

338. *The Homogeneous Catalysis of Stereoisomeric Change in Oximes.*

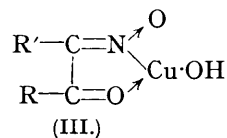
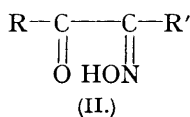
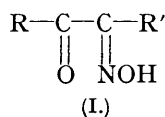
By THOMAS W. J. TAYLOR and D. C. V. ROBERTS.

It has been long recognised that, in general, one isomeride of a pair of geometrically isomeric oximes is more stable than the other, and that the normal direction of isomeric change is for the less stable to pass into the more stable form, or in some cases, perhaps, into an equilibrium mixture in which the latter form predominates. In certain cases the change can be brought about in the reverse direction, the more stable form being converted into the less stable or one of its derivatives. Examples are the well-known action of hydrogen chloride on aromatic aldoximes and that of ultra-violet light on both aldoximes and ketoximes (Ciamician and Silber, *Ber.*, 1903, **36**, 4268; Stoermer, *Ber.*, 1911, **44**, 667; Brady and McHugh, *J.*, 1924, **125**, 547). These two different types of stereoisomeric change will be referred to as the normal and the abnormal change.

The normal change is clearly the simpler, since it is accompanied by a lowering of the free energy of the system; it has been discussed by E. Huckel (*Z. Physik*, 1930, **60**, 455). The rate of change varies greatly in different cases, and can be catalysed to a marked extent by various reagents (for an admirable summary of the present state of knowledge, see Meisenheimer and Theilacker, "Stereochemie," ed. Freudenberg, Leipzig, 1933, pp. 984, 1031, 1065). As to the mechanism of this catalysis nothing is known, nor can it be investigated until a method is devised whereby the rate of change can be measured with reasonable accuracy. In the present work a method of volumetric analysis for alcoholic solutions of mixtures of the two benzilmonoximes has been found; the rate of the normal change of the less stable α -oxime into the more stable β -isomeride with hydrogen chloride and other reagents as catalysts has been measured, and some light is thrown upon the mechanism of the catalysis.

EXPERIMENTAL.

Analytical Method [with P. JULIFF and (Miss) M. S. MARKS].—It has been shown earlier (Taylor and Ewbank, *J.*, 1926, 2818; Taylor, *J.*, 1931, 2782) that when the two stereoisomeric forms of the monoxime of an α -diketone are known, the α -oxime (configuration I) will give rapidly in alcoholic solution with copper acetate a complex of structure (III), while the β -isomeride (configuration II) does not react immediately but only after long standing gives a copper complex which is identical with that obtained from the α -oxime. This distinction in reactivity with copper can be utilised for the quantitative analysis of alcoholic solutions of mixtures of the benzilmonoximes ($R = R' = Ph$).



In the absence of soluble chlorides, the best conditions for obtaining rapid and quantitative precipitation of the insoluble copper complex of the α -oxime are as follows. 10 c.c. of a neutral alcoholic solution which is approximately 0.05M in α -benzilmonoxime are mixed with 25 c.c. of 0.1M-aqueous copper acetate; 250 c.c. of water are added, and the whole kept at room temperature for $\frac{1}{2}$ hour with occasional shaking. The precipitated green complex is filtered off and washed, first with alcohol and then with hot water (approx. 1000 c.c.), until free from soluble copper. The complex is then dissolved on the filter in the minimum of cold glacial acetic acid (approx. 10 c.c.), the filter paper washed free of copper with hot dilute acetic acid, and the copper in the united acetic acid filtrate and washings estimated iodometrically after dilution to 250 c.c. Addition of an aqueous suspension of cuprous iodide before the final titration makes the end-point noticeably sharper. Under these conditions the presence of β -benzilmonoxime, even in very large excess, has no effect; for instance, in one series of experiments, 10 c.c. of a solution of the α -oxime were found to be equivalent to 4.95 c.c. of the thiosulphate used (calc., 5.04 c.c.); to another 10 c.c. 0.2 g. of β -benzilmonoxime was added and the thiosulphate titre was 5.0 c.c. The method is somewhat tedious, but the complete precipitation of the complex cannot be accelerated; addition of ammonia or precipitation in hot solution leads to the formation of the complex by the β -oxime. The presence of soluble chlorides hinders or entirely prevents the formation of the complex by the α -oxime. The most satisfactory, though lengthy, way of overcoming this difficulty is to dilute the alcoholic solution containing the mixed oximes and the chloride (*e.g.*, lithium chloride) largely with water, extract the oximes thoroughly with pure ether and remove the ether at room temperature under reduced pressure. The solid remaining can then be dissolved in pure alcohol and the analysis performed as above. Three samples of a solution which was 0.057M with regard to the α -oxime and 2.06M to lithium chloride gave thiosulphate titres of 8.05, 8.0, 8.05 c.c. (calc., 8.04 c.c.).

