amines. The isotope effect ranges roughly from 5 to 8, *i.e.*, the k.i.e.s are rather well developed although the TS is far from symmetric according to estimates based on the p*K* difference between indene[19] and the amines.

The importance of internal return in studying k.i.e.s of carbanion reactions is well established[20] since the pioneering work of Cram and his co-workers.[21] Referring to equation (3), the observed k.i.e. is determined by the isotope effect on the rate of hydrogen abstraction (k_1^H/k_1^D) and the isotope effect on the ion-pair collapse ratio $(1 + \sigma_H)/(1 + \sigma_D)$. Obviously, as expressed by this relation, the degree of internal return becomes

Table 1. Observed second-order rate constants and k.i.e.s for the rearrangement of 1-methylindene[a] to 3-methylindene using the amines (**3**)—(**5**) as catalysts in the solvent toluene at 20 °C

Base	Conc. (M)[b]	$k^H/[B]^c$ / 10^{-3} mol^{-1} dm^3 s^{-1}	$k^H/k^{D e}$	$k^{3H}/k^{3D e}$
(**3**)	0.096	6.93 ± 0.2	6.06 ± 0.06 (2)	1.096 ± 0.002 (5)
(**4**)	0.23	0.874 ± 0.025	5.03 ± 0.06 (12)	1.103 ± 0.001 (10)
(**5**)[d]	0.16	0.046 3 ± 0.001 1	5.75 ± 0.06 (3)	1.100 ± 0.001 (3)

[a] The concentration of substrate was 0.09—0.5M. [b] The base concentration was chosen to give a convenient rate of reaction. The value is the approximate mean in the kinetic runs. [c] [B] = base concentration. The second-order rate constants vary slightly with concentration of substrate. The rate constants are divided by the number of nitrogen atoms in the amine used. [d] The results were the same, within the error limits given, for experiments using (**5**) prepared by two different synthetic routes. [e] The number of kinetic runs is given in parentheses after each k.i.e. value.

Table 2. Observed second-order rate constants and k.i.e.s for the rearrangement of 1-methylindene[a] to 3-methylindene using the amines (**3**)—(**6**) as catalysts in the solvent dimethyl sulphoxide at 20 °C

Base	pK_a[d]	Conc.(M)[b]	$k^H/[B]^c$ / 10^{-3} mol^{-1} dm^3 s^{-1}	$k^H/k^{D e}$	$k^{3H}/k^{3D e}$
(**3**)	9.6	0.006 3	122 ± 8	7.83 ± 0.1 (4)	1.082 ± 0.002 (8)
(**4**)	8.4	0.015	26.4 ± 0.8	7.29 ± 0.07 (3)	1.088 ± 0.002 (3)
(**5**)	7.1	0.028	1.63 ± 0.05	7.76 ± 0.07 (2)	1.084 ± 0.002 (2)
(**6**)	5.8	0.044	0.104 ± 0.003	7.62 ± 0.07 (2)	1.085 ± 0.002 (2)

[a] The concentration of substrate was 0.09—0.5M. [b] The base concentration was chosen to give a convenient rate of reaction. The value is the approximate mean in the kinetic runs. [c] [B] = base concentration. The second-order rate constants vary slightly with concentration of substrate. The rate constants are divided by the number of nitrogen atoms in the amine used. [d] Taken from ref. 6; the values are statistically corrected for the number of nitrogen atoms in the amines. [e] The number of kinetic runs are given in parentheses after each k.i.e. value.

Table 3. Observed specific optical rotations[a] of the enantiomerically pure 1-methylindenes measured in toluene and Me$_2$SO

Compound	$[\alpha]^{20.00}_{546}$/° (Me$_2$SO–toluene)		$[\alpha]^{20.00}_{436}$/° (Me$_2$SO–toluene)	
(+)-(**1**)		+243.4		+453.6
(−)-(**1**)	−231.6	−243.0	−432.6	−452.9
(+)-[$^2H_2$]-(**1**)	+234.4		+438.4	
(−)-[$^2H_2$]-(**1**)		−245.5		−458.4
(+)-[$^2H_3$]-(**1**)	+223.1	+233.8	+416.5	+435.7
(−)-[$^2H_3$]-(**1**)		−234.5		−436.7

