The Cyclodehydration of Anils. Part II. The Hydrogen Isotope Effect in the Cyclodehydration of 2-Anilinopent-2-en-4-one.*

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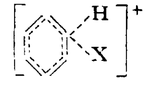
The ratio of the rates of cyclodehydration of 2-(2 : 4 : 6-trideuteroanilino)-pent-2-en-4-one and its protium analogue is found to be approximately 2 : 3 in both 95·5% and 89·2% sulphuric acid–water. It is suggested that although fission of the C–H bond is not the kinetically decisive factor in the cyclodehydration, some weakening of the bond occurs in the rate-determining step.

IN a detailed discussion of the mechanism of aromatic electrophilic substitution, Melander (*Arkiv Kemi*, 1950, **2**, 211) considered the hydrogen isotope effect in the two alternative S_E2 processes—the single step replacement with the activated complex (I), and the two-stage process with an intermediate addition compound (II) regarded as having rather greater stability than the activated complex. In (I) the π-electrons of the benzene ring do not take part in the formation of π-bonds, although they may be polarised by the positive charge; but in (II), two of these electrons are used for the addition of the cation resulting in the appearance of four bonds of the sp^3 type at the nuclear carbon atom. If, experimentally, identical rates of substitution for hydrogen isotopes are found, this implies that the stepwise reaction occurs with a rate-determining first step, since this step does not involve hydrogen loss; if a substantially slower rate is observed for the heavy isotope the substitution may occur either by the stepwise reaction with the second step rate-determining, or by the single-step replacement. The isotopic rate ratio k_T/k_H for the rates of replacement of tritium and protium may be found to have any value from unity to about 0·05. In nitration and bromination experiments, Melander obtained minimum values of 0·74—0·85 for k_T/k_H and concluded that these results established that the hydrogen loss in both substitution reactions was kinetically insignificant. The result for the nitration was confirmed by Bonner, Bowyer, and Williams (*J.*, 1953, 2650) who obtained values of 0·99

(I)



(II)

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* Part I, preceding paper.

and 0·95 for k_D/k_H by direct determination of the rates of nitration of nitrobenzene and pentadeuteronitrobenzene in sulphuric acid solution. For sulphonation a significantly lower isotope ratio of 0·55 for k_T/k_H has been reported by Berglund-Larsson and Melander (*Arkiv Kemi*, **1953**, **6**, 219) and their interpretation of this result favours the step-wise reaction with the second step rate-determining.

Rates of cyclodehydration at 25°.

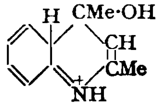
Initial concn. of organic reactant 0·1M. k in min.$^{-1}$.

Medium, % H_2SO_4	Expt. no.	k_H	Expt. no.	k_D	k_D/k_H
95·7	71	0·0124, 0·0122	72	0·00811, 0·00811	0·66
89·2	75	0·00210, 0·00211	78	0·00148, 0·00149	0·71

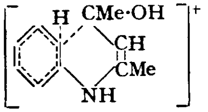
The Isotope Effect in Cyclodehydration.—The ratio k_D/k_H in cyclodehydration was determined by measuring the rates of conversion of 2-anilino-(k_H) and 2-(2 : 4 : 6-trideuteroanilino)-pent-2-en-4-one (k_D) to the corresponding quinoline derivatives by the method described in Part I. The first-order rate constants obtained are shown in the Table.

