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Proton-Mobility in the Indene Ring-System

VI.* Rearrangements of Alkyl-Indenes with Particular Regard to Stereospecific Tautomerism

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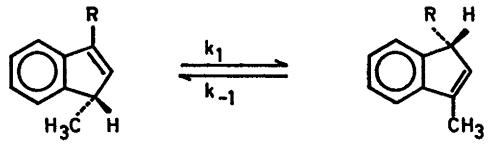
Tautomeric rearrangements of alkyl-substituted indenes have been investigated under various conditions, using the NMR-technique and polarimetric measurements. A completely stereospecific and intramolecular proton transfer was observed when the rearrangement was studied in pyridine solution with various amines ($8.7 < pK_a < 10.9$) as catalyzing agents. The stereospecificity partly disappeared in dimethylsulphoxide solution, and rapid racemization occurred in *tert*-butanol with potassium *tert*-butoxide as catalyst.

The authors recently found[1-3] that the base-catalyzed proton-transfer in the five-membered ring of indene is intramolecular and stereospecific in pyridine solution. In order to elucidate this new mechanism of tautomeric rearrangements, the reactions of some alkylindenes have now been investigated under various conditions. The compounds studied are shown in Fig. 1. The



(a) (b)

R= −H, −CH(CH3)2, −C(CH3)3

(I) (II) (III)

Fig. 1.

* Part V. *Acta Chem. Scand.* 18 (1964) 1483.

reaction rates and equilibria have been investigated by NMR-spectroscopy and polarimetric measurements. In the case of (I) and (III), tautomer (a) was completely rearranged to (b) as far as could be determined within the limits of experimental error. However, (II) still contained about 20 % of 1-methyl-3-isopropylindene (IIa) at equilibrium.

Using pyridine as a solvent, we have investigated the catalytic effects of triethylamine (TEA), butylamine (BUA), 1,4-diaza-bicyclo[2.2.2]octane (DABCO), and α-phenylethylamine (PEA) (Fig. 2). Pyridine itself does not

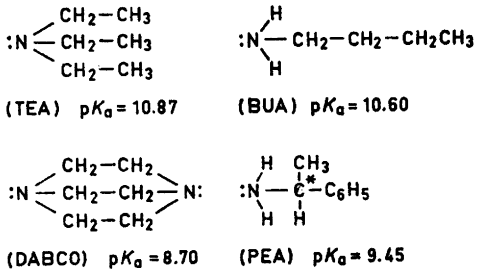


Fig. 2.

cause rearrangement under the conditions employed. Further, some experiments were made in *tert*-butanol solution using potassium *tert*-butoxide as a catalyst. Dimethylsulphoxide (DMSO) has also been used as a solvent in some cases.

EXPERIMENTAL RESULTS

The NMR-spectra were obtained with a Varian A-60 high resolution spectrometer. The course of the rearrangements could be followed by measuring the increase in intensity of the 3-methyl proton peak at approximately 2.0 ppm (δ). In the case of (Ia), a further check on the reaction rate was obtained by measuring the decrease in intensity of the 2-vinylic proton peak, which appears at a higher field in the rearranged product (Fig. 3).

The various liquid catalysts used in the kinetic runs were purified by distillation shortly before use. DABCO (Houdry Process and Chemical Co)* was recrystallized from hexane (spectrograde). All solvents used were analytical grade reagents. Pyridine (Mallinckrodt) was dried by storing over calcium hydride.

The solution of potassium *tert*-butoxide in *tert*-butanol was prepared by addition of the calculated amount of clean potassium to dry *tert*-butanol (Baker), in a nitrogen atmosphere. The exact base concentration was determined by titration.

The syntheses of the various alkyl-indenes used in the experiments have recently been published.[4,5]

All kinetic runs were made at 30°C except when otherwise stated. The experimental kinetic data satisfied function (1), which is a solution of the rate equation for first-order kinetics. In (1), x is any quantity directly proportional to the concentration of the

$$x = (x_0 - x_\infty)e^{-kt} + x_\infty \qquad (k = k_1 + k_{-1}) \qquad (1)$$

* We are indebted to Houdry Process and Chemical Co. for the sample of this catalyst.