Method of Measuring the Rate of Change: α -Benzilmonoxime \rightarrow β -Benzilmonoxime.—All materials used had been purified by the usual methods. The ethyl alcohol referred to as "96%" is the constant-boiling mixture obtained by the use of a long fractionating column: that called "absolute" had been refluxed over selected lime; it was protected from atmospheric moisture and its density showed that it contained 99.95% (vol.) EtOH. "Absolute" methyl alcohol had been dried in a similar way. The pure benzilmonoximes were obtained by the methods of Taylor and Marks (J., 1930, 2305).

The majority of the measurements were made at 55°. Preliminary experiments showed that at this temperature the rate of stereoisomeric change in the absence of catalysts is small enough to be neglected (after 22 $\frac{1}{2}$ hours a solution originally 0.0450M in α -oxime was found to be 0.0443M), and also that with 96% ethyl alcohol as solvent in the presence of 4M-hydrogen chloride there was no detectable hydrolysis to benzil and hydroxylamine in a period of 16 hours. For the velocity measurements with hydrogen chloride as catalyst, the reaction mixtures were made up in the thermostat and samples of known volume withdrawn at measured intervals. The sample was run into a quantity of concentrated alcoholic potash almost sufficient to neutralise the hydrogen chloride, and the neutralisation (methyl-red) completed with a more dilute solution. The whole was then cooled in ice for $\frac{1}{2}$ hour, and the potassium chloride which separated was removed on a fine filter-paper and thoroughly washed with alcohol. The amount of oxime in the combined filtrate and washings was then estimated by the method given above.

When other chlorides were used as catalysts, the samples removed from the reaction vessel were run into 250 c.c. of water cooled in ice, the oximes immediately extracted with pure ether, and the estimation carried out as described above. The results from an experiment were plotted, and the best smooth curve drawn through the points obtained. The velocity coefficients were calculated from values taken from these curves.

Results.

The rate of reaction was found to be unimolecular with respect to the α -oxime; for instance, in 96% ethyl alcohol at 55° with 2.0M-hydrogen chloride as catalyst, the unimolecular velocity coefficient was found to be 3.5×10^{-3} with an initial α -oxime concentration of 0.0923M, and 3.6×10^{-3} when that concentration was 0.0462M. Attempts to ascertain the effect of the addition of neutral salts gave the unexpected result that neutral chlorides soluble in alcohol (*e.g.*, lithium and tetramethylammonium chlorides) are themselves active catalysts. This property is not, however, possessed by all salts; *e.g.*, 2.4M-potassium acetate in 96% ethyl alcohol had no effect whatever in a period of 15 hours at 55°.

The results obtained are given in the table, and the majority of those at 55° are plotted in the figure. In all cases the initial concentration of the α -oxime was between 0.040*M* and 0.054*M*.

Unimolecular velocity coefficients (min.^{-1} ; \log_{10}) for the change $\alpha \rightarrow \beta$ -benzilmonoxime.

