

CCCXL.—*Studies of Dynamic Isomerism. Part XXV.*  
*The Mechanism of Catalysis by Acids and Bases.*

By THOMAS MARTIN LOWRY.

*Catalysis of Mutarotation by Acids and Bases.*

THE fact that mutarotation, like so many other chemical changes, is not a spontaneous process, but depends on the presence of a catalyst (Lowry, J., 1899, 75, 211), compels us to seek an explanation of the part played by the catalyst in effecting the change, and in particular to discover a reason for the unique efficiency of water as a solvent for the mutarotation of the sugars, and for the still more remarkable catalytic activity of acids and bases. The earliest suggestion (*ibid.*, p. 219) postulated that mutarotation could be initiated by any oxygenated solvent, since the changes of rotatory power in these solvents were usually very rapid when compared with the slow changes observed in hydrocarbons and in analogous solvents such as chloroform. This view became untenable, however, when it was found that the mutarotation of nitrocamphor could be "arrested" by adding a trace of carbonyl chloride to *ether*, in order to eliminate basic impurities (Lowry and Magson, J., 1908, 93, 119). It was then pointed out that catalytic solvents all appeared to be of the type HX, and that solvents from which a hydrogen atom cannot be eliminated easily are not able to initiate isomeric change, although (as in the case of ether) they may contain oxygen, and may even possess ionising properties (*ibid.*, p. 132). Subsequent investigations (Lowry and Richards, J., 1925, 127, 1385; Lowry and Faulkner, *ibid.*, p. 1883) showed that, although dry pyridine had been repeatedly cited as an effective catalyst for the mutarotation of glucose (Behrend and Roth, *Annalen*, 1904, 331, 361), pyridine and cresol are alike impotent *in the absence of water*, but that when mixed with one another they develop a catalytic activity which is

far greater than that of water itself. The view was therefore advanced that the prototropic changes which give rise to the mutarotation of the sugars can only take place in an amphoteric solvent, *i.e.*, in a solvent which can both accept a proton from the sugar and give a proton back again to it or to its ion.

An entirely different method of approach to the problem is found in the theory put forward by Euler (Euler and Hedelius, *Biochem. Z.*, 1920, **170**, 150; Euler, Myrbäck, and Rudberg, *Arkiv. Kemi Min. Geol.*, 1923, **8**, No. 281) in order to provide a quantitative basis for determining the influence of acids and alkalis on the mutarotation of glucose. Euler supposes (i) that the velocity of mutarotation of glucose is proportional to the volume concentration of its *ions*, and (ii) that these ions are produced by the formation of *salts* of the sugar, on the one hand with alkalis, and on the other with acids. According to this theory, the velocity of mutarotation of the sugar in a solution of given acidity or alkalinity could be calculated from its acid and basic dissociation constants,  $K_a$  and  $K_b$ , together with the reaction velocities,  $r_a$  and  $r_b$ , of the anion and kation of the sugar salts; but in practice the calculation can only be carried out in the converse direction, since only one of the four fundamental constants has been measured by an independent method. This one independent constant is the acid dissociation constant of glucose in water at 18°, which was determined electrometrically by Michaelis and Rona (*Biochem. Z.*, 1913, **49**, 232) from the change of "hydrogen-ion concentration" on adding the sugar to a dilute alkali. Euler and Hedelius (*loc. cit.*) measured the velocity of mutarotation of glucose in buffer solutions containing sodium citrate and hydrochloric acid of  $N/10$  and  $N/100$  concentration, and deduced (by extrapolation to zero concentration of buffer solution) the value  $k^* = 0.0066$  for the minimum velocity at 20°, and  $p_H = 3.6$  for the hydrogen-ion concentration at this point of maximum stability of the sugar; they then used the value,  $K_a = 6.6 \times 10^{-13}$ , given by Michaelis for the *acid dissociation constant* of the sugar at 18°, in order to calculate an approximate value,  $K_b = 10^{-19}$ , for the *basic dissociation constant*, on the assumption that the point of maximum stability is identical with the isoelectric point and that the hydrogen-ion concentration at the isoelectric point is given by the equation  $[H^+] = \sqrt{K_a K_w / K_b}$ , where  $K_w$  is the dissociation constant of water. In two subsequent papers (*Z. anorg. Chem.*, 1925, **146**, 45; 1926, **152**, 113), Euler used his own measurements of the acid dissociation constant of water at 5.2° in order to deduce values for the concentration of the sugar ions and for their reaction velocities at this temperature, which he

\* The velocity coefficient calculated from logarithms to the base 10.

supposed to be equal to one another, since he obtained symmetrical catenary curves on plotting the velocity of mutarotation at  $5.2^\circ$  and at  $20^\circ$  against the  $p_H$  of the solution. In this way he deduced for the four essential constants at  $5.2^\circ$  the values  $K_a = 1 \times 10^{-13}$ ;  $K_b = 2 \times 10^{-18}$ ; and  $r_a = r_b = 38$ , the half-change period being therefore 0.45 sec. for the ion of either sign.

