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Kinetic and Deuterium-labeling Studies of 2-Aminopyridine Catalyzed 1,3-Proton Transfers

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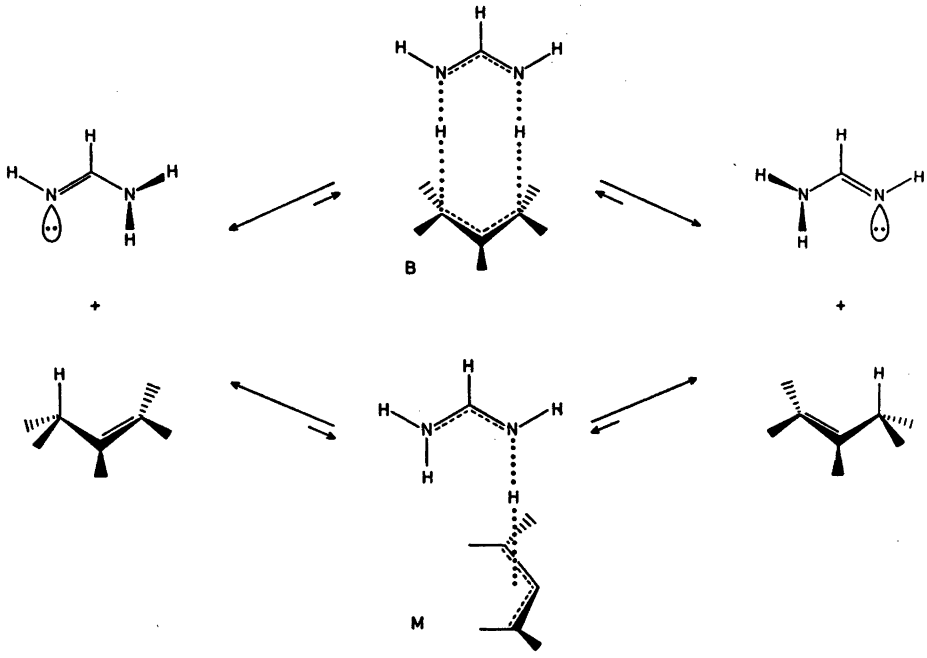
2-Aminopyridine (*1-h*) and *N,N*-dideuterio-2-aminopyridine (*1-d*) have been studied as catalysts for some, 1,3-proton transfer reactions. *β*-9-Fluorenylstyrene (*2*) has been rearranged to 9-*β*-phenylethylidenefluorene (*4*) and 1-methylindene (*3-h*) and 1-deuterio-1-methylindene (*3-d*) to 3-methylindene (*5-h*) and 1-deuterio-3-methylindene (*5-d*), respectively. All rearrangements were carried out in benzene as solvent. Compound *1*, which is a potential bifunctional catalyst, is shown not to act in a concerted bifunctional manner but rather like a monofunctional catalyst. This conclusion is based on the observed absence of H−D exchange in the reactions. The activation parameters, the isotope effect and rate dependence of the base concentration have been measured for the 2-aminopyridine (*1-h*) catalyzed rearrangement of 1-methylindene (*3-h*).

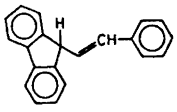
Recently we found in CNDO/2 calculations of the potential energy surfaces for formamidine catalyzed 1,3-proton transfers in propene (Scheme 1) that the bifunctional (B) route is strongly favoured over the monofunctional (M) one.[1,2]

In the present experimental investigation the catalytic mechanism of 2-aminopyridine (*1*),



Scheme 1.

which contains an unsymmetrical structural element resembling formamidine, has been studied in some 1,3-proton transfer reactions. The substrates used in this work contained structural elements related to propene, namely β-9-fluorenylstyrene (*2*), 1-methylindene (*3-h*) and 1-deuterio-1-methylindene (*3-d*). The rearrangement products were 9-β-phenylethylidenefluorene (*4*), 3-methylindene (*5-h*), and 1-deuterio-3-methylindene (*5-d*), respectively. All rearrangements were performed in benzene as solvent.



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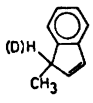
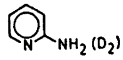
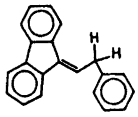


3-h(d)



1-h(d)



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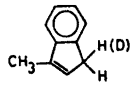


5-h(d)

Earlier we have reported some results of *N,N'*-di-*tert*-butylformamidine catalyzed rearrangements of 1-methyl-3-*tert*-butylindene to 3-methyl-1-*tert*-butylindene.[3] However, the mechanism of this amidine catalyzed rearrangement could not be elucidated due to the interference of a fast H−D exchange process. Presumably this exchange process became competitive with the rearrangement by steric hindrance. Such steric hindrance is avoided by using *1* as catalyst.