[a] The specific rotation (measured in toluene solution) was shown to be constant over the concentration interval used in the kinetic measurements. The accuracy is ±0.5%.

important for the interpretation of observed k.i.e. only if there is an isotope effect on the collapse ratio, *i.e.*, when $\sigma_H \neq \sigma_D$. One difficulty in this connection is that the collapse ratio (or the degree of internal return) for the methylindenylium-substituted ammonium ion-pair intermediate is not accurately known. In the investigations[11] of enantioselectivity in the quinidine-promoted 1,3-proton transfer it was assumed that k_{-1}^+/k_{-2}^+ and k_{-1}^-/k_{-2}^- are <0.05. This assumption was based on rather crude experiments,[1c] in which the rearrangement of (**1**) to (**2**) was performed in pyridine–D_2O as solvent system using deuteriated hexylamine as catalyst.

If the isotope effect on the collapse ratio is negligible or, as was assumed earlier, the amount of internal return is very small, the observed k.i.e. equals the k.i.e. on the hydrogen-abstraction step. Despite the structural similarity between DABCO and the other amines used, the theoretically predicted smooth increase in k.i.e. as a function of reaction rate and basicity is not observed. Steric effects, as judged from inspection of simple molecular models, seem closely similar for the amines used. Consequently the tunnelling contribution is presumably constant. Further experimentation, for example with similar amines and related substrates, successive isotopic labelling, as well as model calculations may prove helpful.

The better stabilization of a polarized TS than of the nonpolar reactant molecules in a polar aprotic solvent may place the TS earlier along the reaction co-ordinate, thus making the TS more symmetric. This provides an explanation for the fact that the present primary k.i.e.s are all stronger in Me$_2$SO (7.29—7.83) than in toluene (5.03—6.06). Other factors may, however, also be important. A general increase in k.i.e. in polar media has been predicted by calculations based on the quantum-statistical theory by Dogonadze and his co-workers.[22] A different degree of internal return in the two solvents may also contribute.

Secondary β-Deuterium K.i.e.—The β-deuterium secondary isotope effect[18] has been utilized in the investigation of aliphatic nucleophilic substitution reactions[23] and acyl-transfer reactions,[24] the latter also in enzymic systems.[25] Several mechanisms, such as steric, inductive, and hyperconjugative effects, have been employed in explaining the force-constant changes responsible for the β-deuterium k.i.e.[18] Among these, the hyperconjugative effect seems to have received most attention, at least in carbocation chemistry.[26]

In carbanionic reactions, only a limited number of β-secondary k.i.e.s have been determined. The concept of anionic hyperconjugation has given rise to considerable controversy.[27] However, it is obviously a theoretically justified concept which allows for simple rationalization of experimental data.[28] In the gas phase, β-deuterium isotope effects on proton-transfer equilibria, involving formation of the methylamino, methoxy, and thiomethoxy anions, have been measured[29] by pulsed ion cyclotron resonance spectroscopy by Hehre and his co-workers. They explained the results by assuming interaction between the negative charge and the antibonding π^* orbital of the adjacent methyl group. This interaction weakens the CH bonds of the methyl group in the TS leading to a normal isotope effect. The results were in agreement with estimations of the CH stretching force constant based on *ab initio* calculations.

β-Secondary k.i.e. on reactions with carbanion-like TS measured in solution[30] are generally lower than in the gas phase.

The observed secondary k.i.e.s given in Tables 1 and 2 are all normal; the lighter molecule reacts faster than the heavier. The effects range between 8 and 10% for one methyl group and are of the same order of magnitude as reported for other base-promoted proton-abstraction reactions. The secondary k.i.e.s correlate with the primary k.i.e.s. Amines (**3**), (**5**), and (**6**) show a decrease in secondary k.i.e. as the primary k.i.e. and the reaction rate increases with base strength. The strongest secondary, and weakest primary, k.i.e. was obtained for DABCO. The values are all lower in Me_2SO than in toluene. Since the contribution by the collapse-ratio factor to the observed secondary k.i.e. is presumably negligible, the following considerations are relevant.