Euler's ionic theory of mutarotation was at once adopted by Kuhn and Jacob (*Z. physikal. Chem.*, 1924, **113**, 389) as the basis for their numerical calculations. These authors made a new series of measurements of the velocity of mutarotation of glucose at  $25^\circ$  in solutions of different degrees of acidity and alkalinity, and showed that it could be expressed by an equation which differed only slightly from that of Hudson. Since this equation contains a term which does not depend on the acidity or alkalinity of the solution, they concluded that the neutral molecules of glucose, as well as the kations and anions derived from them, undergo isomeric change. Moreover, since the two arms of their catenary curve were not symmetrical, they concluded that the reaction velocity of the anions and kations are not equal (as Euler supposed) but that the reaction velocity of the anions is 2.1 times as great as that of the kations. They therefore assigned to the reaction velocities at  $25^\circ$  of the neutral molecules of the sugar and of the kations and anions derived from them the values  $r_u = 0.0104$ ,  $r_b = 54.4$ , and  $r_a = 113.2$ . The dissociation constants of the sugar at this temperature were given as  $K_a = 10.5 \times 10^{-13}$  and  $K_b = 7.8 \times 10^{-17}$ .

In his later papers, Euler also adopted the view that mutarotation is not due exclusively to the anion and kation of the sugar, but he suggested that the constant term in Hudson's equation need not necessarily represent the isomeric change of the undissociated molecules of the sugar, since it could also be attributed to a "zwitterion" (or bipolar molecule, compare J., 1925, **127**, 1371) carrying both a positive and a negative charge, or to "some form of glucose which is present at a concentration proportional to that of the uncharged molecules."

It will be seen that, whilst the simple ionic theory of mutarotation can be used to calculate hypothetical values for the ionisation of the sugar, and for the reaction velocities of its ions, it does not provide any numerical data which can be checked by independent experiments. It is, moreover, definitely incompatible with our more recent observations on mutarotation in non-aqueous solutions, and must be rejected for the following reasons :

(i) If the sugar is capable of being ionised by mere dissolution in water, according to the scheme  $HS \rightleftharpoons H^+ + S'$ , it must obviously be ionised even more readily to form an ionised pyridinium salt accord-

ing to the scheme  $C_5H_5N + HS \rightleftharpoons C_5H_5NH' + S'$ , when dissolved in anhydrous pyridine.\* If then the ion  $S'$  has a definite reaction velocity, as Euler supposes, this ion must at once undergo isomeric change and give rise to a very rapid mutarotation, since the half-life period of the ion (according to Euler's calculation) is less than a second. In reality, however, nothing of the sort happens, since the mutarotation of tetramethyl glucose in pyridine can be stopped completely over a period of 2 or 3 hours by very moderate purification and drying (Lowry and Richards, *loc. cit.*, p. 1398).

(ii) Conversely, if the sugar is capable of being ionised, either by removal of hydroxyl or by addition of hydrogen, according to the scheme  $HOS \rightleftharpoons HO' + S'$  or  $S + H' \rightleftharpoons HS'$ , it seems certain that this ionisation must be promoted by dissolving the sugar in an acidic solvent, such as cresol, which would form an ionised salt according to the scheme  $C_7H_7 \cdot OH + HOS \rightleftharpoons C_7H_7 \cdot O' + S' + H_2O$ , or  $C_7H_7 \cdot OH + S \rightleftharpoons C_7H_7O' + HS'$ . The ionic theory then indicates once more that this ionisation must be followed by a rapid isomeric change, and consequent mutarotation, in accordance with the ordinary laws of mass action and reaction velocity. Actually, however, the velocity of mutarotation of tetramethyl glucose in cresol is almost inappreciable, since it is at least forty times less than in pure water.