2-Aminopyridine (*1*) has been reported to be a bifunctional acid-base (tautomeric) catalyst for the mutarotation of the aldohexose tetramethylglucose (TMG) by Swain and Brown.[4a] However, this result has been questioned by Rony and Neff,[4b] who conclude that *1* is not to be considered a tautomeric catalyst of that reaction.

RESULTS AND DISCUSSION

If 2-aminopyridine (*1*) acts in a bifunctional manner, *i.e.* the catalysis takes place through a B-like transition state (Scheme 1), deuterium labeling in the proper positions of either substrate or catalyst would result in products where the deuterium is found in the base or the substrate, respectively (of structures *1* − *3*). This predicted experimental outcome of bifunctional catalysis is quite different from that expected if *1* is operating as a monofunctional catalyst, *i.e.* with an M-like transition state (Scheme 1). If other processes are not interfering with monofunctional catalysis, a deuterium labeled catalyst will stay labeled when operating on an unlabeled substrate and *vice versa*; *i.e.*, the rearrangement is intramolecular.[5a,b]

Of course, more complex experimental results could be found than the two extreme types suggested above if other reactions are interfering.[5b]

Molecule *1* exists in tautomeric equilibrium with *6* (Scheme 2).

1-h(d) *6-h(d)*

Scheme 2.

This equilibrium is reported to strongly favour *1*. The equilibrium constant (K_{taut}) was estimated to be 5×10^{-6} (at 21 °C, aqueous solution), which corresponds to $\Delta G_{taut} = 31$ kJ mol^{-1} (7.3 kcal mol^{-1}).[6] In each of *1* and *6* either one or both of the nitrogens could act as monofunctional catalytic centers. However, simple resonance theoretical arguments predict the iminonitrogens to be catalytically more active than primary amino-nitrogens. In Table 1 are summarized the experimental conditions as well as some of the results obtained.

In run 2 the reaction of *3-h* with *1-d* was allowed to proceed for $20 \times t_{1/2}$. The reaction products were isolated by a quench-extraction method and analyzed by ^{1}H NMR. The product was exclusively *5-h* and thus no significant deuterium incorporation was observed. Furthermore in run 5, *3-d* was rearranged with *1-h* in benzene and the product analyzed as above. No significant protium incorporation was observed by ^{1}H NMR. These results definitely exclude the concerted bifunctional mechanism of Scheme 1 as being responsible for the catalysis. Instead the results appear to favour the monofunctional mechanism.

Table 1. Rate and product data of 2-aminopyridine (*1*) catalyzed 1,3-proton transfers in benzene. Absolute temp. accuracy ±0.05 °C; relative temp. accuracy ±0.02 °C. Analytical methods: NMR (Run 1–5, 16–18), GLC (Run 6–15).

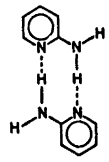
Run No.	Temp./ °C	Substrate	[Substrate]/ M[a]	Catalyst	[Catalyst]/ M[a]	k_{obs} / 10^{-6} s^{-1}	k_{obs}/(Catalyst] / 10^{-6} M^{-1} s^{-1}
1	55.00	*3-h*	0.305	*1-h*	0.968	45.0(36)	46.5(37)
2	55.00	*3-h*	0.329	*1-d*	1.196	—[b]	—[b]
3	55.00	*3-d*	0.327	*1-h*	0.998	10.6(9)	10.6(9)
4	55.00	*3-d*	0.326	*1-h*	0.981	10.3(9)	10.5(9)
5	55.00	*3-d*	0.299	*1-h*	0.911	—[c]	—[c]
6	55.00	*3-h*	0.309	*1-h*	0.976	45.4(10)	46.5(10)
7	55.00	*3-h*	0.313	*1-h*	0.552	22.4(4)	40.5(8)
8	55.00	*3-h*	0.308	*1-h*	0.255	9.00(18)	35.3(7)
9	55.00	*3-h*	0.306	*1-h*	0.123	4.05(8)	32.9(7)
10	55.00	*3-h*	0.305	*1-h*	0.062	1.96(4)	31.7(7)
11	55.00	*3-h*	0.303	*1-h*	0.032	1.00(2)	31.3(6)
12	55.00	*3-h*	0.302	*1-h*	0.016	0.490(8)	30.7(5)
13	75.00	*3-h*	0.105	*1-h*	0.504	80.9(13)	170.2(28)[d]
14	55.00	*3-h*	0.105	*1-h*	0.504	19.8(3)	40.7(6)[d]
15	35.00	*3-h*	0.105	*1-h*	0.504	4.08(8)	8.21(16)[d]
16	35.00	*2*	0.029	*1-h*	0.099	8.38	84.7[e]
17	55.00	*2*	0.044	*1-d*	1.30	—[b]	—[b]
18	35.00	*2*	0.032	*1-d*	0.101	7.62	75.4