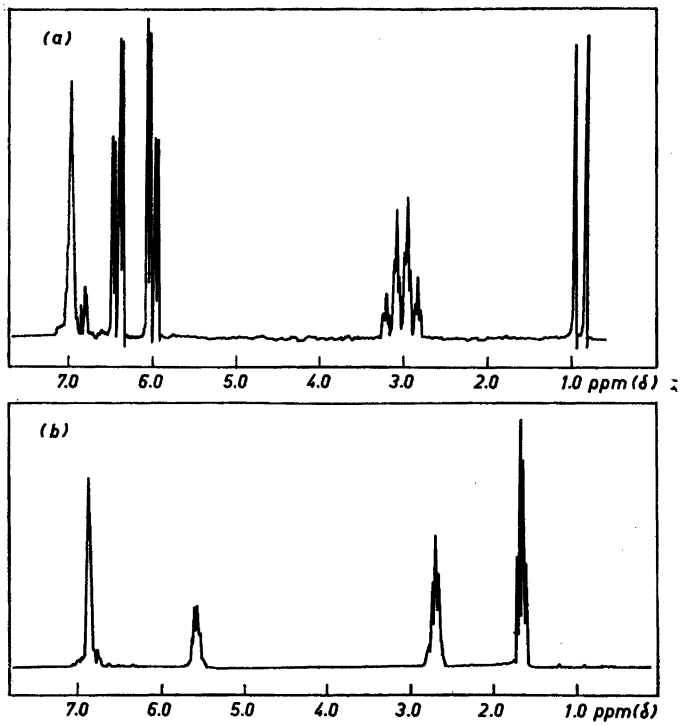


Fig. 3. NMR-spectra of (a) 1-methylindene and (b) 3-methylindene. (The aromatic proton peaks in (a) and (b) and the methyl proton peak in (a) are recorded at lower spectrum amplitudes than the other signals).

tautomeric species. The method of least squares was used to obtain the best fitting of the experimental measurements to function (1). These operations were made on the Alwac-III E electronic computer at the Quantum Chemistry Group, Uppsala University. Logarithmic plots of the results of the rate measurements are given in Figs. 4—20, and a review of the pertinent data is presented in Table 1. The polarimetric measurements usually give fairly accurate rate constants (quadratic mean error about 3 %). However, the automatic registration of the peak-intensities in NMR spectra is less accurate and the uncertainty in the rate constants found by this method is therefore sometimes as high as 6 %.

DISCUSSION

The experiments performed in pyridine solution reveal several interesting features. Concerning 1-methylindene, the isomerization rate, as measured by the NMR-technique, is directly proportional to the base concentration (Fig. 4, [1,2]*). The rate of racemization, which is also proportional to the

* The numbers appearing in brackets in the following discussion refer to run-number in Table 1.

Table 1.

