82. *Mechanism of Substitution and Rearrangement in Prototropic Systems. Racemisation and Hydrogen Exchange in Methylene-azomethines.*

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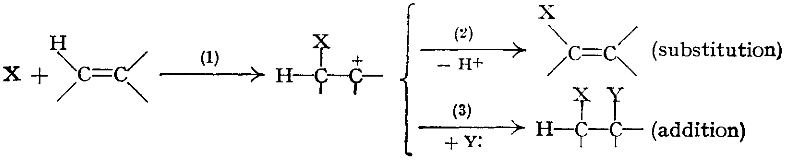
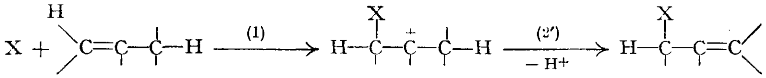
A brief résumé of heterolytic mechanisms in prototropic rearrangement and electrophilic substitution is presented. It is shown that the initial rates of hydrogen exchange and of racemisation in (+)-benzylidene-α-*p*-diphenylylbenzylamine * are equal. Regard being paid also to a previous demonstration of the equivalence of the rates of racemisation and of isomerisation, the results establish that the synchronous, termolecular mechanism of bond-formation and bond-fission is applicable in this instance.

Of the possible forms of heterolysis of a carbon–hydrogen bond, *viz.*, R | • • H (1*a*) and R • • | H (1*b*) (the dots represent electrons), the type (1*a*), involved in nucleophilic substitution at the carbon centre, is relatively unimportant, mainly because of the low anionic stability of hydrogen. In simple, saturated aliphatic hydrocarbons, R–H, the form of heterolysis (1*b*), required for electrophilic substitution, may also be expected to be difficult. In a saturated carbon system, the valency electrons are mainly localised between two nuclei and are largely protected from electrophilic attack. Furthermore, a simple aliphatic alkyl group does not possess sufficient electron affinity to undergo easy separation from hydrogen by appropriating both of the electrons of the R–H bond.† In carbon-hydrogen bonds, therefore, special structural features are required for facile heterolysis, as we shall proceed to describe.

In an unsaturated system, the π-electrons are vulnerable to attack by a positive (electrophilic) entity, and the carbon cation, formed in this interaction, may suffer internal neutralisation with the loss of a proton to a base, *e.g.*,



In unsaturated aliphatic compounds, reaction with a nucleophilic reagent (3) may intervene, resulting in a partial or complete eclipse of the substitution process. In aromatic systems, the reaction corresponding to (2) is usually dominant and facile, doubtless because of the tendency, in $\overset{+}{\mathrm{Ar}}\!<^{\mathrm{H}}_{\mathrm{X}}$, to reach the resonance-stabilised structure, ArX. In an olefin possessing a replaceable hydrogen atom in an attached alkyl substituent, the following change may also be formulated :



In general, the combination (1) and (2′) constitutes a reaction path for substitution with rearrangement, but, in the special case for which X = H^+, it also represents a mechanism of isomerisation (" three-carbon " prototropy in this instance). A concerted mechanism may also be envisaged, in which the first and second stages in the above scheme are fused

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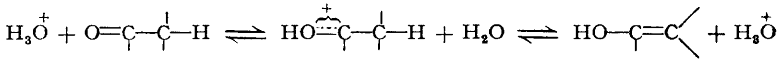
* In previous papers relating to this compound, Ingold *et al.* (see below) had named it as a derivative of benzhydrylamine, but as the term " benzhydryl " was discarded by the I.U.P.A.C. recommendations of 1949, the present name has been substituted.