Steric contributions are presumably very small since non-bonded interactions involving the methyl group seem similar in reactant and TS. Eventually, a small inverse effect results from slightly increased repulsion from the nearest aromatic hydrogen. A blend of inductive and hyperconjugative effects is, however, more plausible. Both should contribute to a normal k.i.e. One would expect a better developed carbanion character of the TS for the weakest base, and a correspondingly larger secondary k.i.e. due to stronger inductive and hyperconjugative interaction between the methyl group and the negative charge localized on C(1). The hyperconjugative contribution should also increase since progress towards planar sp^2-hybridization brings the methyl group into a conformation more favourable for hyperconjugation.

The lower values in Me_2SO are in accordance with a less carbanionic TS which might be expected from the faster rate of reaction and the stronger primary k.i.e.

Experimental

The ^1H n.m.r. and the proton-noise-decoupled ^{13}C n.m.r. spectra were obtained with a JEOL FX100 pulse Fourier transform spectrometer operating at 100 and 25 MHz, respectively, and equipped with a 5 mm $^1H-^{13}C$ dual probe, quadrature phase detector, and FAFT 80/81 (820412) software. All spectra were run at 24 °C. Tetramethylsilane was used as internal standard. The ^1H n.m.r. spectra of $[^2H_2]$- and $[^2H_3]$-(**1**) were run using double-precision acquisition and data processing. When processing data, a window function consisting of a decreasing exponential leading to a line broadening of 0.3 Hz for ^1H n.m.r. and 1 Hz for ^{13}C n.m.r. spectra and a trapezoidal part linearly decreasing over the last 10% of the data points were used.

Analytical g.l.c. was run on a Hewlett–Packard 5830A gas chromatograph equipped with electronic integrator (GC Terminal 18850A) or a Hewlett–Packard 5880A (Terminal 5880A Series) instrument, each equipped with a flame ionization detector.

Optical rotations were measured with a Perkin-Elmer 241 photoelectric polarimeter at 546 or 436 nm. The kinetic runs were performed with the same instrument equipped with an automatic data acquisition system consisting of a Discan CM 4040 and a Teletype. The water-jacketted polarimetric cells (optical path length 10 cm, volume 0.9 ml) were 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. During the runs the temperature did not deviate more than 0.02 °C from the average value and was thus 20.00 ± 0.04 °C.

Indenes.—The synthesis of the optically active and isotopically substituted 1-methylindenes has been described earlier.[1] The 1-methylindenes were purified by preparative gas chromatography on a 0.6 m long and $\frac{3}{8}$ in wide column, packed with 15% Apiezon L on Diatom W, 80—100 mesh. A Varian Aerograph model 90P4 gas chromatograph with thermal conductivity detector was used with helium as carrier gas. A sample of 50 μl of the indenes was injected: injection temperature 110—120 °C, detection temperature 115—120 °C, column oven temperature 105—110 °C, and carrier gas flow 100 ml min^{-1}. The fractions were collected in ice-cooled glass traps equipped with a drying tube ($CaCl_2$). The indenes were stored under nitrogen in the freezer.

The optical rotation of each batch of purified indene was measured in a short polarimetric microcell (optical path length 1 cm, volume 0.09 ml, neat). Optical rotations measured neat and in the appropriate solvents are collected in Table 3. The loss of optical activity in (**1**) was *ca.* 0.5% after one week in the freezer.

The purity of the indenes was checked by g.l.c. on a 2.9 m long and $\frac{1}{8}$ in wide column, packed with 2% Apiezon L on 80—100 mesh Chromosorb W (AW, DMCS). A solution of the indene in diethyl ether was injected: column oven temprature 120 °C, injection temperature 130 °C, detection temperature 160 °C, and carrier gas (N_2) flow 25 ml min^{-1}. The retention time for 1-methylindene was *ca.* 5.5 min and for 3-methylindene *ca.* 9.2 min under these conditions. All samples used in the measurements showed only one peak. The isotopic purities of the deuteriated compounds were calculated from the ^1H n.m.r. data, shown below. The accuracy is ±10%.

