

Base- and Acid-catalyzed Prototropic Rearrangements of 1-Methyl-2-(*N*-piperidyl)indene

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The 1,3-tautomerization of an amino-substituted indene I has been investigated by using basic or acidic catalysts in pyridine solution. Compared to 1,2-dialkylsubstituted indenenes the isomerization rate found for I is considerably decreased when basic catalysts (DABCO or quinuclidine) are used. This retarding effect, caused by the 2-nitrogen, is in agreement with acidity differences obtained by simple Hückel calculation. Alkylsubstituted indenenes do not undergo acid-catalyzed 1,3-isomerization. However, I rearranges rapidly in the presence of small amounts of strong acid due to the enamine character. Rate constants are given for the base- and acid-catalyzed isomerizations.

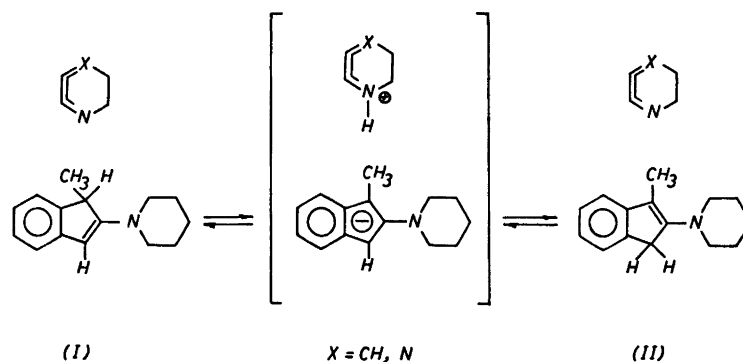
The alkylsubstituted indenenes have, by kinetic and stereochemical studies, been found to undergo base-catalyzed rearrangements, which proceed in a suprafacial mode under certain conditions.^{1,2} An alkyl substituent was found to decrease the rate constant for this reaction but the magnitude of this effect also depends on the nature of the catalyst.¹⁸ In connection with these studies of the 1,3-proton transfer reactions we wanted to investigate the influence on the rate of a nitrogen atom directly bonded to the carbon atom in the 2-position of the indene ring. Under similar conditions as those used in the indene studies, we have earlier reported that none or a very slow rearrangement could be observed using aliphatic amines as catalysts, like triethylamine.¹¹ Base-catalyzed 1,3-proton shifts in enamines have not been studied earlier but a carbanion mechanism has been proposed to account for the *cis-trans* isomerizations of aliphatic enamines in basic media.³ Furthermore, these compounds would be expected

to undergo acid-catalyzed rearrangement owing to their enamine structure. This behaviour of enamines is a well-documented fact,⁴ but no detailed investigation has yet been published. A few years ago Johnson mentioned that the presence of one thousandth percent of acid caused equilibration of substituted enamines in 5 min at room temperature.⁵ Apparently, the observed thermodynamic equilibrium must be established through an immonium structure possibly preceded by an *N*-protonated salt.^{4a}

RESULTS AND DISCUSSION

The present paper is limited to a study of the base-catalyzed and the acid-catalyzed tautomerizations of 1-methyl-2-(*N*-piperidyl)indene (I), (Scheme 1,3). Concerning the 1,2-dialkylsubstituted indenenes the thermodynamic equilibrium favours almost completely the 2,3-substituted isomer since an alkyl substituent at the double bond afforded a more stable form.¹⁸ In the case of isomeric enamines the thermodynamic ratio is determined by a balance between steric and electronic effects which affect the overlap between the nitrogen lone pair and the double bond.⁶ Thus we have found that the equilibrium constant between II and I (Scheme 1) is 0.41 ± 0.01 in pyridine solution.

We have studied the base-catalyzed proton transfer in pyridine, a protophilic solvent of moderate polarity, using effective catalysts like 1,4-diaza-bicyclo[2.2.2]octane (DABCO) and quinuclidine. These bases have been shown to be superior to aliphatic amines in prototropic



Scheme 1.

indene rearrangements owing to their rigidity and consequent lower activation entropy.¹³ The reaction was found to follow the kinetics of a pseudo-first order reversible reaction, the observed rate constant being proportional to the base concentration within the limits of experimental error. No significant isomerization could be noticed in the absence of base in a parallel experiment showing that pyridine is too weak a base to be responsible for any catalytic effect. The phenomenological rate constant k_1 for the forward reaction $I \xrightleftharpoons[k_{-1}]{k_1} II$