† In homolytic reactions, *e.g.*, Y· + R·¦·H ⟶ Y–R + ·H, a high degree of polarisation or electron availability in the breaking bond is not such a vital condition. Consequently, the paraffinic hydrocarbons exhibit their most facile substitution reactions under conditions conducive to homolysis, *e.g.*, in halogenation processes in which halogen atoms participate (cf., especially, the observations of Kharasch and his co-workers in recent years).

into a single synchronous process. A similar mechanism applies to acid-catalysed prototropy in situations involving atoms other than carbon, *e.g.*, in carbonyl compounds :



$$\overset{+}{H_3O} + O{=}C{-}C{-}H \rightleftharpoons \overset{+}{HO{=}C}{-}C{-}H + H_2O \rightleftharpoons HO{-}C{=}C\langle + \overset{+}{H_3O}$$

Under basic conditions, high reactivity associated with the heterolytic fission of a C–H bond at a saturated carbon centre may occur in the following way : If a powerful electron-appropriating group, for instance, a carbonyl, nitro-, or cyano-substituent, is present (*e.g.*, in $H{-}C{-}C{=}O$), the hydrogen atom will be more weakly held, and transfer of the proton may take place from the organic structure to the basic catalyst. This condition is well known in prototropic changes and in condensation processes, such as the aldol, Claisen, and allied types.

Attention may now be focused on the detailed course of prototropic change under basic conditions. Two principal mechanisms have been advanced. In the "bimolecular" mechanism, which was postulated first by Ingold, Shoppee, and Thorpe (*J.*, 1926, 1477), there is a proton transfer to the catalyst, a mesomeric anion being produced, which may recombine with a proton to form either the one or the other component of the tautomeric system, *e.g.*,

$$B\colon + H{-}X{-}Y{=}Z \rightleftharpoons B{-}H + [X{\cdots}Y{\cdots}Z]^- \rightleftharpoons X{=}Y{-}Z{-}H + \colon B$$

Because of the possible reversal of the formation of the anion, the rate of heterolysis by this mechanism should, in general, be greater than the rate of isomerisation. In evenly balanced tautomeric systems, the rates should clearly be notably different. If the partitioning of the anion is very unequal, the rate of isomerisation may be, depending on the direction of the inequality, nearly equal to, or much less than, the rate of heterolysis. Indications of some of the relationships to be expected from this mechanism have been obtained (see, especially, Ingold, Wilson, and co-workers, *J.*, 1936, 1328; 1938, 78; *Trans. Faraday Soc.*, 1938, **34**, 175; *J. Chim. phys.*, 1948, **45**, 232).

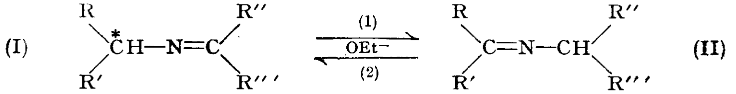
In the second mechanism, first advanced by Lowry (*J.*, 1927, 2554), the removal of one proton by a base is accompanied by the addition of another proton in a different position, the added proton being derived, for example, from the solvent or the conjugate acid of the base :

$$B\colon + H{-}X{-}Y{=}Z + H{-}B \rightleftharpoons B{-}H + X{=}Y{-}Z{-}H + \colon B$$

We shall henceforth be concerned mainly with evidence relating to this mechanism.

In this one-stage, termolecular mechanism, no intermediate entity is involved. Every molecule which suffers scission of the bond containing the mobile hydrogen atom should isomerise; the rates of isomerisation and of bond-fission should, therefore, be equal. Now, the rate of fission of a hydrogen–X bond, *e.g.*, in H–X–Y=Z, may be determined by measuring the rate of racemisation of an optically active structure with an asymmetric centre at X, and this may be compared with the chemically measured rate of isomerisation. Measurements of this type have been carried out in the methyleneazomethine systems (I⇌II) indicated in Table 1.

TABLE 1.



	R	R′	R″	R‴	Equilm. ratio, (I) : (II)
(*a*)	C_6H_5	CH_3	C_6H_5	p-Cl·C_6H_4	50 : 50 at 85°
(*b*)	C_6H_5	CH_3	C_6H_5	C_6H_5	68 : 32 at 85°
(*c*)	p-Ph·C_6H_4	C_6H_5	C_6H_5	H	56 : 44 at 25°
(*d*)	p-MeO·C_6H_4	H	C_6H_5	H	24 : 76 at 74°

The relation between the chemically determined isomerisation rates and racemisation rates was studied in examples (*a*), (*b*) and (*c*) (Ingold and Wilson, *J.*, 1933, 1493; 1934, 93; Hsü, Ingold, and Wilson, *J.*, 1935, 1778). In each case, the rate of reaction (1), for example, was found to be equal to the rate of loss of optical activity at C* (see Table 1).