[a] Reaction mixtures prepared at 23 °C. Catalyst and substrate conc. refer to this temperature. [b] No deuterium incorporation in product. [c] No protium incorporation in product. [d] The catalyst conc. used in the evaluation of the second order rate constant has been calculated at the running temperature using the benzene volume expansion coefficient $\beta = 1.15 \times 10^{-3}$ K^{-1}. [e] One point kinetics.

Why do these results contrast with those found with the theoretical methods mentioned in the introduction, where bifunctional catalysis was found to be strongly favoured? A possible reason could be that the chosen experimental model system deviates too much from our theoretical one. In the catalyst part of the model system the tautomeric equilibrium (Scheme 2) disfavours a bifunctional mechanism, since *6* is found to be substantially less than *1*. Furthermore, the substrate is more similar to cyclopentadiene than to propene, and it is also much more acidic ($pK_a \sim 20$) than propene ($pK_a = 35.5$).[7] These facts are expected to favour monofunctional rather than bifunctional catalysis.

In order to have a substrate more like propene, β-9-fluorenylstyrene (*2*) was prepared in the pure state. In run 17 compound *2* was rearranged to 9-β-phenylethylidenefluorene (*4*) by *1-d* in benzene. The rearrangement product was found to be exclusively *4*, and the ^{1}H NMR-spectrum revealed no significant incorporation of deuterium. This result seems to indicate that the catalysis of the rearrangement of this propene resembling, but highly acidic compound (*4*) is also of the monofunctional type.

Another reason for observing monofunctional catalysis would be that the catalyst is not a monomer like *1* or *6* but rather mainly a dimer (or polymer) like structure *8*.



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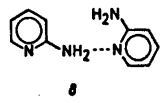

8

Of dimers *7* and *8* only *8* is predicted to be catalytically active through the use of the non-hydrogen bonded imino-nitrogen as catalytic center. The dimer *8* could be classified as a bifunctional catalyst and could be more active than the monomer *1*.

The rearrangement was in all kinetic runs found to be strictly pseudo first-order, *i.e.*

$$\text{rate} = k_{obs}\,[\text{substrate}] \quad (1)$$

If now monomeric as well as dimeric species (assumed to be in equilibrium with each other) are catalytically active, we find that

$$k_{obs} = k_2[M] + k_3K[M]^2 \quad (2)$$

where $K = [D]/[M]^2$, M = monomer and D = dimer, and k_2 is the bimolecular rate constant and k_3 the termolecular one. In order to get further information about the catalysis and the structure of the catalytic system, the rearrangement rate of *3-h* was studied as a function of the 2-aminopyridine concentration (runs 6 – 12). In Fig. 1 is plotted $k_{obs}/[1]$ *vs.* [*1*] using the assumption that the 2-aminopyridine is mainly monomeric. As seen in Fig. 1 the observations fall close to a straight line with non-zero slope. Using eqn. 2 and extrapolation to zero-[*1*] in Fig. 1 yields $k_2 = 30.6 \times 10^{-6}$ M^{-1} s^{-1} and the slope is identified as $k_3K = 15 \times 10^{-6}$ M^{-1} s^{-1}. These results indicate that at 0.5 M of *1* ca 20 % of the catalysis could take place in a termolecular fashion.

On the other hand if it is assumed that the 2-aminopyridine is present mainly in dimeric form, one would expect to observe a curve

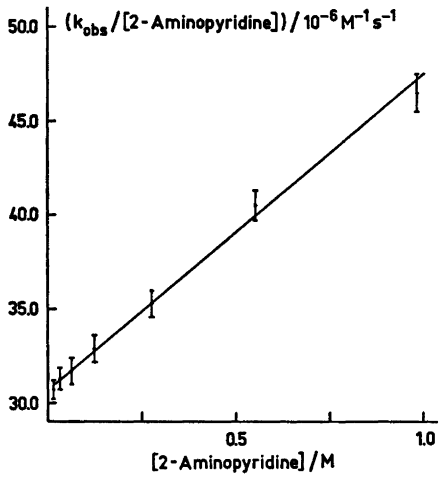

Fig. 1. $k_{obs}/[2\text{-aminopyridine}]$ from runs 6 – 12 in Table 1 plotted *vs.* [2-aminopyridine] (*cf.* eqn. 2).