A definite isotope effect is evident, but the ratio is sufficiently close to unity to exclude the possibility that the fission of the C–H bond is the sole rate-determining factor. The reaction is an intramolecular electrophilic substitution within the cation formed by proton uptake from the medium and differs from a bimolecular electrophilic substitution in that the formation of the product requires the elimination of a molecule of water instead of a proton. In a mechanism corresponding to the formation of the intermediate addition compound (II) the cation would assume the structure (III). Elimination of a molecule of water from this intermediate in strongly acidic media should be rapid. Further, if interaction with sulphuric acid were kinetically significant, then the simple relation between the rate constant and the ratio $[H_2SO_4]/[HSO_4^-]$ found experimentally (Part I), *viz.*, $k = \text{const.}[H_2SO_4]/[HSO_4^-]$, could hardly be expected; the derivation of this equation assumes that the only interaction between the organic reactant (A) and the solvent species is that involved in the equilibrium, $A + H_2SO_4 \rightleftharpoons AH^+ + HSO_4^-$. It follows that if the reaction occurs by a two-step process through the intermediate compound (III), it is the formation of this compound which is the rate-determining step, and the small isotope effect must be accepted as a feature of this mechanism. The alternative single-step mechanism represented by the transition complex (IV) is less likely since the difference in zero-point energies of the C–H and C–D bonds should lead to a much lower k_D/k_H ratio than that found experimentally. The effect might not be so pronounced if a proton-acceptor participates in the transition state, but this would almost certainly lead to a more complex relation between k and the solvent species than that found experimentally. Hammond (*J. Amer. Chem. Soc.*, 1955, **77**, 334), in a discussion of Melander's results for bromination and nitration has suggested that, although they show that the breaking of the C–H bond makes little progress in the attainment of the first transition state leading to the formation of the intermediate (II), they do not establish that the C–H bond is not broken in the rate-determining step of the reaction, since the removal of a proton from the intermediate (II) may require only a very slight weakening of the C–H bond to yield the second transition state preceding the formation of the products. The further observation is made that some loosening of the C–H bond might be expected in the formation of the intermediate in the change from the trigonal to the tetrahedral configuration of the nuclear carbon atom, although Melander (*loc. cit.*, p. 246) does not hold this view. It is probable that some stretching and bending of the C–H bond is more likely to occur in cyclodehydration than in nitration or bromination during the formation of a transition state (whether this leads to the intermediate or directly to the products) since the electrophilic attack of the side-chain is sterically hindered as a result of its attachment to the ring; a small isotope effect would then be the expected result.

(III)



(IV)



EXPERIMENTAL

Preparation of 2-(2 : 4 : 6-*Trideuteroanilino*)*pent-2-en-4-one*.—2 : 4 : 6-Trideuteroaniline was prepared by Best and Wilson's method (*J.*, 1946, 2391). Aniline hydrochloride (13 g.) was heated with heavy water (20 g.) in a sealed tube in boiling water for 24 hr. This treatment was repeated five times, the water being removed by vacuum-distillation and replaced by a fresh sample each time. The first five treatments were carried out with heavy water containing 99·73 atoms % of deuterium and the last with a sample containing 99·95 atoms % of deuterium. The deuteroaniline was removed by making the residue alkaline and extracting it with ether. After removal of the ether, the liquid was distilled and the fraction boiling at 180° was collected. It was condensed with a slight excess of acetylacetone as described in Part I. Colourless crystals, m. p. 51—53°, of the *deutero-compound* were obtained from light petroleum (b. p. 40—60°). We are greatly indebted to Dr. R. I. Reed and Mr. A. Macdonald, of the University of Glasgow, for a mass-spectrographic examination of the water formed by combustion of this product (and of the quinoline compound obtained from it, referred to in the next paragraph). Their analysis gave 5·71 ± 0·02% D_2O by wt. from 0·0427 g. of the deuteroanilino-ketone diluted with 0·1416 g. of the protium-analogue (Calc. : 5·82% D_2O).

Test for Deuterium Exchange during Cyclodehydration.—The 6 : 8-dideutero-2 : 4-dimethylquinoline formed in the kinetic experiments in 95·7% sulphuric acid was separated by addition of sodium hydroxide and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), and filtered, and the ether was removed. Mass-spectrographic examination of the water obtained by combustion gave 4·68 ± 0·02% D_2O by wt. from 0·1060 g. of sample (Calc. : 4·78% D_2O). Deuterium exchange with the medium during the cyclodehydration was therefore not significant.

Kinetic Measurements.—The rates of cyclodehydration of the protio- and deutero-compounds in the two sulphuric acid media were measured by the method described in Part I.

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