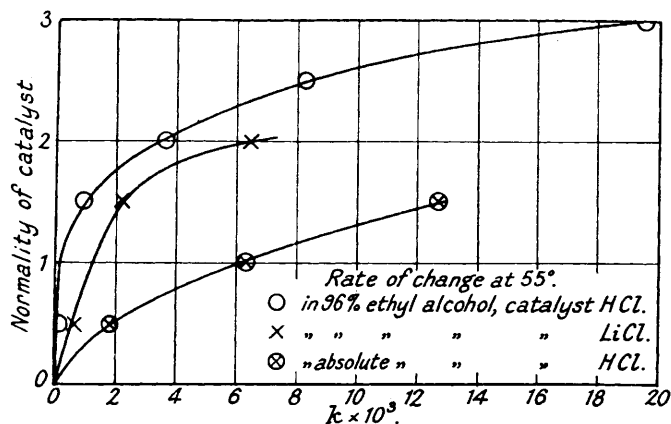
Values of $k \times 10^5$ at 55°.

Catalyst and concentration.

Solvent.	HCl, 0.5 <i>M</i> .	HCl, 1.0 <i>M</i> .	HCl, 1.5 <i>M</i> .	HCl, 2.0 <i>M</i> .	HCl, 2.5 <i>M</i> .	HCl, 3.0 <i>M</i> .	LiCl, 0.5 <i>M</i> .	LiCl, 1.5 <i>M</i> .	LiCl, 2.0 <i>M</i> .	NMe ₄ Cl, 0.5 <i>M</i> .	KCl, 0.5 <i>M</i> .
56% EtOH	1.4	—	15.0	—	—	—	—	—	—	—	85.3
96% EtOH	13.7	—	92.4	364	824	1960	67.2	220	640	412	—
Abs. EtOH	182	631	1270	—	—	—	—	—	—	—	—

Values of $k \times 10^2$ at 48°.

Abs. MeOH	Catalyst, 2.5 <i>M</i> -HCl	1.17
Abs. EtOH	" "	1.93



From these results the following main generalisations appear: (i) With hydrogen chloride as catalyst, the rate is not even approximately proportional to the concentration of the acid; it is inappreciable when the catalyst concentration is less than 1*M*, and above that value increases very rapidly. (ii) The addition of water to the system diminishes the rate markedly; thus, with 1.5*M*-acid as catalyst in absolute alcohol, the rate is decreased nearly 14 times by the addition of 4% of water. (iii) Lithium chloride and tetramethylammonium chloride are more efficient as catalysts than hydrogen chloride at an equivalent concentration.

It is immediately clear from these generalisations that the effective catalytic agent cannot be the hydrogen ion. Further, the change of the nitrogen atom of the oxime group from the tervalent to the quadricovalent state, such as must take place with hydrogen chloride when the oxime becomes a kation, or may take place with lithium chloride by co-ordination between the nitrogen and lithium atoms, cannot be an essential factor in the stereoisomeric change, since tetramethylammonium chloride is a very active catalyst, and with this compound there seems no possibility of co-ordination with the nitrogen atom of the oxime group. From the results, especially those in 96% ethyl alcohol, it can be seen that the species which is active catalytically is one whose concentration becomes appreciable only in concentrated solutions of the electrolyte, and thus it would seem that the most probable species is the undissociated molecule of the electrolyte (or the associated ion-pair).

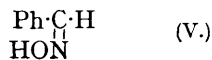
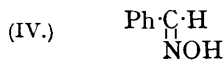
This view could be tested directly if the vapour pressure of hydrogen chloride above its solutions in ethyl alcohol were known at 55°, since the partial pressure could be taken, as a first approximation, as proportional to the concentration of the undissociated molecules. Unfortunately, the only measurements recorded are at 25° (Jones, Lapworth,

and Linford, J., 1913, **103**, 252), but it is interesting to notice that these workers found that addition of water lowered the partial pressure markedly. This observation is in agreement with the effect of the addition of water on the rate of change, catalysed by hydrogen chloride, if the catalysis is interpreted as one by undissociated molecules.