The ^1H n.m.r. (^{13}C n.m.r.) spectra were obtained using a spectral width of 1 kHz (5 kHz), 8 192 data points, pulse width 30° (50°) and duration of a 90° pulse 48 μs (10 μs), data acquisition time of 4.09 s (0.82 s), delay time of 9.09 s (1.82 s), and 32 scans (1 000 scans). The concentration of sample was 0.7M. N.m.r. (**1**) were as follows: (C_6D_6 ultra puriss >99.95 atom % D, Ciba-Geigy, δ_H 1.08 (3 H, d, J_{HH} 7.5 Hz, Me), 3.22 (1 H, q, J_{HH} 7.5 Hz, of triplets, 1-H), 6.2 [1 H, dd, J (2-H, 3-H) 5.4, J (2-H, 1-H) 2.0 Hz, 2-H], 6.64 [1 H, dd, J (2-H, 3-H) 5.4, J (3-H, 1-H) 1.8 Hz, 3-H], and 7.0—7.4 (4 H, m, aromatic); δ_C 16.1 (methyl), 45.4 (C-1), 121.4, 122.9, 125.2, 126.8, 130.6 (C-3), 141.3, 144.3 (s), and 149.5 p.p.m. (s); $[^2H_2]$-(**1**) (C_6D_6) δ_H 1.07br (3 H, s, Me), 3.22 (0.016 H, q, J_{HH} 7.7 Hz, 1-H), 6.21 (1 H, s, 2-H), 6.64 [0.007 H, d, J (2-H, 3-H) 5.7 Hz, 3-H], and 7.0—7.4 (4 H, m, aromatic); δ_C 16.0 (methyl), 121.4, 122.9, 125.2, 126.8, 141.1, 144.2, and 149.5 p.p.m.; $[^2H_3]$-(**1**) (C_6D_6) δ_H 1.07 (0.063H, d + m, $[^2H_3]$Me), 3.20br (1 H, s, 1-H), 6.21 [1 H, dd, J (2-H, 3-H) 5.3, J (2-H, 1-H) 1.8 Hz, 2-HJ, 6.64 [1 H, dd, J (2-H, 3-H) 5.3, J (3-H, 1-H) 1.8 Hz, 3-H], and 7.0—7.4 (4 H, m, aromatic); δ_C 45.1 (C-1), 121.4, 122.9, 125.1, 126.7, 130.5, 141.2, 144.3, and 149.4 p.p.m.

Catalysts and Solvents.—All handling of the purified amines was performed in a glove box, where the atmosphere was circulated through molecular sieves (5Å), in the presence of Ascarite to lower the amount of carbon dioxide in the atmosphere. The glove box was flushed with nitrogen before use. The flasks containing the stock solutions of the amines and the dried Me_2SO were stored in larger bottles filled with dry nitrogen and containing silica gel or 5Å molecular sieves.

Quinuclidine (1-azabicyclo[2.2.2]octane) (**3**) was liberated from quinuclidine hydrochloride (Fluka or EGA-Chemie; *Purum*) by addition of aqueous 5M-sodium hydroxide. The basic solution was extracted eight times with diethyl ether (*p.a.*) and the combined extracts, were dried with calcium oxide (Baker; *p.a.*; newly heated). The ether was slowly distilled through a Vigreux column. The residue was sublimed twice at 20 °C and 13 Pa. The purity of the quinuclidine was checked by ^{1}H n.m.r.

1,4-Diazabicyclo[2.2.2]octane (DABCO) (**4**) (Fluka; *purum*) was dissolved in toluene in a flask equipped with a Dean–Stark water separator. The solution was refluxed under nitrogen until no more water separated. It was then concentrated and left at room temperature. The crystals formed were filtered under nitrogen and recrystallized twice from n-hexane (*p.a.*; redistilled). The product was dried at reduced pressure at 40 °C, m.p. 159—161 °C.

1,3,5-Triaza-adamantane (1,3,5-triazatricyclo[3.3.1.1^{3,7}]decane) (**5**) was prepared by two different routes.

A. By condensation of 1,3-diamino-2-aminomethylpropane with paraformaldehyde.[6,31] This compound was a gift from Dr. L. Meurling.

