64. *Prototropy in Relation to the Exchange of Hydrogen Isotopes. Part IV. Isomerisation and Exchange in Methyleneazomethines.*

By Eduardo de Salas and Christopher L. Wilson.

Measurements are recorded of the rates of isomerisation and isotopic hydrogen exchange of the following pair of tautomerides under uniform conditions:

$$p\text{-MeO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{N}{:}\text{CHPh} \rightleftharpoons p\text{-MeO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}{:}\text{N}\cdot\text{CH}_2\text{Ph}$$

Previous evidence is reviewed which shows that the interconversion of these structures proceeds by the simultaneous abstraction and addition of a proton. On this basis each act of isomerisation will lead to exchange. However, the experimental results show that exchange, at least for one isomer and possibly for both, occurs faster than isomerisation. It is therefore suggested that an additional mechanism of exchange exists which involves the direct replacement of the mobile hydrogen by deuterium without isomerisation. The stereochemical course of this superimposed exchange reaction is considered.

In some investigations closely related to those of the present series, it was shown that tautomerism in the methyleneazomethine system (I $\rightleftharpoons$ II) involves the simultaneous rather than the consecutive withdrawal and addition of a proton (Hsü, Ingold, and Wilson, J., 1935, 1778):

$$\text{(I.)}\qquad \text{R}^1\text{R}^2\text{CH}\cdot\text{N}{:}\text{CR}^3\text{R}^4 \rightleftharpoons \text{R}^1\text{R}^2\text{C}{:}\text{N}\cdot\text{CHR}^3\text{R}^4 \qquad \text{(II.)}$$

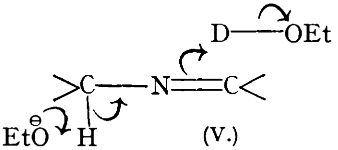
This followed from the observation that, independently of the nature of R^1 .... R^4, the racemisation of an isomeride could be quantitatively accounted for by the cycle: active (I) ⟶ inactive (II) ⟶ inactive (I); for, had the proton transfers been consecutive, the rate of racemisation should have been augmented by the cycle: active (I) ⟶ inactive anion ⟶ inactive (I); whereas no such increase of rate was observed.

We have now studied the isotopic hydrogen exchange of a pair of tautomeric methyleneazomethines. This paper describes measurements of the rate with which each isomer of the system (III $\rightleftharpoons$ IV) exchanges its protium for deuterium of the solvent, ethyl alcohol, together with a determination of the velocity of interconversion of the isomerides under the same conditions. The tautomerism of these compounds

$$\text{(III.)}\qquad p\text{-MeO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\cdot\text{N}{:}\text{CHPh} \rightleftharpoons p\text{-MeO}\cdot\text{C}_6\text{H}_4\cdot\text{CH}{:}\text{N}\cdot\text{CH}_2\text{Ph} \qquad \text{(IV.)}$$

in alcoholic solution with catalysis by ethoxide ions has already been investigated (Ingold and Shoppee, J., 1929, 1199). In the present work, each compound was allowed to isomerise for various times in alcohol containing a known proportion of deuterium ethoxide and the sodium ethoxide catalyst, and the isolated mixtures of azomethines were analysed both for isomeric composition and for deuterium content.

It is evident [see formula (V)] that if the interconversion of the compounds (III) and (IV) conforms to the suggested mechanism of simultaneous transfers, each act of isomerisation will lead to hydrogen exchange, *i.e.*, the replacement of original protons by either new protons or deuterons. The rate of hydrogen exchange must, therefore, be at least equal to that of the tautomerism: it may, however, be the larger, if, besides the isomerisation, any other mechanism of exchange exists not involving tautomerism.



(V.)

The results are in the table, but before considering the rates, it may be noted that each molecule has three hydrogen atoms which would be expected to undergo replacement. The fact that three are indeed replaced is supported by the data obtained in the experiments run for long times: the exchange numbers are 1·9—2·0, and if the number of atoms replaceable is 3, then the average equilibrium constant for the separate exchanges must be 2·0/3∼0·7, a value quite close to that expected from known vibration frequencies.

Owing to the reversibility of isomerisation and to the three successive stages of exchange, it is convenient to consider initial rates : these involve only the forward reaction and exchange with respect to only one position. Even so, the results can be treated only qualitatively, since we do not know the relative rates of transference of protium and deuterium in the forward reaction of either isomeride. If we were able to assume these rates to be the same, then the figures termed " Isomerisation % " in the table would be directly comparable with those labelled " Exchange % ". Inasmuch as protons have always been found to be transferred more rapidly than deuterons in the same reaction, the real percentages of exchange are probably greater than the tabulated figures, and the excess of the real over these " apparent " percentages is likely to be greater in the more dilute deuterium solvent, where the competition of the more mobile protons is relatively more serious.