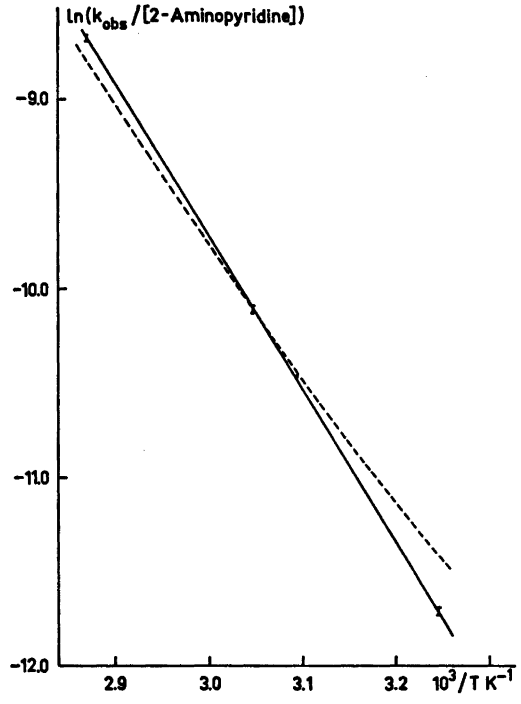

Fig. 2. $\ln(k_{obs}/[2\text{-aminopyridine}])$ *vs.* $1/T$ plots; ———, obtained experimentally (runs 13 – 15); - - -, simulated using assumptions given in the text.

with a [2-aminopyridine]-dependent slope and not a straight line. Since we have been working with quite large concentrations of *1*, we cannot exclude the possibility that a considerable catalyst medium effect could be a cause for the slope in Fig. 1. It has been inferred from freezing point depression measurements that 2-aminopyridine is mainly dimeric in benzene [8] in the concentration range covered by the present work. However, these results may be masked by possible effects of the medium. In order to avoid the influence of medium effects, but still get information about the relative importance of bimolecular and termolecular catalytic pathways, the temperature dependence of the rate of rearrangement was studied.

If it is assumed that ca 20 % of the catalysis is taking place with termolecular reactions and that the dimerization equilibrium ($2M \rightleftharpoons D$) is assumed to have a $\Delta S = -125.5$ J K^{-1}, mol^{-1} (−30 cal K^{-1}, mol^{-1}) and that the dimer and

the monomer have approximately the same activation entropy, the dashed line in Fig. 2 is simulated. This line is found to be significantly curved. However a good straight line is obtained experimentally, *i.e.* no significant curvature was observed (Fig. 2).

Thus it seems most likely that the catalysis either is made by monomeric *1* and that *1* is mainly monomeric or that the catalysis is carried out by a dimer and that *1* is mainly dimerized.

Using the first of these two alternatives we have calculated the activation parameters to be $\Delta G^{\ddagger}$(55 °C) = 108.215 ± 0.042 kJ mol^{-1} (25.864 ± 0.010 kcal mol^{-1}), $\Delta H^{\ddagger}$ = 64.98 ± 0.75 kJ mol^{-1} (15.53 ± 0.18 kcal mol^{-1}), and $\Delta S^{\ddagger}$ = −132.2 ± 2.1 J K^{-1} mol^{-1} (−31.6 ± 0.5 cal K^{-1} mol^{-1}).

The isotope effect k^{H}_{obs}/k^{D}_{obs} for the rearrangement is calculated from runs 3 and 6 in Table 1 to be 4.4 ± 0.5 at 55 °C. This value is similar to 4.2 ± 0.3 (25 °C) obtained with diazabicyclo[2.2.2]octane in the rearrangement of 1,3-dimethylindene in benzene, a rearrangement which is reported[9] to have a $\Delta H^{\ddagger}$ = 64.0 ± 3.8 kJ mol^{-1} (15.3 ± 0.9 kcal mol^{-1}) and $\Delta S^{\ddagger}$ = −109 ± 17 J K^{-1} mol^{-1} (−26 ± 4 cal K^{-1} mol^{-1}).

Other reaction systems which are more similar to the theoretical one mentioned above are under study in our laboratories.

EXPERIMENTAL

All glassware, including calibrated volumetric flasks, used in the kinetics were treated with chromic acid, water, 2 M ammonia and distilled water and finally dried at 120 °C for 24 h and stored in a desiccator.

The ^{1}H NMR spectra were obtained with a Varian A60-D analytical NMR spectrometer.

