ChemComm

Experimental evidence of partially rate limiting ion-pair interconversion in a base catalyzed 1,3-proton transfer reaction

Anita Hussénius,* Olle Matsson and Göran Bergson

Institute of Chemistry, Uppsala University, Box 531, S-751 21 Uppsala, Sweden. E-mail: anitah@kemi.uu.se

Received (in Liverpool, UK) 7th October 1998, Accepted 26th October 1998

The relative rates for interconversion and reprotonation of the ion-pair intermediates are of the same order of magnitude in the piperidine catalyzed 'degenerate' rearrangement of 1,3-dimethylindene, as investigated using ^{1}H and ^{2}H NMR spectroscopy by letting the 1,3-hydron transfer reaction compete with isotope (^{1}H/^{2}H) exchange.

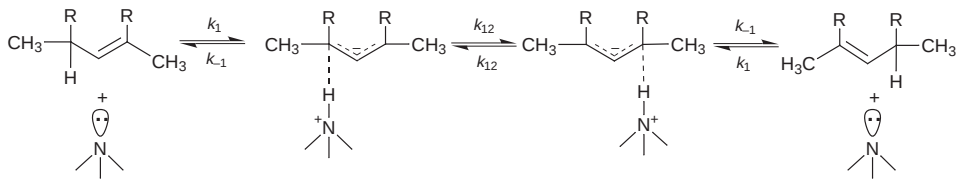
Many organic and biochemical reactions involve the transfer of a proton from a carbon acid to a base. Hydrogen bonded carbanions have been postulated as intermediates in essentially all hydron transfer reactions from carbon acids.[1] Therefore, mechanistic interpretations of observed phenomena such as kinetic isotope effects and enantioselectivities require detailed knowledge of processes involving carbanion ion pairs. The simple example shown in Scheme 1 illustrates this point (the 'degeneracy' of this rearrangement reduces the number of different rate constants, thus simplifying the kinetic analysis). Application of the steady-state approximation to the two reactive ion-pair intermediates gives the relation [eqn. (1)]

$$k = k_1/[2 + (k_{-1}/k_{12})] \quad (1)$$

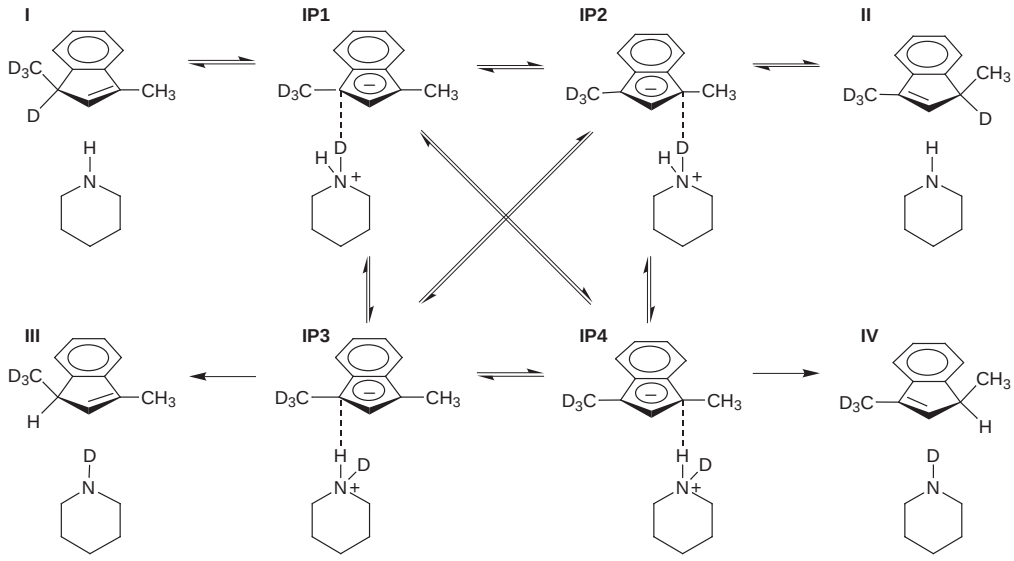
between the phenomenological rate constant k (which can be determined experimentally) for this 1,3-proton transfer reaction, and the mechanistic rate constants, k_1, k_{-1} and k_{12}. If and only if the interconversion of the ion pairs (k_{12}) is much faster than collapse back to a covalent entity (k_{-1}), can observed effects on k be discussed straightforwardly in terms of the proton abstraction step (k_1). Thus, it is of great importance to know the magnitude of the rate constant ratio (k_{-1}/k_{12}).