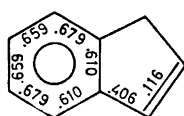
was found at unit base concentration to be about $0.49 \times 10^{-3} \text{ l mol}^{-1} \text{ min}^{-1}$ and $0.12 \times 10^{-3} \text{ l mol}^{-1} \text{ min}^{-1}$ for quinuclidine and DABCO,

respectively, at 35°C (cf. Table 1). Including the statistical factor this shows that quinuclidine is about eight times more effective than DABCO, a ratio close to that found for the rearrangement of 1-methylindene.¹³ Substitution of the hydrogen in the 2-position by the *N*-piperidyl moiety causes a very large decrease in the isomerization rate. A slower rate is also observed for 1,2-dimethylindene (Table 2) as well as for other 1,2-dialkylsubstituted indenenes, but the difference between 1,2-dimethyl- and 1-methyl-2-ethylindene is small.¹⁸ Thus we conclude that in determining the exceptionally low rate for I the conjugation between the nitrogen lone pair and the indene π -system plays a major role. A Hückel π -electron energy

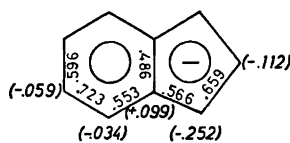
Table 1. Rate constants for the base- and acid-catalyzed isomerization of 1-methyl-2-(*N*-piperidyl)indene (I) in pyridine. Concentration of substrate: 2 M.

$I \xrightleftharpoons[k_{-1}]{k_1} II$ Equilibrium constant: 0.41 ± 0.01 .

Temp. (°C)	Catalyst	Conc. (M)	$(k_1 + k_{-1}) \times 10^3$ (min ⁻¹)	$(k_1 + k_{-1}) \times 10^3$ (catalyst) (l mol ⁻¹ min ⁻¹)	$k_1 \times 10^3$ (catalyst) (l mol ⁻¹ min ⁻¹)
35.0	DABCO	0.500	0.212 ± 0.005	0.424 ± 0.010	0.12 ± 0.01
35.0	DABCO	0.750	0.315 ± 0.009	0.420 ± 0.012	0.12 ± 0.01
35.0	DABCO	1.00	0.398 ± 0.007	0.398 ± 0.007	0.12 ± 0.01
35.0	Quinuclidine	0.150	0.252 ± 0.005	1.68 ± 0.03	0.49 ± 0.02
35.0	Quinuclidine	0.200	0.335 ± 0.004	1.68 ± 0.02	0.49 ± 0.02
35.0	Quinuclidine	0.300	0.497 ± 0.010	1.66 ± 0.04	0.48 ± 0.02
27.0	Perchlorate	0.00040	0.290 ± 0.008	725 ± 20	211 ± 10
27.0	Perchlorate	0.00060	0.414 ± 0.007	690 ± 12	201 ± 7
27.0	Perchlorate	0.00100	0.703 ± 0.019	703 ± 19	204 ± 9

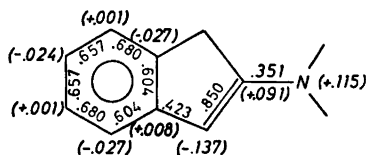


$$E_{\pi} = 10.424$$

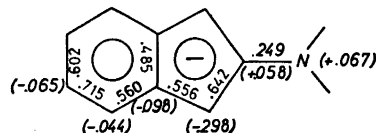


$$E_{\pi} = 12.171$$

$$\Delta E_{\pi}(\text{indene}) = 1.747 \Rightarrow pK_A \approx 21$$



$$E_{\pi} = 13.702$$

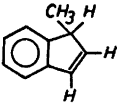
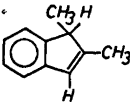
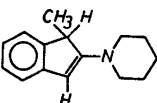


$$E_{\pi} = 15.367$$

$$\Delta E_{\pi}(\text{aminoindene}) = 1.665 \Rightarrow pK_A \approx 23$$

Scheme 2.

Table 2. Isomerization rate constants using DABCO as catalyst at 35°C in pyridine.