Run	Substance	Conc. of indene (M)	Technique	Temp. °C	Catalyst	Conc. of catalyst (M)	Solvent	$(k_1 + k_{-1})^* \times 10^2$ min^{-1}	$(k_2+k_{-2})^* \times 10^2$ l, $mole^{-1}$, min^{-1}	Fig.
1	I a	2.0	NMR	30°	TEA	0.257	pyridine	1.89±0.05	7.35	4
2	"	"	"	"	"	0.129	"	0.92±0.04	7.13	4
3	(+)−I a	0.1	Pol.	24.8°	"	0.351	"	1.98±0.03	5.64	5,23,24
4	"	"	"	24.9°	"	0.176	"	1.09±0.02	6.19	5
5	"	"	"	19.4°	"	0.351	"	1.48±0.04	4.22	23,24
6	"	"	"	29.8°	"	"	"	2.71±0.05	7.72	23,24
7	II a	1.0	NMR	30°	BUA	0.70	"	0.60±0.02	0.86	6
8	"	"	"	"	"	1.00	"	0.75±0.04	0.79	6,20
9	"	"	"	"	"	1.50	"	1.28±0.04	0.85	6
10	"	0.5	"	"	"	1.00	"	0.86±0.04	0.86	7,20
11	"	1.5	"	"	"	"	"	0.67±0.03	0.67	20
12	"	2.0	"	"	"	"	"	0.55±0.03	0.55	7,20
13	(−)−II a	0.1	Pol.	"	"	1.00	"	0.92±0.02	0.92	8,20
14	"	"	"	"	"	2.00	"	2.23±0.05	1.12	8
15	"	0.05	"	25°	"	1.00	"	0.68±0.05	0.68	
16	(−)IIa⇌(+)IIb°	"	"	"	"	"	"	$(2.32\pm0.09)\times10^{-2}$	2.32×10^{-2}	9
17	I a	2.0	NMR	30°	DABCO	0.0142	"	2.03±0.09	143	10
18	"	"	"	"	"	0.00709	"	0.95±0.04	134	10
19	(+)I a	0.1	Pol.	"	"	0.0198	"	3.17±0.07	160	11
20	II a	1.0	NMR	"	"	0.402	"	1.20±0.04	2.99	12
21	(−)II a	0.1	Pol.	"	"	0.497	"	1.66±0.08	3.34	11
22	III a	1.5	NMR	"	"	0.359	"	0.70±0.02	1.95	12
23	(+)III a	0.1	Pol.	"	"	0.494	"	1.03±0.03	2.09	11
24	I a	2.0	NMR	"	TEA	0.052	DMSO	1.50±0.08	28.9	13
25	(+)I a	0.1	Pol.	"	"	0.071	"	2.71±0.04	38.2	14
26	III a	1.5	NMR	"	t.BuOK	0.0261	tert-BuOH	2.48±0.09	95.0	15
27	(+)III a	0.1	Pol.	"	"	0.0360	"	43.2±0.9	1200	16
28	I a	2.0	NMR	"	rac.PEA	0.274	pyridine	1.01±0.03	3.69	17
29	(+)I a	0.1	Pol.	25°	(+)PEA	0.392	"	1.20±0.03	3.06	18
30	"	"	"	"	(−)PEA	"	"	1.19±0.03	3.04	18
31	"	"	"	"	rac.PEA	0.397	"	1.21±0.03	3.05	18
32	"	"	"	30°	"	0.390	"	1.62±0.03	4.15	19

*) k_{-1} and $k_{-2} \approx 0$ in runs 1−6, 17−19, 22−32; $k_2 = k_1/[\text{Base}]$, $k_{-2} = k_{-1}/[\text{Base}]$.
o) Slow racemization of (II a) and (II b)

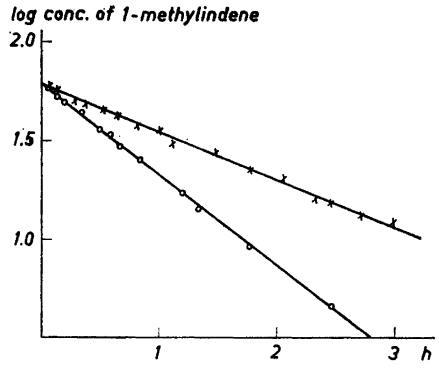


Fig 4. Rate of isomerization of 1-methylindene to 3-methylindene at different base concentrations: ×, 0.129 M TEA; O, 0.257 M TEA. (30°).

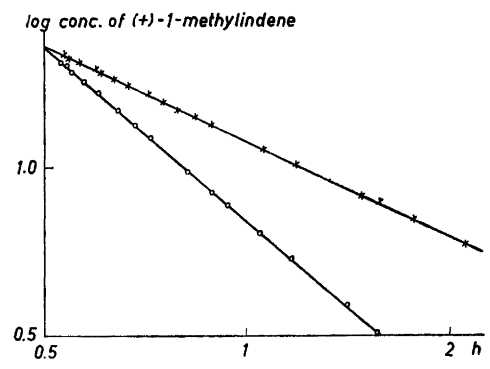


Fig. 5. Rate of racemization of (+)-1-methylindene at different base concentrations: ×, 0.176 M TEA; O, 0.351 M TEA. (25°).