Arguments for rapid interconversion ($k_{12} >> k_{-1}$) of the intermediates arise from the fact that no covalent bonds are formed or broken in this process, making it plausible that the ammonium ion, once formed, should be able to slide between the 1- and 3-positions with very low activation energy. Evidence for the existence of two ion-pair intermediates not in equilibrium with each other has, however, been presented by Ahlberg and Thibblin.[2,3] Thus, the assumption of rapid interconversion of ion pairs has to be tested, if possible, for each specific system.

Herein, we report on an experimental investigation aimed at retrieving information about the relative rates referred to above. The crucial point is that the 1,3-hydron transfer is allowed to compete with isotopic exchange of the 'mobile' hydron mediated by ammonium ion rotation within the ion pair.[4–6] Our system (Scheme 2) mimics the simple case given in Scheme 1. 1,3-Dimethylindene, in which a trideuteriomethyl group is substituted for one of the methyl groups, was used as a substrate. The CD_3 group served only as a label making it possible to distinguish between the 1- and 3-positions and to follow the time evolution of the concentrations of all four species (**I**–**IV**) by ^{1}H and ^{2}H NMR spectroscopy. The expected small secondary isotope effects due to this labelling can be neglected



Scheme 1



Scheme 2

in the present context. The reaction was run in benzene solution and the secondary amine piperidine was used as base-catalyst and (^{1}H/^{2}H) −exchange agent. If the substrate is deuteriated in the C1 position, the use of protic base results in incorporation of protium in the dimethylindene due to rotation of the ammonium ion within the ion pair. If the base is used in large excess, the ^{1}H/^{2}H exchange is practically irreversible. The kinetics of this protium incorporation, in the 1- and 3-positions respectively, provides a measure of the relative rates of ion-pair equilibration and collapse.

In Scheme 2 a mechanistic model for our system is depicted. Starting at the upper left corner, the amine abstracts a deuteron from 1,3-dimethylindene **I** and an ion-pair intermediate **IP1** is formed. Either the hydron transfer proceeds, *via* interconversion to the ion pair **IP2**, to the rearranged product **II** without deuterium/protium exchange, or a new ion pair **IP3** is formed through ammonium ion rotation (a direct route from **IP2** to **IP4** cannot be excluded, but the presence of such a route does not influence our conclusions). Now, the ion pairs **IP3** and **IP4** can interconvert, just as **IP1** and **IP2**. If the ion-pair interconversion is much faster than collapse, the two exchange products **III** and **IV** will appear in equal amounts (or more precisely in the ratio 1.04, which is the magnitude of the secondary equilibrium isotope effect, determined as the average from several kinetic experiments) from the very start of the reaction. On the other hand, if these products, **III** and **IV**, appear in unequal amounts, the assumption of fast ion-pair interconversion is not valid. Thus, by studying the kinetics of formation of the exchange products **III** and **IV**, information can be obtained regarding the relative rates of ion-pair interconversion and ion-pair collapse.

The present kinetic data have been obtained from ^{1}H and ^{2}H NMR spectra of quenched and concentrated samples, taken at regular time intervals from the reaction mixture. The experiments were performed in benzene solution at 20 °C. The secondary amine piperidine was used as base catalyst, in an excess of 45–50 equiv. of the substrate concentration. The use of a large excess of base permits the ^{1}H/^{2}H exchange reaction, to a good approximation, to be regarded as irreversible. In principle it is possible to start from either of the four different isotopically substituted 1,3-dimethylindenes but all kinetic experiments reported here have started from the substrate 1-[^{2}H$_3$]methyl-3-methyl[1-^{2}H]indene[7–9] and protic piperidine.

In the kinetic procedure, the isotopically substituted 1,3-dimethylindene (70–100 mg) was weighed into a calibrated 10 ml volumetric flask. A stock solution of piperidine in benzene was prepared in a volumetric flask which was then sealed with a tight PTFE septum and a screwcap. Both flasks were thermostatted at 20.00 °C. The temperature was measured with a calibrated mercury thermometer with an absolute accuracy of 0.02 °C. The temperature did not deviate more than 0.02 °C from the average value during the kinetic runs and was thus 20.00 ± 0.04 °C. Base solution was withdrawn by means of a nitrogen flushed syringe and the 10 ml flask was filled to the mark. A clock was started when half of the base solution had been added. The flask was sealed with a septum and a screwcap and was then rapidly shaken and replaced in the thermostat bath. Samples (1–1.5 ml) were taken at regular time intervals. The reaction was quenched with 2–3 ml of 5 M HCl, which was cooled to at least −10 °C. The organic phase was separated and washed with brine and distilled water. The solution was concentrated by evaporation and ^{2}H NMR spectra were recorded. Residual solvent was removed at reduced pressure, the residue was dissolved in C^{2}HCl$_3$ (Ciba-Geigy, > 99.9 atom% ^{2}H) and finally the ^{1}H NMR spectra were recorded. When the pure substrate was subjected to the work-up conditions it was recovered unchanged.