The observations therefore support the termolecular mechanism. The results exclude the bimolecular route for these compounds, for, since the intermediate should partly revert to the original structure in the balanced systems examined, the formation of a mesomeric anion requires that the rate of isomerisation should be lower than the rate of anionisation (or of racemisation).

Most informative evidence of mechanism may be derived by comparing the rate of isomerisation with the rate of exchange of hydrogen, which may be determined isotopically. Employing this method, a demonstration may be sought which includes the proof that in the H–X fission the hydrogen is lost to the solvent and not in an intramolecular manner. In a pure deuteroxylic solvent, which provides only deuterons, the termolecular mechanism requires that, for every original molecule once converted, one deuteron is admitted to the system in the concerted process. In the absence of other exchange mechanisms, there should therefore be initial equality between the rate of isomerisation of one tautomer and the rate of uptake of deuterium by the isomerising system. In the bimolecular mechanism, only a certain proportion of the intermediate anions lead to isomerisation, whereas, in a deuteroxylic solvent, anionisation should result always in the uptake of deuterons by the total isomerising system. For the latter mechanism, therefore, the rate of isomerisation of compounds such as those described in Table 1 should be lower than the rate of exchange of hydrogen.

An attempt to determine mechanism by using this principle was made by de Salas and Wilson (*J.*, 1938, 319) with system (*d*) (Table 1). Chemically measured isomerisation rates were compared with the rate of uptake of deuterium by the total system from an incompletely deuterated hydroxylic solvent. The relative rates of transference of protons and deuterons from the solvent to the solute system being undetermined, the results showed only that the initial rates of isomerisation and of hydrogen exchange were of similar magnitude. de Salas and Wilson were of the opinion that the results indicated a somewhat faster rate of deuterium exchange than of isomerisation, especially for compound (II) of example (*d*) (Table 1). Taking into account the equivalence of the rates of racemisation and of isomerisation—a result which had been demonstrated for methyleneazomethines—they suggested tentatively that a direct substitution mechanism at a single carbon centre was involved, this exchange proceeding without rearrangement and with retention of configuration and optical activity.

We now present the results of a rate comparison for system (*c*), *i.e.*,

$$\text{(I)}\qquad p\text{-Ph}\cdot\text{C}_6\text{H}_4\cdot\text{CHPh—N=CHPh} \rightleftharpoons p\text{-Ph}\cdot\text{C}_6\text{H}_4\cdot\text{CPh=N—CH}_2\text{Ph}\qquad\text{(II)}$$

The equivalence of isomerisation rates and racemisation rates having been previously observed, the rate of loss of optical activity and the rate of uptake of deuterium, during the isomerisation of (I) under catalysis by ethoxide ions in the deuteroxylic solvent EtOD, were determined under strictly comparable conditions. The results are summarised in Table 2.

TABLE 2. *Racemisation and hydrogen exchange in benzylidene-α-*p*-diphenylylbenzylamine.*

Conditions: NaOEt (~ 0·1M) in dioxan–EtOD (2 : 1 by vol.) at 25°.

Time (hrs.)	6·0	17·0	29·5	53·5
Racemisation (%)	12·3	30·8	48·0	68·5
Exchange (%) *	11·9	31·0	58·4	93·3

* The results are calculated on the assumption that the isotope enters one position. An allowance is made to take account of a small proportion (0·9%) of ionisable protium in the heavy alcohol, the correction being applied on the assumption that protons and deuterons are transferred at the same specific rate. It is probable that protons are introduced at a faster rate than deuterons but the uncertainty introduced is unimportant when the available protium content of the medium is small. The change in the isotopic composition of the solvent during the progress of the reaction is disregarded.