Electrolytic conductivity measurements give, of course, information about the tendency of an electrolyte in solution to ionic association (the formation of undissociated molecules). It is impossible to obtain any quantitative correlation between the results of such measurements and the reaction velocities recorded here, because at the high concentrations of electrolyte at which alone the velocities can be observed the conductivity results cease to have any simple meaning. If, however, the deviation of the conductivity-concentration curve of an electrolyte from the theoretical Onsager slope at high dilutions is taken as a qualitative measure of its tendency to form ion-pairs at all concentrations, there is good agreement with its activity as a catalyst for the stereoisomeric change; greater deviation as observed from the conductivity measurements goes with greater catalytic power as observed in our experiments. Thus, Murray-Rust, Gatty, Macfarlane, and Hartley (*Ann. Reports*, 1930, **27**, 342) state that "in alcohols the tetrasubstituted ammonium salts show the maximum deviation from the theoretical slope," while we find that tetramethylammonium chloride has by far the greatest catalytic activity of the substances examined. Again, they say, "for hydrochloric acid there is more ionic association in ethyl alcohol than in methyl alcohol"; the results in the table show that, at the same temperature and at equal concentration, hydrogen chloride is 1.65 times as efficient a catalyst in ethyl alcohol as it is in methyl alcohol. Finally, they state that "in alcohols the tendency to associate in any series of salts with the same anion increases with the atomic number of the kation"; the chlorides of the alkali metals above lithium are too insoluble in the alcohols to be used as catalysts, but we find that potassium chloride (0.5*M*) in 56% ethyl alcohol is 1.27 times as efficient a catalyst as is lithium chloride in 96% alcohol at the same temperature, so there is little doubt that in 96% alcohol its activity would be much greater than that of lithium chloride, and thus that this third conductivity generalisation finds an example in our velocity measurements.

Further support for our view is afforded by experiments with benzene and ether as solvents. Mr. O. L. Hughes has informed us that he finds that hydrogen chloride in dry benzene shows no electrolytic conductivity whatever, and is thus presumably entirely in the form of undissociated molecules; in each solution it should thus be a very powerful catalytic agent for the conversion of α - into β -benzilmonoxime. When the α -oxime was added to a solution of hydrogen chloride (0.45*M*) in dry benzene at room temperature, it dissolved; on shaking, a thick white precipitate was rapidly formed, which, after being collected and dried, melted over the range 70—100° (β -benzilmonoxime + $\frac{1}{2}$ C₆H₆ has a non-congruent m. p. 62°), and, after one recrystallisation from carbon disulphide, at 112°. Determination of mixed m. p. and tests with alcoholic copper acetate show that it is pure β -benzilmonoxime. The same result was obtained in ether, both at room temperature and at -20°; conversion into the β -oxime seems complete in less than two minutes.

If it is conceded that in these cases of catalysis of normal stereoisomeric change in oximes the active agent is the undissociated molecule of electrolyte, the question remains as to the actual mechanism of the catalysis. This question is complicated by the fact that catalytic power in concentrated solution is not possessed by all uni-univalent salts. The choice of salts is very much restricted by the sparing solubility of the majority in solvents in which the benzilmonoximes are soluble, but experiment showed that potassium acetate (2.2*M*) in ethyl alcohol at 55° had no effect whatever in 15 hours and potassium ethyl sulphate (0.205*M*) none in 24 hours. The reality of this result is confirmed by our experiments with the benzaldoximes. Of these, the α -oxime (m. p. 35°, IV) is the stable form. The normal direction of stereoisomeric change is thus for the β -oxime (m. p. 127°, V) to pass into the α -oxime, and this change takes place readily on heating (Beckmann, *Ber.*, 1887, **20**, 2767).



Since no method has been devised for the analysis of mixtures of these two oximes, the experiments were qualitative. It was found that the pure β -oxime (recrystallised from ether and light petroleum) could be left in 96% alcoholic solution for 14 hours at room temperature and then recovered by diluting largely with water, extracting with ether, and removing the ether at room temperature without bringing about any change into the α -oxime. If, however, the β -oxime is dissolved in a 2*M*-alcoholic solution of lithium chloride, the oxime recovered after 14 hours by the same procedure is shown by its m. p. to be the pure α -oxime. When the lithium chloride is replaced by potassium acetate, the β -oxime is recovered unchanged, and no stereoisomeric conversion has taken place. There is thus the same specificity in the action of the electrolytes as with the benzilmonoximes.