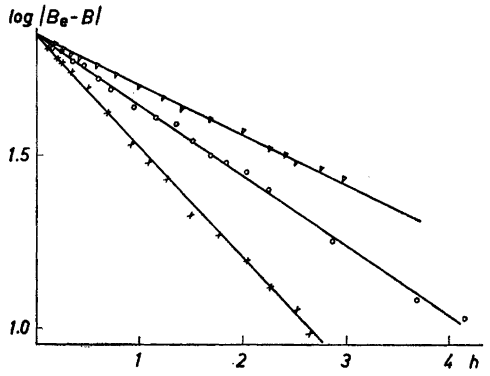


Fig. 6. Rate of isomerization of 1-methyl-3-isopropylindene (A) to 1-isopropyl-3-3-methylindene (B) at different base concentrations: ▽, 0.70 M BUA; ○, 1.00 M BUA; ×, 1.50 M BUA. (30°). Concentration of (B) at equilibrium = B_e.

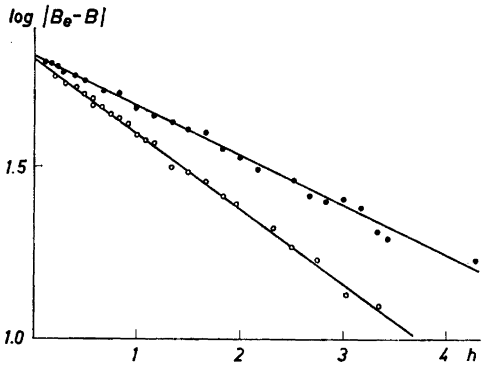


Fig. 7. Rate of isomerization of 1-methyl-3-isopropylindene (A) to 1-isopropyl-3-methylindene (B) at different indene concentrations: ●, 2.00 M (A); ○, 0.50 M (A). (30°C). Concentration of (B) at equilibrium = B_e.

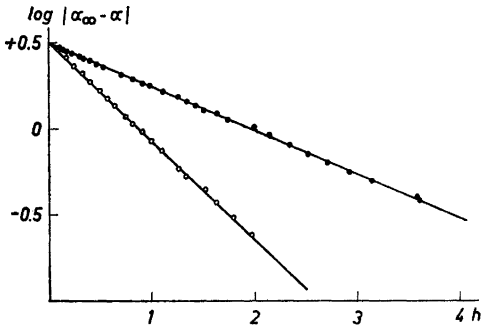


Fig. 8. Rate of isomerization of (−)-1-methyl-3-isopropylindene to (+)-1-isopropyl-3-methylindene at different base concentrations: ●, 1,00 M BUA; ○, 2.00 M BUA. (30°).

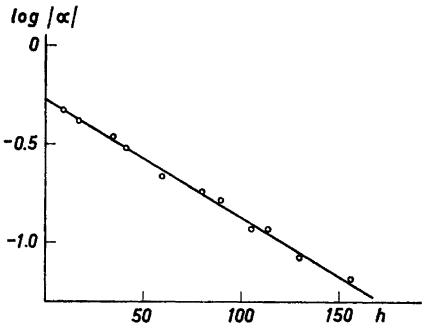


Fig. 9. Rate of racemization of (+)-methyl-isopropylindene with BUA as catalyst at 25°C.

catalyst concentration, is furthermore approximately equal to the isomerization rate (Fig. 5, [3,4]). This observation is not consistent with a stepwise mechanism, involving the formation of a mesomeric carbanion which is subsequently protonated by the conjugate acid of the basic catalyst. Protonation of the methyl-indenyl anion is unlikely to occur exclusively in the unsubstituted position. A concerted mechanism can be excluded since the reaction medium contains no protonating agents which can attack the indene simultaneously with the base. It should be remembered that the amines used as catalysts are all comparatively weak bases ($pK_a < 11$), thus excluding any appreciable predissociation of the indenes (pK_a of indene is 21). The

rearrangement was also studied under similar conditions but with 5.5 mole/litre of D_2O added to the reaction medium. In this case a negligible amount of deuterium was incorporated into the indene system during the isomerization time. Thus, D_2O cannot act as a deuterating agent, which also excludes the possibility that a second indene molecule, a much weaker acid than D_2O, is involved in the activated complex as a protonating species. The unimportance of free BH^+ ions (B = catalyzing base) in the rate determining step is also obvious, since hydrogen exchange would be expected to take place between D_2O and BH^+.