B. By hydrogenolysis of 7-bromo-1,3,5-triaza-adamantane,[32] prepared from 7-nitro-1,3,5-triaza-adamantane *via* the 7-amino compound. The amine was purified by crystallization three times from benzene–heptane (1:5, v:v) followed by slow sublimation at 75 °C and 1.3 kPa. The cold finger of the sublimator was chilled with boiling liquid nitrogen. The material initially collected was discarded. More than 50% of the material was left as residue. The purification was followed by g.l.c. using a glass column (1 m × 0.003 m) packed with 3% PS 400–Chrom W HP 80—100 (oven temperature 155 °C; injection temperature 270 °C; detection temperature 200 °C) and carrier gas (N_2) flow 40 ml min^{-1}. The sublimed amine contained 0.3% (calculated as g.l.c. peak area) of an unknown impurity. The amines prepared by methods A and B showed identical mass spectra (run on an LKB 2091 mass spectrometer at 70 eV), δ_H (C_6D_6) 0.56br (1 H,br s, 7-H), 3.27 (6 H, s, 6-, 8-, 10-H), 4.20 [3 H, dd, J_{gem} 12.8, J_4(eq-eq) 1.6 Hz, 2-, 4-, 9-H_{eq}], and 4.40 (3 H, d, J_{gem} 12.8 Hz, 2-, 4-, 9-H_{ax}); δ_C 26.5 (C-7), 58.3, and 75.4 p.p.m.

1,3,5,7-Tetra-aza-adamantane (hexamethylenetetramine) (**6**) (Merck; *p.a.*) was twice sublimed at 85 °C and 1.3 kPa.

Toluene (Merck; *p.a.*) was treated with calcium hydride, distilled under nitrogen, and stored over freshly activated molecular sieves (3 Å), b.p. 111 °C.

Dimethyl sulphoxide (Riedel-De Haen; getrocknet, max. 0.01% H_2O, für Analyse, Merck; getrocknet max. 0.03% H_2O, zur Analyse) was treated with calcium hydride overnight. More hydride was then added and the solvent distilled in vacuum. The first 20% was discarded and the middle fraction was collected over freshly activated molecular sieves (3Å). A slow stream of nitrogen was passed through the solvent during distillation and the still pot temperature was not allowed to exceed 50 °C, b.p. 32—34 °C at 13 Pa. After flushing with nitrogen, the solvent was stored in the freezer in a nitrogen atmosphere. The water content was estimated by ^{1}H n.m.r. to be < 70 p.p.m. (the water peak area was compared with one ^{13}C side band of Me_2SO).

Kinetic Procedure.—All glassware used was cleaned with chromic acid, rinsed successively with water, dilute ammonia, dilute hydrochloric acid, and distilled water and dried at 160 °C for at least 6 h. The polarimetric cells were cleaned in the same way, rinsed with absolute ethanol and ether (*p.a.*), and dried in a stream of warm air. The syringes were cleaned successively with absolute ethanol and ether (*p.a*) and dried with warm air. Different procedures were used for the preparation of the substrate mixture. In all cases freshly prepared ($\leqslant$ one week old) indenes were used. In the original procedure earlier reported (a) the isotopic indenes were mixed to near zero optical rotation in a polarimetric cell. The composition of the mixture was then determined from calibration curves constructed by measuring the optical rotation of at least four different mixtures with known composition of the two substances. The correlation coefficient of the best straight line fitted to the experimental points was never less than 0.999 98. The specific rotations of the enantiomerically pure substances were also determined by numerical extrapolation using the equation for the calibration curve. The specific rotations obtained in this way were the same,* within the limits of experimental error, as those determined by measurement on the pure enantiomer in solution.

In modified procedures the appropriate substrate was prepared by mixing weighed quantities of the indenes either (b) into one batch, from which samples were taken for several kinetic runs, or (c) in an amount just enough for one kinetic run. Experimental results were within the same limits of error independently of the procedure used. Procedure (c) was, however, somewhat easier to use, and was followed in the later runs.

The substrate prepared in one of these ways [when procedure (c) was followed the indenes themselves, *ca.* 0.06 ml of each] was weighed into a 2 ml calibrated volumetric flask by means of a gas-tight syringe.