A clear distinction should be drawn between the kind of catalysis discussed here and attributed to undissociated molecules of certain electrolytes and cases such as that of Comstock (*Amer. Chem. J.*, 1897, 19, 485), who found that α -benzaloxime in toluene solution will react with cuprous chloride to give a copper complex containing only β -benzaloxime, or the case of the prolonged action of alcoholic copper acetate on β -benzilmonoxime (Taylor, J., 1931, 2782) in which a copper complex of α -benzilmonoxime is formed. In these two cases the change is in the abnormal direction, the more stable form giving a complex containing the less stable, and the essence of such abnormal changes must be the actual chemical interaction of the oxime grouping with the copper atom. In the cases investigated here, the intermediate formation of compounds between oxime and catalyst seems unlikely to be the cause of the phenomenon; no such complexes could be obtained from lithium chloride and any of the benzilmonoximes or benzaloximes. Further, it is difficult to see how tetramethylammonium chloride, which is a powerful catalyst, could unite to form a covalently linked complex with the oxime group.

The essence of the catalysis of the normal stereoisomeric change must be that the torsional rigidity of the double bond between carbon and nitrogen, which in the absence of the catalyst is sufficient to prevent the less stable oxime going over readily into the more stable isomeride, is decreased in the presence of the catalyst. There is the comparable case of geometrical isomerides in the carbon series, where free atoms, such as sodium or bromine, and paramagnetic molecules, such as nitrogen peroxide, act as catalysts for the normal direction of stereoisomeric change. For these cases R. Kuhn (*Solvay Report*, "Molecules organiques," 1931, p. 361 *et seq.*) has already suggested that the catalysis has its origin in the odd-electron structure of such atoms and molecules; he supposes that such structures are capable of interacting with the electronic system of the carbon-carbon double bond and causing profound alteration in its properties. He has further suggested that the hydrogen ion and other kations might have a similar effect.

The most probable cause of the catalytic effects observed in the present work would seem to be a somewhat similar interaction between the undissociated electrolyte and the carbon-nitrogen double bond. It is possible that the close approach of the electric fields of the ion-pair and the oxime grouping may give rise to an interaction which brings about a decrease in the torsional rigidity of the double bond, so that normal stereoisomeric change takes place at a temperature at which the less stable form would exist unchanged in the absence of the catalyst. That salts such as potassium acetate have no catalytic power is not easy to explain. It may be due to some steric cause; such molecules may have a shape which prohibits the right kind of close approach to the oxime grouping. There are, however, other possible factors, such as solvation of the ion-pair, which may be playing a part; too little is known of the nature and properties of the ion-pair for an adequate discussion of the point.

It is to be noticed that the effect suggested by Kuhn, *viz.*, that the hydrogen ion and other kations may have sufficient polarising action on the double bond to facilitate stereoisomeric change, does not seem to be present to any noticeable extent in the oximes which we have studied.

Finally, attention may be directed to the striking difference between the action of hydrogen chloride and lithium chloride on the benzilmonoximes and the benzaloximes. In the former case, both substances act as catalysts for the normal change of the α - into the β -oxime; in the latter, lithium chloride has no effect on the more stable α -benzaloxime

and acts normally in catalysing the change of the β - into the α -oxime, while hydrogen chloride is entirely different and is the classical reagent for the abnormal conversion of the α - into the β -oxime. This difference arises from the fact, demonstrated by Luxmoore (J., 1896, **69**, 179) and by Brady and Dunn (J., 1916, **109**, 679), that with the aldoximes an entirely new factor not present in the ketoximes comes into play, *i.e.*, the stabilities of the aldoxime hydrochlorides are the reverse of those of the free aldoximes; α -benzaloxime is more stable than its β -isomeride, but the α -hydrochloride is less stable than the β -hydrochloride, and passes spontaneously into it even at a low temperature.

SUMMARY.

1. A method is described for the volumetric analysis of mixtures of α - and β -benzilmonoximes in alcoholic solution.

2. The rate of stereoisomeric change of α -benzilmonoxime into its β -isomeride with various electrolytes as catalysts and in various solvents has been measured.

3. The results indicate that the undissociated molecules of the electrolyte (or ion-pairs) are responsible for the catalytic effect.

4. The mechanism of the catalysis is discussed; it seems probable that, in essence, it is an interaction between the electronic systems of the ion-pair and the carbon-nitrogen double bond.

THE DYSON PERRINS LABORATORY, OXFORD.

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