These considerations lead us to propose that the tautomeric proton-transfer is intramolecular in the sense that the proton in the 1-position of (Ia) is identical with the proton occurring in the rearranged product (Ib). Thus, it is possible that the rearrangement is also stereospecific and, in order to test this hypothesis, we have investigated the disubstituted indenes (II)

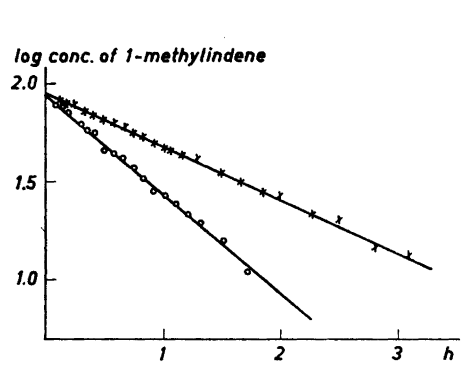


Fig. 10. Rate of isomerization of 1-methylindene to 3-methylindene at different base concentrations; ×, 0.709×10^{-2} M DABCO O, 1.42×10^{-2} M DABCO. (30°C).

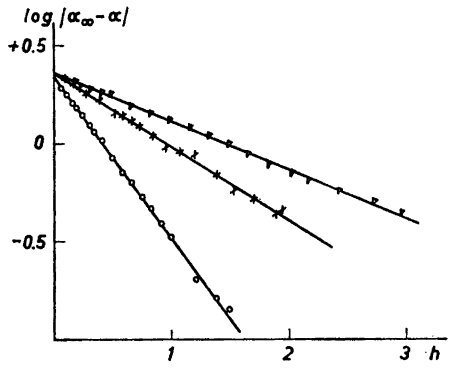


Fig. 11. Rate of isomerization of ▽, (+)-1-methyl-3-*tert*-butylindene to (−)-1-*tert*-butyl-3-methylindene; ×, (−)-1-methyl-3-isopropylindene to (+)-1-isopropyl-3-methylindene; O, (+)-1-methylindene to 3-methylindene, with DABCO as catalyst (30°C).

and (III). As briefly reported earlier,[2] we found in fact that (−)-IIa isomerized to (+)-IIb, with almost complete stereospecificity. The isomerization rates (IIa → IIb and IIIa → IIIb) revealed the same characteristics as the isomerization Ia → Ib with respect to the variation of base concentration (Figs. 6, 8, 11, 12 [7—9, 13, 14, 20—23]). However, we found that TEA only catalyzed the rearrangement at elevated temperatures, and we therefore used BUA and DABCO, which we found to be suitable catalysts at 30°C. In the rearrangement of 1-methylindene, DABCO was found to be about 20 times more effective than TEA (Figs. 4, 10 [1, 17]). A factor of two is statistically expected. The pK_a of DABCO (8.70) is considerably lower than that of TEA, so that the great difference in the catalytic effect is certainly

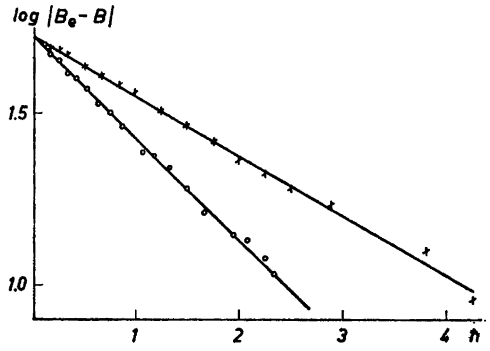


Fig. 12. Rate of isomerization of; ×, 1-methyl-3-*tert*-butylindene to 1-*tert*-butyl-3-methylindene and O, 1-methyl-3-isopropylindene to 1-isopropyl-3-methylindene with DABCO as catalyst (30°C).