The samples of the quenched reaction contain four different isotopically substituted 1,3-dimethylindenes resulting from rearrangement and exchange reactions (see Scheme 2). There are three signals of interest in the NMR spectra: the signal at δ 1.28 from the methyl group at the C1 position of the indene ring system, the signal at δ 2.13 from the methyl group at the C3-position, and the signal at δ 3.40 from the protium (deuterium) at C1. Computer resolution of the ^{1}H signals at δ 1.28 was performed using a curve fitting routine, to be able to solve for the four unknown concentrations. The signal at this shift consists of a doublet from **IV**, a singlet from **II** (see Scheme 2) and also a signal from traces of protium in the trideuteriomethyl group at the 1-position. Utilizing computer resolution the ^{1}H NMR spectrum is, in principle, sufficient for determination of the content of each species. The ^{2}H NMR spectra have been recorded in order to allow for a double check of the relative concentrations.

Table 1 Relative concentrations[a] of the four 1,3-dimethylindenes in the reaction mixture at different tmies, in a piperidine[b] catalyzed rearrangement/exchange experiment starting from 1-[^{2}H$_3$]methyl-3-methyl[1-^{2}H]indene **I** in benzene at 20 °C

t/s	**I**	**II**	**III**	**IV**	**III/IV**
0	0.988	—	0.012	—	—
1835	0.819	0.0237	0.104	0.0527	1.97
1690	0.718	0.0367	0.143	0.103	1.39
5400	0.643	0.0370	0.175	0.145	1.21
7200	0.586	0.0312	0.202	0.181	1.12
12600	0.428	0.0338	0.270	0.268	1.01
∞	0.0102	0.00990	0.497	0.483	1.03

[a] The total concentration of substrate was 0.0677 M. The concentration is normalized to 1 in the table. [b] [Piperidine] = 3.149 M.

In Table 1 the results from a typical kinetic experiment are displayed. In the beginning of the experiment (18% reaction) the isotopically exchanged indene **III**, produced by collapse of **IP3**, appear in the reaction mixture in a concentration almost twice as high as that of indene **IV**, produced from **IP4** ([**III**]/[**IV**] = 1.97). The concentration ratio of the exchanged indenes then gradually decreases towards the secondary equilibrium isotope effect (for simplicity, the reversible piperidine catalyzed rearrangement between **III** and **IV** has been omitted from Scheme 2). The conclusion is thus that the assumption of fast ion-pair equilibration is not valid for the system studied. This is in accordance with recently published theoretical calculations for a similar rearrangement.[10] In that study it was found that the relevant activation barriers were dependent of the structure of the catalyzing base as well as on the solvent. A full account including a detailed kinetic analysis of the present reaction system will be published in due course.

Notes and references

1 D. J. Cram, *Fundamentals of Carbanion Chemistry*, Academic Press, New York 1965, pp. 86–103.
2 A. Thibblin, S. Bengtsson and P. Ahlberg, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1569.
3 A. Thibblin, *Chem. Scr.*, 1983, **22**, 182.
4 D. J. Cram and R. Gosser, *J. Am. Chem. Soc.*, 1963, **85**, 3890.
5 D. J. Cram and R. Gosser, *J. Am. Chem. Soc.*, 1964, **86**, 2950, 5445 and 5457.
6 G. Bergson and L. Ohlsson, *Acta Chem. Scand.*, 1967, **21**, 1353.
7 L. Ohlsson, I. Wallmark and G. Bergson, *Acta Chem. Scand.*, 1966, **20**, 750.
8 C. F. H. Allen and F. W. Sprangler, *Org. Synth.*, 1955, **Coll. Vol. 3**, 377.
9 G. Bergson, O. Matsson and S. Sjöberg, *Chem. Scr.*, 1977, **11**, 25.
10 M. Agback, S. Lunell, A. Hussénius and O. Matsson, *Acta Chem. Scand.*, 1998, **52**, 541.

Communication 8/07798C