Preparative GLC was made with a Varian Aerograph 90P and the analytical work with a Perkin-Elmer 990 Gas Chromatograph. The 1-methylindenes were purified with a 0.6 m × 10 mm column containing 15 % Apiezon L on Chromosorb W 60/80 using an N_2 flow of 100 ml/min and an oven temperature of 120 °C.

For analytical purposes a 3 m × 3 mm column packed with 2 % Apiezon on Varaport 30 100/120 was used at 172 kPa N_2 and an oven temperature of 100 °C.

2-Aminopyridine was analyzed on a 2.5 m × 3 mm steel column packed with 20 % UCON-LB 550X, 20 % KOH on Chromosorb P 80/100, 172 kPa N_2 at 100 °C.

Kinetics. All kinetics were performed in HETO 01PT 623 thermostats. Most of the runs were made in ampoules which were broken at proper reaction times and the reaction mixture was quenched by shaking with 1 M HCl twice. The two phases were separated by centrifugation and the benzene layer was analyzed by GLC and occasionally by ^{1}H NMR. Before the ^{1}H NMR analysis the solutions were concentrated in vacuum. The relative amount of product or substrate in the reaction mixture was evaluated by triangulation of GLC peaks. This method as well as the quench technique was calibrated by using substrate/product mixtures of known composition, *i.e.* the mixtures were made by weighing varying amounts of substrate and product.

Calibration of the quench-extraction-GLC method gave maximum errors of ±0.5 % (absolute %) in the mixture composition (expressed as % of one component in the mixture). This error was used in the determination of the error in the rate constant.

When the quench-^{1}H NMR technique was used, error limits are only assigned to those runs where 1-methylindene has been used as a substrate, because only with this substrate was the technique calibrated. Every sample was integrated 5 − 10 times. From these data the mean value was calculated, and the maximum difference between the mean value and the integrals was used in calculation of the error in the rate constant. Calibration of the technique gave maximum errors ±1.5 % (absolute %) in the mixture composition.

All estimated errors are considered to be maximum errors, including both systematic and random errors ($\sim 2\sigma$).

2-Aminopyridine (*1-h*) (Merck) was distilled in vacuum and twice recrystallized from petroleum ether, b.p. 60 − 71 °C. GLC showed purity > 99.9 %.

N,N-*Dideutero-2-aminopyridine* (*1-d*) was prepared from pure 2-aminopyridine. A benzene solution was shaken with D_2O and the phases separated by centrifugation. This procedure was repeated four times. The degree of deuteration was found by NMR to be 94 ± 3 %.

1-Methylindene (*3-h*) was prepared[5a] and purified by preparative GLC. Analytical GLC showed that the purity was > 99.9 %.

1-Deuterio-1-methylindene (*3-d*) was prepared,[5a,b] purified and analyzed as above and was found to have a purity > 99.9 % and by NMR it was found to be > 99.5 % deuterated. In this last analysis a ^{13}C satelite was employed.

β-9-Fluorenylstyrene (*2*) was prepared[10] and analyzed by NMR and TLC. No trace of impurities was noticed.

3-Methylindene (*5-h*) was prepared[5c] and purified by preparative GLC. Purity was found to be > 99.9 % by analytical GLC.

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REFERENCES

1. Niemeyer, H. M. and Ahlberg, P. *Chem. Commun.* (1974) 799.
2. Niemeyer, H. M., Goscinski, O. and Ahlberg, P. *Tetrahedron 31* (1975) 1699.
3. Ahlberg, P. and Ladhar, F. *Chem. Scr. 3* (1973) 31.
4. a. Swain, C. G. and Brown, J. F. *J. Amer. Chem. Soc. 74* (1952) 2538; b. Rony, P. R. and Neff, R. O. *Ibid. 95* (1973) 2896.
5. a. Weidler, A.-M. and Bergson, G. *Acta Chem. Scand. 18* (1969) 1484; b. Almy, J. and Cram, D. J. *J. Amer. Chem. Soc. 91* (1969) 4459; c. Weidler, A.-M. and Bergson, G. *Acta Chem. Scand. 17* (1963) 2724.
6. Angyal, S. J. and Angyal, C. L. *J. Chem. Soc.* (1952) 1461.
7. Cram, D. J. *Fundamentals of Carbanion Chemistry.* Academic, New York 1965, p. 19.
8. Molchanova, T. S. and Tsarevskaya, M. N. *J. Gen. Chem. USSR (Engl. Transl.)* (1974) 1066.
9. Ohlsson, L., Wold, S. and Bergson, G. *Ark. Kemi 29* (1968) 351.
10. a. Garden, W. D. and Gunstone, F. D. *J. Chem. Soc.* (1952) 2650; b. Campbell, N. and Delahunt, K. *Ibid.* (1966) 1810.

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