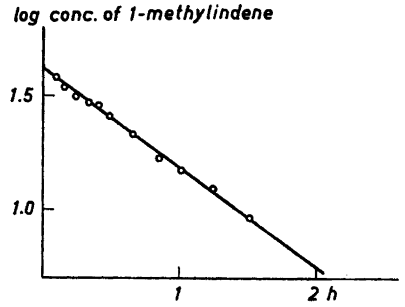


Fig. 13. Rate of isomerization of 1-methylindene to 3-methylindene with TEA as catalyst in DMSO (30°C).

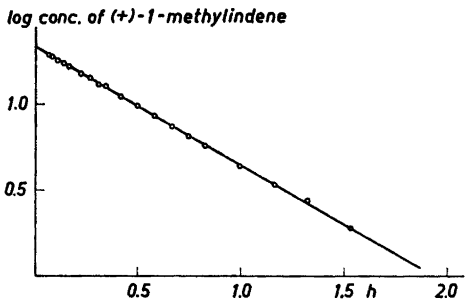


Fig. 14. Rate of racemization of (+)-1-methylindene with TEA as catalyst in DMSO (30°C).

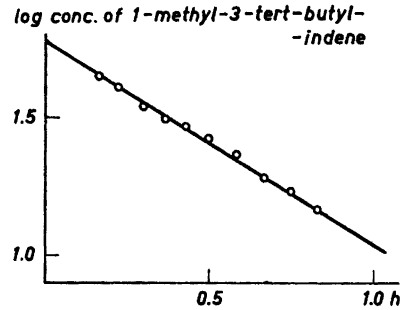


Fig. 15. Rate of isomerization of 1-methyl-3-*tert*-butylindene to 1-*tert*-butyl-3-methylindene with potassium *tert*-butoxide as catalyst in *tert*-butanol (30°C).

due to the rigidity of the bicyclic ring system. Steric hindrance in the attack on the indene molecule is thus decreased. The greater catalytic effect of BUA as compared to TEA is explainable by the presence of two hydrogen atoms instead of the bulky ethyl groups on the nitrogen.

An accurate comparison of the isomerization rate (NMR-technique) and the rate of change in optical rotatory power is desirable. Since the polarimetric measurements were made at an indene concentration of 0.1 mole/litre and the NMR-measurements were most conveniently run at 2 moles/litre of indene, a small difference in the character of the reaction medium cannot be excluded. The dependence of the specific reaction rate on the indene concentration was therefore studied. The results (Fig. 7, [8, 10—12]) show that the isomerization rate constant is slightly increased with decreased concentration of the indene. By extrapolation of the NMR-results to a concentration of

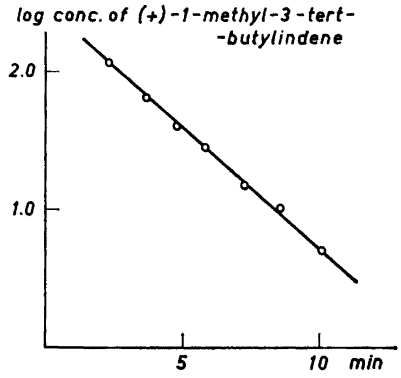


Fig. 16. Rate of racemization of (+)-1-methyl-3-*tert*-butylindene with potassium *tert*-butoxide as catalyst in *tert*-butanol (30°C).

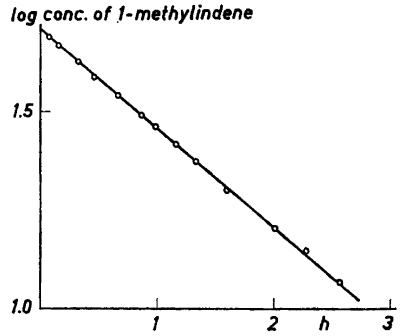


Fig. 17. Rate of isomerization if 1-methylindene to 3-methylindene with racemic PEA as catalyst (30°C).