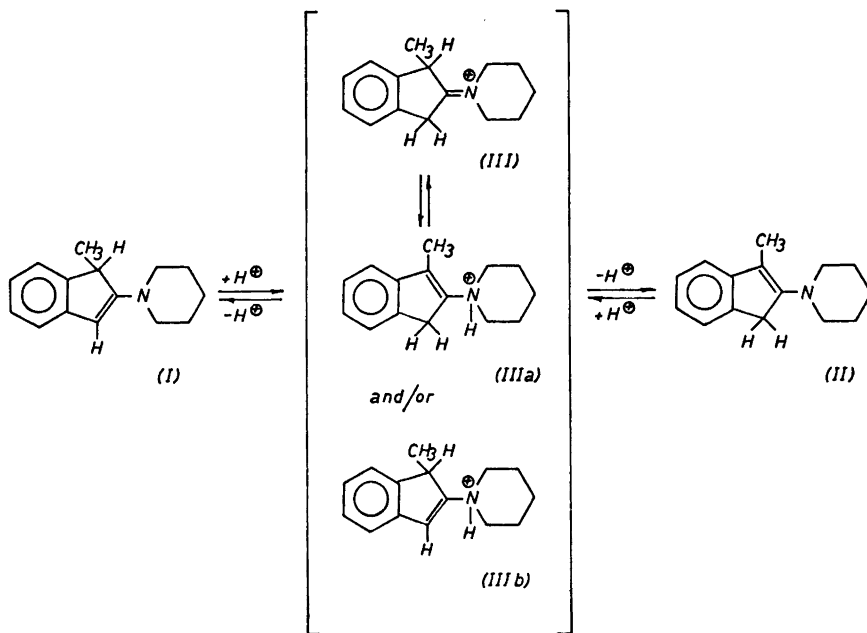
Compound	$k_1 \times 10^3$ l mole ⁻¹ min ⁻¹
	216 ^a
	29 ^b
	0.12

^a From Ref. 1j. ^b Estimated from rearrangement at 30°C. See Ref. 1g.

calculation (Scheme 2) predicts that 2-aminoindenes should be less acidic than indene by about 2 pK_A units. A lower acidity should, of course, result in a decreased isomerization rate due to correlation between the kinetic and

thermodynamic acidity.^{7a} The acidity of 2-aminoindene was estimated using the correlation given by Streitwieser^{7b} between pK_A and the difference in Hückel total π -energy between the carbon acid and the corresponding anion. We used the same parameters in our calculation as recommended earlier⁸ *i.e.* $h_{\text{N}} = 1.5$ and $k_{\text{CN}} = 0.8$. This implies, of course, that we have assumed maximum overlap of the nitrogen lone pair and the π -system in the indene ring. Thus our calculation gives an upper limit for the effect of the nitrogen atom in the π -electron system. Scheme 2 also shows the net charges and the bond orders in our systems. In Scheme 1 we have proposed that the rearrangement between I and II proceeds *via* an ion pair in analogy with the mechanisms put forward for the other 1,3-prototropic reactions.^{1,2} An interesting question in this connection is whether there exists a discrete ion pair in which the substituted ammonium ion is situated above the nitrogen atom in the piperidine ring and whether an internal rotation within such an ion pair can be affected by rotation around the C₂-N bond. These questions cannot be answered since we have not as yet been able to prepare optically active substrates.

The acid-catalyzed isomerization between I and II is represented in Scheme 3. The reac-



Scheme 3.

tion was initiated by addition of a small amount (*ca.* 10^{-3} M) of the perchlorate salt III. Thus the intermediate III in the reaction also serves as the catalyst. As can be seen from Table 1, the reaction is strictly pseudo-first order within the limits of experimental error. The rate is remarkably rapid k_1 being about 200×10^{-3} l mol $^{-1}$ min $^{-1}$ at unit catalyst concentration. Thus very low catalyst concentrations must be used, but in pyridine the reaction is slow enough to permit a usual kinetic study probably due to the fact that pyridine interacts through hydrogen bonding to the catalyst. A preliminary experiment using acid-free chloroform as a solvent, where such bonding cannot occur, gives a rearrangement rate about fifty times as great as in pyridine solution. The *N*-protonated enamines IIIa and/or IIIb are possibly involved in the reaction since *N*-protonation is presumably favoured kinetically compared to *C*-protonation in our system.¹² However, the *C*-protonated form III is thermodynamically more stable than (IIIa)/(IIIb).

EXPERIMENTAL

All PMR-work was performed on a JEOL

C-60 HL instrument. The mass spectrum was obtained with an LKB 9000 mass spectrometer. The GC-analyses were made on a PYE M64 with a flame ionization detector and nitrogen as the carrier gas.