Isomerisation and Deuterium Exchange of the Methyleneazomethines (III) *and* (IV) *in Deuterium Ethoxide catalysed by Ethoxide Ions.*

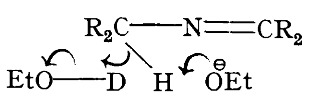
D content of solvent, 100[EtOD]/([EtOD] + [EtOH])		31·5.				94·4.	
Compound (III) used	Time (hrs.)	4·0	8·0	984	—	0·5	1·0
	Isomerisation (IV %)	21·0	39·0	—	—	15·0	22·5
	Combustion water: excess *d* (p.p.m.)	322	541	4316	—	493	987
	Combustion water: D, atoms %	0·299	0·504	4·02	—	0·459	0·919
	D (atoms %) in one position *	4·48	7·56	60·3	—	6·89	13·79
	Exchange (%) †	14·3	24·0	191·4	—	7·3	14·6
Compound (IV) used	Time (hrs.)	4·0	8·0	24·0	744	0·5	1·0
	Isomerisation (III %)	6·5	12·3	23·4	—	4·2	7·8
	Combustion water: excess *d* (p.p.m.)	329	605	1344	4502	422	900
	Combustion water: D, atoms %	0·306	0·563	1·25	4·19	0·393	0·838
	D (atoms %) in one position *	4·59	8·45	18·8	62·8	5·40	12·57
	Exchange (%) †	14·6	26·8	59·6	199·4	5·7	13·3

* These figures are obtained from those of the previous line by multiplication by 15, the number of hydrogen atoms in the compounds burnt.

† These are percentage expressions of so-called exchange numbers, *i.e.*, the average number of atoms per molecule exchanged, calculated as if one atom in each molecule is exchangeable and as if deuterons and protons are always transferred at the same specific rate. The slight fall in isotopic composition of the solvent during a run is disregarded.

Viewing the initial rates in this light, we can conclude that, at least in the example of compound (IV), and possibly also in its isomeride (III), the rate of exchange is greater than can be accounted for by isomerisation alone.

This suggests an additional exchange mechanism and one naturally postulates simultaneous proton transfers at the same carbon atom as illustrated in (VI). Again no quantitative conclusions can be drawn, because we do not know the relation of the two component rates (introduction of H and D) of this extra reaction to those of the exchange dependent on isomerisation, or how this unknown relation is modified by a change of solvent. We can say, however, that whatever the mechanism of the additional reaction may be, it cannot lead to racemisation (which goes no faster than isomerisation) so that if indeed it has the form shown in (VI) the stereochemical configuration of the carbon atom attacked must remain unaltered by the substitution. It should perhaps be explained that, as stated by Hsü, Ingold, and Wilson (*loc. cit.*), we do not regard the proton transfers as quite simultaneous : the organic ion is considered to be partly liberated, but not completely enough, or for long enough, to change its stereochemical form. On account of this conclusion we have put in hand several series of experiments, designed directly to test this stereochemical course of the substitution of hydrogen for hydrogen by the various recognised mechanisms.



(VI.)

EXPERIMENTAL.

*Benzylidene-*p*-methoxybenzylamine* (III) *and* p*-Methoxybenzylidenebenzylamine* (IV).—The azomethines were prepared by Ingold and Shoppee's method (*loc. cit.*); (III) was purified by distillation, b. p. 170°/0·2 mm. (yield 64%); and (IV) by recrystallisation from petrol (b. p. 40—60°), then having m. p. 42—43° (yield 71%).

Analysis of Mixtures of the Azomethines.—A modification of the method described by Shoppee (J., 1931, 1232) was used. Twice the theoretical amount of *p*-nitrophenylhydrazine was dissolved in concentrated hydrochloric acid (2 c.c.), the solution diluted to 20 c.c. with water, and filtered at about 60° into a mixture of the azomethines and water (50 c.c.). The resulting liquid was shaken for 3 hours and the precipitated hydrazones were filtered off, washed with dilute hydrochloric acid and water until free from excess of the hydrazine, dried, and weighed (yield, quantitative), and their m. p.'s determined.

The composition of the mixture was obtained by reference to a graph of the figures obtained from mixtures of the *p*-nitrophenylhydrazones prepared in the above manner from artificial mixtures of the azomethines. It is estimated that the isomerisation figures in the table are accurate to ± 1·0%.

Preparation of Deuterium Ethoxide Solutions.—A solvent containing 31·5 mols. % of deuterium ethoxide was prepared according to Ingold, de Salas, and Wilson (J., 1936, 1333). Hydrolysis of ethyl sulphite by a little more than the equivalent amount of deuterium oxide gave a product which, dried by freshly ignited lime and magnesium amalgam, had $d_{4^\circ}^{25^\circ}$ 0·8033 and contained 94·4 mols. % of deuterium ethoxide.

Isomerisation of the Azomethines in Deuterium Ethoxide.—The appropriate azomethine (x g.) was dissolved in 0·1N-sodium ethoxide (2·5x c.c.) prepared in the deuterium ethoxide. The solutions were heated for various times in sealed bulbs to 74·0°. Reaction was arrested by cooling and breaking the bulbs under water; the azomethines were then extracted with ether. The ethereal solution was well washed with distilled water to remove alcohol, dried, and evaporated. The residual azomethine mixture was thoroughly dried in a vacuum over phosphoric oxide. A portion of the mixture was treated with *p*-nitrophenylhydrazine as already described, and the remainder was analysed for deuterium by the customary method involving combustion and density determination of the water so produced. The results are in the table.

The authors thank Professor C. K. Ingold, D.Sc., F.R.S., for his help in this work.

THE SIR WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON. [*Received, December 4th,* 1937.]