A stock solution of the amine in the appropriate solvent was prepared in a volumetric flask which was then closed with a tight TFE septum and a screw-cap. Both flasks were thermostatted. Base solution was withdrawn by means of a nitrogen-filled syringe and the 2 ml flask filled to the mark. The syringe was equipped with a filter (Millipore; Fluoropore; 0.5 µm) to prevent introduction of dust from the molecular sieves in the polarimetric cell. The flask was rapidly shaken and part of the contents was transferred to the polarimetric cell. The clock of the data sampling system was started when half the base solution had been added. Observations were recorded at regular intervals to near completion of the reaction.

The base concentration was determined in the following way. The density, ρ (g ml^{-1}), of the reaction solution was determined using a calibrated 1 ml flask. The mass (w_2 g) of base solution added to the reaction flask (V ml) was calculated as $w_2 = V\rho - w_1$, where w_1 is the mass of substrate. The molar concentration of base was then calculated as $10^3\ w_2 w_B V^{-1} M^{-1}$, where M is the molecular weight of the base, and w_B the mass fraction of base in the stock solution.

Evaluation of the Rate Parameters and Error Analysis.—The optical rotation as a function of time is described by equation (4) where k^H and k^D are the observed pseudo-first-order rate

$$\alpha = a_1 e^{-k^H t} - a_2 e^{-k^D t} + \alpha_\infty \qquad (4)$$

constants for reaction of (**1**) and [^{2}H]-(**1**), respectively. The pre-exponential factors a_1 and a_2 are functions of the initial concentration of substrates (g_1 and g_2 in g ml^{-1}), the specific rotations of enantiomerically pure substances ($[\alpha]^1$ and $[\alpha]^2$), and the isotopic purity {assumed to be 100% for (**1**) and 100φ_2% for [^{2}H]-(**1**)†} according to equations (5) and (6). The rate

$$a_1 = [\alpha]^1 \{g_1 - g_2(1 - \varphi_2)\} \qquad (5)$$

$$a_2 = -g_2\{[\alpha]^2 + (1 - \varphi_2)[\alpha]^1\} \qquad (6)$$

constants were calculated by least-squares fitting of the model equation (4) to the experimental kinetic data (α; t) using subroutines from the program package STEPT.[33] The main program CURVFIT with the minimization routine STEPIT

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* A discrepancy reported earlier was due to erroneous calibration of a volumetric flask.

† Since no meaningful correction of the optical rotation could be made for the protium content of the CD_3-groups φ_2 was set to zero for compound [$^2H_3$]-(**1**).

and the sub-routines STSET and STBEG were used. The program was modified to run on an array processor FPS-164 attached to a VAX 11/780. The arithmetic precision was 15 decimal digits. The number of kinetic data points were 100—500 in each kinetic run. One of the pre-exponential factors was usually fixed at its experimentally determined value, while the other was allowed to vary in the fitting procedure. The value of the optical rotation at infinite reaction time, α_∞, was also fixed (it was zero or 2×10^{-3}° depending on which solvent and polarimetric cell was used). Starting values of k^H and k^D were obtained from the observed maximum optical rotation, $\alpha_{max.}$, and the corresponding reaction time, $t_{max.}$, by use of equations (7) and (8).[1]

$$\alpha_{max.} = a_1(bS)^{S/(1-S)} - a_2(bS)^{1/(1-S)} \qquad (7)$$

$$t_{max.} = [1/(k^H - k^D)] \ln(bS) \qquad (8)$$

$$b \equiv a_1/a_2;\ S \equiv k^H/k^D \qquad (9)$$

The error limits displayed in Tables 1 and 2 are *maximal errors* obtained by estimation of the experimental errors involved. The discrepancy between fitted and experimentally obtained values of the pre-exponential factor was typically 0.2—0.4% and in some runs 1—2%. The *precision* expressed as the 95.5% confidence limits of the mean ($2\sigma/\sqrt{N}$) was calculated for some cases where the number of kinetic runs were large enough to permit meaningful statistical treatment. The secondary k.i.e. for amine (3) (Me_2SO, 8 experiments) obtained in this way is 1.082 3 ± 0.000 8, and the limits for the second-order rate constants for amine (3) (Me_2SO, 9 experiments) and (4) (toluene, 10 experiments) are ±3 and 1%, respectively. The standard deviation of the residuals in the fitting was typically 0.001—0.003°, which is approximately the specified precision of the polarimeter used.

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