1-Methyl-2-(*N*-piperidyl)indene (I). The contaminated 1-methyl-2-(*N*-piperidyl)indene (4 % of II) was prepared as earlier described.¹² To a solution of 3.99 g of this enamine (0.0187 mol) in 30 ml methanol a small amount of triethylamine was added to avoid fast isomerization. Crystallization at 0°C overnight yielded 1.22 g pure I (0.0057 mol, 19 % from 1-methylindan-2-one) as colourless large prisms, m.p. 33.0–33.5°C. PMR spectrum in tetrachloroethylene was free from any traces of isomeric impurities (Fig. 1).

The perchlorate salt (III). The perchlorate salt was synthesized in analogy with a method reported by Blomquist and Moriconi.⁹ To an ethereal solution of 2.0 g of 1-methyl-2-(*N*-piperidyl)indene (0.0094 mol) a mixture of 25 ml 70 % perchloric acid and 25 ml absolute ethanol was added to the blue colour of Congo red paper (pH < 3). The immonium salt precipitates immediately. One recrystallization from acetone gave colourless needles of III. Yield: 1.8 g (61 % 0.0057 mol) m.p. 156–158°C.

Solvent, substrate and catalysts. Pyridine (Mallinckrodt analytical reagent) was kept over potassium hydroxide for two weeks before being fractionally distilled¹⁰ and then, finally, stored over calcium hydride under nitrogen

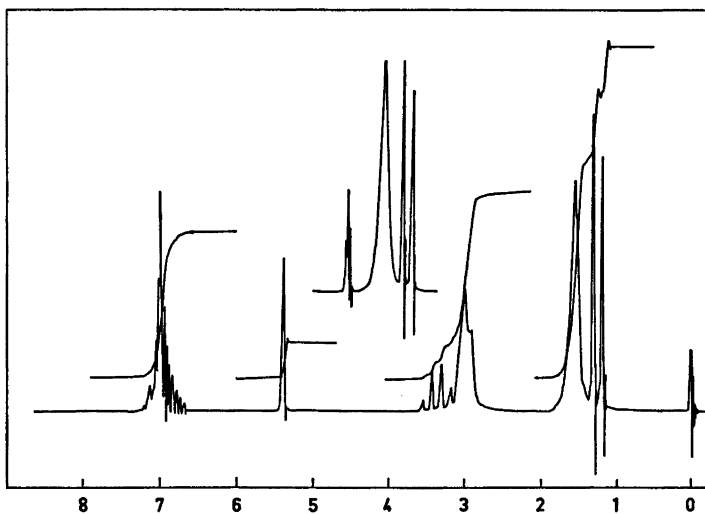


Fig. 1. PMR spectrum of pure 1-methyl-2-(*N*-piperidyl)-indene (I) in tetrachloroethylene with TMS as internal reference. Concentration: 2 M. Temperature: 27°C. (Compare the inset part of the spectrum from the thermodynamic mixture.)

atmosphere. GLC-analysis of the pure isomer I (1 % Apiezon L on Chromosorb W: 300 cm × 6 mm: Det. 180°C/col. 150°C/inj. 210°C. 1 % SE 30: 180 cm × 6 mm: Det. 180°C/col. 150°C/inj. 180°C. 1 % XE 60: 180 cm × 6 mm: Det. 140°C/col. 120°C/inj. 180°C) shows at least 99.5 % purity except for isomeric contamination, since attempts to resolve the two isomers have been unsuccessful. DABCO (Kebo *purum*) was recrystallized from hexane. Quinuclidine was generated from its hydrochloride (Fluka) and purified by sublimation.

Kinetics. All glassware including NMR-tubes, was dried at 150°C for at least 16 h. Pure I and the desired amount of the catalyst were weighed in a 5 ml volumetric flask and were then diluted with pyridine. Concerning the base-catalyzed runs, the rearrangement was performed at a constant temperature ($35.0 \pm 0.1^\circ\text{C}$) in a thermostat (Colora Ultra-Thermostat Type MB). From the reaction solution 0.5 ml aliquots were drawn and the appropriate PMR-signal measured.