(iii) Finally, if the simple ionic theory were correct, mutarotation must inevitably occur *in any ionising solvent*, whereas experience has shown that it is only in the case of media which possess definite amphoteric properties that we can assert with any degree of confidence that the pure solvent is a complete catalyst for mutarotation. Thus, even in the case of methyl alcohol, which is quite a good ionising solvent, the very low velocity coefficient observed by Faulkner and Lowry (J., 1926, 1938) has been reduced about 8-fold in the recent experiments of Worley and Andrews (*J. Physical Chem.*, 1927, **31**, 742), so that the residual velocity of change is now altogether insignificant.

On all these grounds the simple ionic theory of catalysis is seen to be untenable in the light of experiments on mutarotation in non-aqueous solutions.

#### *An Electrolytic Theory of Catalysis.*

A mechanism of catalysed mutarotation, which is in harmony with the observations cited above (and which actually led to the experiments by which most of the relevant facts were discovered)

\* It is assumed that the pyridine has not been dried so perfectly as to inhibit completely the formation of a salt, as in Baker's experiments on dry ammonia and hydrogen chloride.

was described in 1925 (J., 127, 1371). This mechanism depends on an initial *addition and subtraction of a proton* by a medium possessing both acid and basic properties, giving rise to the formation of a bipolar molecule or "zwitterion"; the rupture of a bond (by the conversion of the covalency into an electrovalency) then produces just those electric charges which are needed to neutralise the charges already present in the bipolar molecule, and thus gives rise immediately to the intermediate aldehydic form of the sugar. Only two additional points are needed in order to make this mechanism cover also Dawson's recent experiments on the iodination of acetone in presence of acids and their salts, as well as the new observations on mutarotation which are described in Part XXIV (preceding paper). These additional points are (i) a clear recognition of the fact that prototropic change involves a *flow of electrons through the molecule*, in addition to the transfer of a proton to and from the medium, and (ii) an extended conception of the meaning of the terms acid and base, to include all those ions and molecules which are able to give or to receive a proton. The isomeric change is then seen to depend on a process which is closely analogous to an electrolysis of the prototropic compound between positive and negative poles provided by the basic and acid components of the medium.

(a) *Electron-migration as a Condition of Isomeric Change.*—It is not generally realised that the process of isomeric change in unsaturated compounds involves a flow of electrons through the molecule, as well as the migration of a radical. It is, however, obvious that, if the *radical* migrates in the form of an *ion*, it must deliver up an electric charge at its new point of attachment, whilst leaving behind a charge of opposite sign at the point of departure; the elimination of these electric charges is therefore an essential feature of the isomeric change. It is then easy to show that the rearrangement of bonds (described by Jacobsen as "desmotropy"), which accompanies isomeric change in unsaturated and conjugated systems, actually consists in a transfer of valency electrons from atom to atom, and that this transfer produces a flow of electrons of precisely the kind that is required to neutralise the charges set up by the migration of the ion.

Since the iodination of acetone, which has formed the basis of Dawson's recent experiments on catalysis, depends on the enolisation of the ketone (Lapworth, J., 1904, 85, 30), it will be convenient to select this type of isomeric change as an illustration of the general proposition set out above. We will therefore suppose that an enol is to be changed into a ketone by an ionic mechanism of the same general character as that postulated by Euler and by Kuhn and Jacob for an action catalysed by bases. The four consecutive



necessary to elaborate this point in connexion with the simpler case of keto-enolic change.

(ii) When compared with the simple ionic theory described above, the electrolytic theory is seen to depend on a *ternary reaction* between the sugar and the acid and basic components of the solvent, whereas Euler postulated a *binary reaction* between the sugar and a catalyst, which may be either acid or basic, but not both. It is, of course, possible that, if the sugar were ionised, say by the removal of a proton with the help of an alkaline catalyst, the resulting anion might be discharged by a proton coming into contact with the opposite "terminal" of the sugar, instead of with the "terminal" from which the proton had been originally removed, thus giving rise to an isomeric form of the sugar; but no provision is made in Euler's theory for any independent supply of protons for this purpose, apart from those which were derived in the first instance from the sugar by ionisation. The electrolytic theory, on the other hand, definitely requires that the medium, instead of being merely an ionising solvent, must be one which can act both as a "proton source" and as a "proton sink."