The observations show that the rate of loss of optical activity and the rate of uptake of deuterium are initially approximately equal. Having regard also to the previously demonstrated equality between the rate of racemisation and the rate of isomerisation (Hsü, Ingold, and Wilson, *loc cit.*), it may be concluded that the termolecular mechanism is operative for this compound under basic conditions. The divergence between the rate of racemisation and the rate of exchange in the later stages of reaction (Table 2) provides no evidence against this conclusion. Near the beginning of the isomerisation of (I), practically all the formed (II) will have gone through the simple history (I) ⟶ (II), which allows only one deuterium atom to enter a molecule of (II). Later, some (II) will be present which has gone through a more complicated history, such as (I) ⟶ (II) ⟶ (I) ⟶ (II), providing for the admission of more than one deuterium atom into one molecule of finally formed (II).*

The optical results for the racemisation process, which adheres to a first-order rate law with respect to the optically active compound (cf. Hsü, Ingold, and Wilson, *loc. cit.*), are unaffected by such complications. This also is consistent with our deduction, though it is not, in itself, diagnostic of mechanism. Loss of optical activity being the result of fission of the C–H bond at the asymmetric centre, the rate of racemisation should be independent of any subsequent changes in the initial (inactive) product. Thus, the optical measurements refer throughout the course of reaction to the simple conversion (I) ⟶ (II), and, since the concentration of the basic catalyst is constant during the change, and the medium conditions are uniform throughout, the rate of racemisation varies only with the concentration of the optically active compound.

While the results establish the termolecular mechanism, and leave little scope for alternative suggestions in this instance, it should be emphasized that a different situation obtains in other cases (cf., especially, Ingold, Wilson, and co-workers, *locc. cit.*; Swain, *J. Amer. Chem. Soc.*, 1950, **72**, 4578; Bell and Clunie, *Nature*, 1951, **167**, 363). It is also clear that, for the reaction which we have investigated, there is no evidence of hydrogen exchange by electrophilic substitution without rearrangement.

EXPERIMENTAL

(±)- and (+)-Benzylidene-α-*p*-diphenylylbenzylamine were prepared as described by Hsü, Ingold, and Wilson (*locc. cit.*).

The Catalyst Solution.—The same solution, made from sodium (0·21 g.), dioxan (48 c.c.), and deuterium ethoxide (24 c.c.), was used in the exchange and racemisation experiments. Deuterium ethoxide of 99% isotopic purity was obtained as follows: Sodium (11·5 g.) was melted under decalin in a three-necked flask, fitted with a stirrer, a dropping-funnel, and a condenser. After being shaken and cooled to 60°, the "powdered" metal was treated with dry alcohol (23 g.), and the contents of the flask were stirred and heated under reflux for six hours. The condenser was then turned downwards, and the temperature was gradually increased to 170—180° to eliminate any traces of alcohol. Deuterium oxide (99·6% D_2O; 10 g.) was added under reflux during one hour, and the mixture was heated, with stirring, at 120—130° for two hours. The deuteralcohol was distilled, dried by successive distillations from fused barium oxide and sodium, and fractionated from traces of decalin. The yield of purified material was 80%, and the estimation of ionisable deuterium, as described by Ingold, de Salas, and Wilson (*J.*, 1936, 1328), showed that the sample contained 99·1 mols. % of deuterium ethoxide.

Exchange Experiments.—Portions of a solution (0·2M) of (±)-benzylidene-α-*p*-diphenylylbenzylamine in the catalyst medium were enclosed in sealed tubes and kept for various times at 25·0°. The azomethines were isolated, and analysed for deuterium, as described by de Salas and Wilson (*locc. cit.*; cf., *J.*, 1934, 493, 1593; 1936, 1550). The results are given in Table 2.

Racemisation Experiments.—(+)-Benzylidene-α-*p*-diphenylylbenzylamine (1·25 g.) was dissolved in 20 c.c. of the catalyst medium and the rotation (initially, $\alpha_D^{25} = 0{\cdot}53°$) was followed in a 2-dm. jacketed tube kept at 25·0°. The first-order rate coefficient, obtained from the plot of log α against *t*, was 0·0217 hr.$^{-1}$.

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* An experiment in which the tautomeric system was left in contact with the medium for a period approaching the time required for total reaction showed that the deuterium content, calculated on the basis of exchange in one position only, was 180%. The medium contained an appreciable proportion of available protium at this point, and this figure, which has not been corrected for isotopic impurity, is expected to be lower than the value corresponding to complete exchange (200% for two replaceable hydrogen atoms).