In the acid-catalyzed runs a desired volume was drawn from a 100 ml 0.01 M solution of III in pyridine and injected to a given solution volume of I. From this mixture a 1 ml sample was withdrawn and filled into an NMR-tube under nitrogen. After careful sealing of the tube, the isomerization was performed at 27.0°C in the PMR-probe. The estimated errors in temperature measurements were $\pm 0.3^\circ\text{C}$. The inaccuracies in weighing (± 0.0001 g) and pipetting are considered to be small compared to those involved in the kinetic parameters and are therefore neglected in Table 1.

The rearrangement was followed by PMR-technique by measuring the increase in intensity of the 3-methyl proton peak at approximately 2 ppm. No significant rearrangement could be observed without any added catalyst. The equilibrium constant was determined by integration over the vinylic proton signal from the least substituted isomer and over the 3-methyl peak from the most substituted one. No change in the equilibrium proportions could be observed in the different runs. A least squares program PROGAEXP¹¹ has been used to evaluate the rate parameters. The residuals were randomly generated. The accuracy of the estimated values was set to two times the standard deviation ($\pm 2\sigma$).

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REFERENCES

1. a. Bergson, G. and Weidler, A.-M. *Acta Chem. Scand.* 17 (1963) 862; b. Bergson, G. and Weidler, A.-M. *Ibid.* 17 (1963) 1798; c. Weidler, A.-M. *Ibid.* 17 (1963) 2724; d. Weidler, A.-M. and Bergson, G. *Ibid.* 18 (1964) 1484; e. Weidler, A.-M. and Bergson, G. *Ibid.* 18 (1964) 1487; f. Bergson, G. and Weidler, A.-M. *Ibid.* 18 (1964) 1498; g. Plénat, F. and Bergson, G. *Ark. Kemi* 25 (1965) 109; h. Ohlsson, L., Wallmark, I. and Bergson, G. *Acta Chem. Scand.* 20 (1966) 750; i. Bergson, G. and Ohlsson, L. *Ibid.* 21 (1967) 1393; j. Ohlsson, L., Wold,

- S. and Bergson, G. *Ark. Kemi* 29 (1968) 351; k. Sörlin, G. and Bergson, G. *Ibid.* 29 (1968) 593; l. Bergson, G. *Acta Chem. Scand.* 22 (1968) 702; m. Bergson, G. and Ohlsson, L. *Ibid.* 23 (1969) 2175; n. Edlund, U. and Bergson, G. *Ibid.* 25 (1971) 3625; o. Ahlberg, P. *Chem. Scr.* 4 (1973) 33; p. Ahlberg, P. *Ibid.* 3 (1973) 183; q. Ahlberg, P. and Ladhar, F. *Ibid.* 1 (1971) 31.
2. a. Almy, J., Uyeda, R. T. and Cram, D. J. *J. Amer. Chem. Soc.* 89 (1967) 6768; b. Almy, J. and Cram, D. J. *Ibid.* 91 (1969) 4459; c. Almy, J. and Cram, D. J. *Ibid.* 92 (1970) 4316; d. Almy, J., Garwood, C. and Cram, D. J. *Ibid.* 92 (1970) 4321; e. Almy, J., Hoffman, D. H., Chu, C. C. and Cram, D. J. *Ibid.* 95 (1973) 1185.
 3. Rivière, M. and Lattes, A. *Bull. Soc. Chim. Fr.* 2 (1972) 730.
 4. a. Mazarquil, H. and Lattes, A. *Tetrahedron Lett.* (1971) 975; b. Pocar, D., Stradi, R. and Bianchetti, G. *Gazz. Chim. Ital.* 100 (1970) 1135.
 5. Johnson, F. *Int. Symp. on Enamine Chemistry*, Salford, 15–16 July 1969.
 6. Gurowitz, W. D. and Joseph, M. A. *J. Org. Chem.* 32 (1967) 3289.
 7. a. Cram, D. J. *Fundamentals of Carbanion Chemistry*, Academic, New York 1965; b. Streitwieser, A., Jr. *Molecular Orbital Theory*, Wiley, New York, London 1961, p. 135.
 8. Pollmann, M. J. M., Reus, H. R., Pandit, U. K. and Huisman, H. O. *Rec. Trav. Chim. Pays-Bas* 89 (1970) 929.
 9. Blomquist, A. T. and Moriconi, E. J. *J. Org. Chem.* 26 (1961) 3761.
 10. Müller, R., Griengl, F. and Mollang, J. *Monatsh. Chem.* 47 (1926) 88.
 11. Wold, S. *Acta Chem. Scand.* 21 (1967) 1986.

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