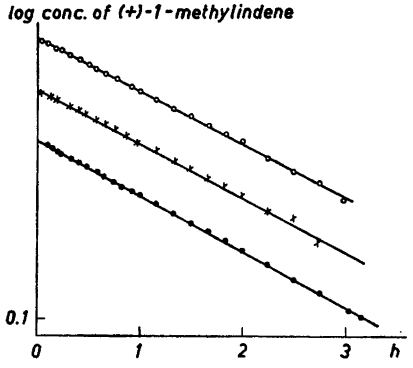


Fig. 18. Rate of racemization of (+)-1-methylindene with: O, (−)-PEA; ×, (+)-PEA; ●, rac. PEA as catalyst (25°C). (The curves are displaced parallelly along the ordinate).

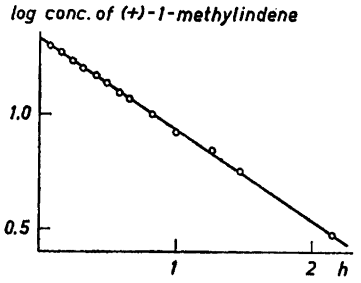


Fig. 19. Rate of racemization of (+)-1-methylindene with racemic PEA as catalyst at 30°C.

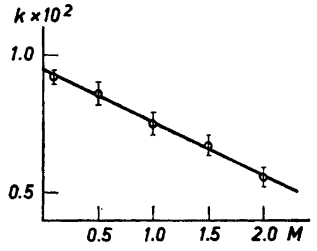


Fig. 20. Plot of $k \times 10^2$ against concentration of 1-methyl-3-isopropylindene (30°C). The quadratic mean errors are marked in the plot.

0.1 mole/litre (Fig. 20) of indene, the constants found by the different methods are in very good agreement. This fact, and the observation that the optical rotation asymptotically approaches a final value with an opposite sign to the initial reading, proves the very high degree of stereospecificity in this proton transfer. For example, in the rearrangement of (IIIa) with DABCO as catalyst (Fig. 11, [23]), no change in the final rotation was observed over a period of three weeks. However, a slow racemization took place in the system IIa $\rightleftharpoons$ IIb (80 % of IIb at equilibrium). The rate of this slow racemization (Fig. 9, [15, 16]) is of such a small magnitude compared to the isomerization rate, that it can be neglected in the evaluation of the rearrangement rate constants.

The absolute configurations of the starting materials (Ia-IIIa) are known.[5] However, we have not yet established the absolute configurations of IIb and IIIb, but, in view of the intramolecular nature of the proton transfer, it seems highly probable that they have opposite configurations to IIa and IIIa (Fig. 21). We therefore propose the reaction mechanism illustrated

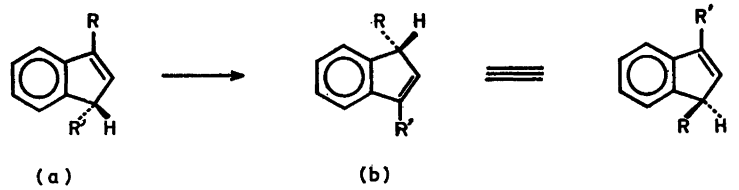


Fig. 21.

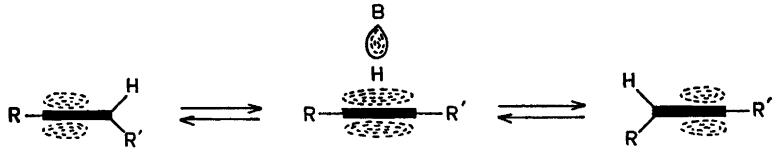


Fig. 22.

in Fig. 22, where the molecules are viewed in the plane of the aromatic ring system. The activated complex may be imagined as a π-complex or an ion pair with a proton held between the π-electron cloud of the aromatic system and the lone pair of the base.

Activated complexes, as proposed in Fig. 22 containing optical antipodes of the catalyzing base, would on fact be diastereomers and thus possess different free energies. It is difficult to predict if this difference is sufficiently great to make it possible to observe any difference in the reaction rates when the (+)- and (−)- forms of the base, respectively, are used as catalysts. We have hitherto only studied the catalytic effect of the antipodes of α-phenylethylamine (Fig. 18, [29—31]) and in this case no difference in reaction rates was observed. We plan to investigate this point further using more selective bases.

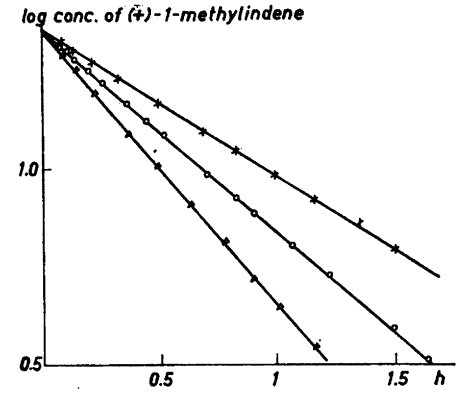


Fig. 23. Rate of racemization of (+)-1-methylindene at different temperatures: ×, 19.4°C; O, 24.8°C; △, 29.8°C.

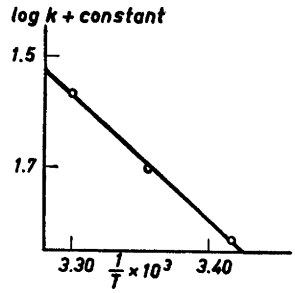


Fig. 24. Arrhenius plot of log k against $1/T \times 10^3$ for the racemization of (+)-1-methylindene.

The rates of racemization of 1-methylindene in pyridine solution were measured at different temperatures (Fig. 23, [3, 5, 6]) and, from the Arrhenius plot (Fig. 24), we found $\Delta H^{\ddagger} = 9.9$ kcal, mole^{-1}, and $\Delta S^{\ddagger} = -0.039$ kcal. degree^{-1} mole^{-1}. Further studies of the activation energies are in progress.

Pyridine seems to be a suitable solvent for stereospecific proton transfer. In DMSO, for example, the racemization occurs at a comparable rate to the rate of isomerization of (II a) (Fig. 25). In the case of 1-methylindene we

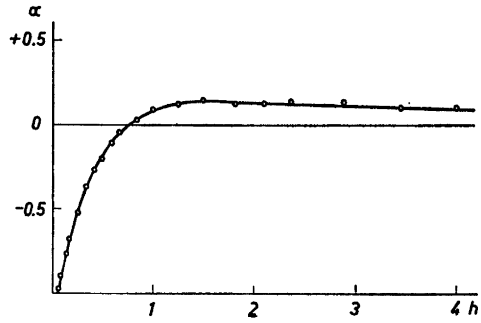


Fig. 25. Plot of rotation against time for the BUA-catalyzed isomerization of (−)-1-methyl-3-isopropylindene in DMSO (30°C).

observed an appreciable difference in the racemization rate as compared to the isomerization rate in contrast to the observations in pyridine solution (Figs. 13, 14, [24, 25]). This also clearly indicates the incomplete stereospecificity in DMSO-solution (without a catalyst no rearrangement occurs). It is possible that DMSO causes partial dissociation of the ion pair, leading to reduced stereospecificity.

A completely different situation was encountered when potassium *tert*-butoxide was used as a catalyst in *tert*-butanol solution. In this case the

racemization rate was found to be approximately ten times faster than the isomerization rate (Figs. 15, 16, [26, 27]). It is difficult to interpret these results with certainty, but several explanations are possible. A step-wise mechanism is consistent with the observations, since protonation of the free anion would preferably occur on the methyl-substituted carbon atom for steric reasons. It is also possible that the racemization results from a simultaneous attack of *tert*-butoxide and *tert*-butanol at the centre of asymmetry. For a more extensive study of the effects of various solvents on the stereochemistry of carbanions we refer to the excellent work of Cram.[6,7] Partial intramolecular proton transfer in a simple allylic system has recently been found by Cram and Uyeda.[8] However, our recent preliminary report [2] described the first example of a stereospecific tautomeric rearrangement and the results presented in the present paper provide further proof for the existence of such a mechanism.

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