(iii) A third feature of the electrolytic theory is to be found in the suggestion that the easiest way of effecting isomeric change is to bring the organic compound into a circuit in which it is in contact *simultaneously* with a proton acceptor and a proton donator. It has already been suggested (J., 1925, 127, 1383, footnote) that the changes in question "may occur simultaneously in the same electric circuit, as in Armstrong's theory of chemical change"; but this tentative suggestion is now advocated as affording for the first time an adequate explanation of the impotence of acids and bases to produce mutarotation when acting alone, and of their wonderful efficiency when acting together. The obvious alternative is to suppose that the acid and basic components of the medium may act on the sugar *consecutively* instead of simultaneously. Thus the action might be supposed to depend on *two consecutive bimolecular actions*, in which the acid and basic components act independently on the sugar (i) to produce a sugar ion by the addition (or removal) of a proton, and (ii) to discharge this ion through the body of the sugar by the removal (or addition) of a proton at the opposite "terminal" of the labile system. The initial stage in this action is, however, an endothermic process, in which the molecules of the sugar are converted into ions of such an unstable character that the dissociation constants are said to be of the order of  $10^{-13}$  and  $10^{-19}$ . The exact amount of energy required to produce these ions is unknown; but it is obvious that, if we can regard the entrance and the exit of the proton as simultaneous, no energy at all is needed beyond the small

amount that is required to cover the difference in energy content of the two isomerides, and perhaps to overcome the "frictional" resistance to the migration of an electron through the sugar. The ternary reaction therefore exhibits, in a characteristic form, the essential feature of a catalysed reaction, since, by making use of a "coupled reaction" in place of two consecutive reactions, it avoids the necessity for lifting the molecule to the high energy level represented by its extremely unstable ions.

*Acidity and Basicity as Factors in Catalysis.*

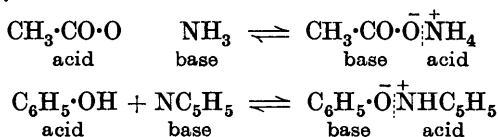
In order that the electrolytic theory of catalysis may cover Dawson's experiments, as well as the new results set out in the preceding paper, it is necessary to abandon the narrow definition which measures acidity in terms of hydrogen-ion concentration and basicity in terms of hydroxyl-ion concentration, and to make use of definitions and constants which are not limited to the special case of aqueous solutions. Thus, when water is the solvent, the basicity of a solution can be expressed in terms of its alkalinity, as measured by the concentration of hydroxyl ions in the liquid; but this is no longer true of solutions of nitrogenous bases in non-aqueous solvents, many of which do not contain any oxygen at all. We have, therefore, adopted the more modern view, which regards acidity as a characteristic property of all those hydrogen compounds which can give up a proton to some other molecule or ion, whilst basicity is the more general and passive property of being able to accept a proton from an acid.

(a) *Acid catalysts.* If this conception is adopted we must include as *acids* all those ions or molecules which can give a proton to acetone or to a sugar. Of these acidic catalysts, we may exclude from our consideration the *free hydrogen ion*,  $H^+$ , which is probably non-existent in solution, since its formation can only take place by an endothermic action involving the absorption of about 260,000 calories; it can, however, be replaced (perhaps quantitatively) by the *oxonium ion*,  $OH_3^+$ , which is probably the principal form in which "hydrogen ions" exist in the solution, although the presence of  $OH_4^+$  is not excluded. The *undissociated acid*,  $HX$ , must also be classed with the oxonium ion as a proton donator, and may therefore be an active catalyst, apart altogether from any pre-existent ionisation, since there is nothing to prevent the molecule of acid from giving a proton directly to the acetone or to the sugar, instead of passing it on (as an oxonium ion) through the agency of a molecule of water; it is also clear that the undissociated molecule of a strong acid is necessarily a more powerful proton donator than the molecule of a weak acid, and must therefore be a much more powerful catalyst,



as Snethlage and others have found to be the case. *Neutral water* also must be classed as a proton donator, quite independently of its pre-existent ionisation, since here again there is no reason why one molecule of water should be compelled to make use of a second molecule of water as an agent for transferring a proton to the ketone or to the sugar.\* According to our theory, however, these proton donators can only act in conjunction with a proton acceptor, which in dilute aqueous solutions will usually be a molecule of the solvent.

(b) *Basic catalysts.* Amongst the bases or proton acceptors it is usual to reckon only the *hydroxyl ion* as having any catalytic activity, but for the present purpose the molecule of *neutral water* must also be included as a basic catalyst, in view of the readiness with which it can combine with a proton from the acetone or from the sugar to form an oxonium ion. More novelty is to be found in the perfectly logical conclusion of Brönsted (*Rec. trav. chim.*, 1923, **42**, 718) that *the anion of an acid* is also a base or proton acceptor, in view of the fact that it can combine with a proton to form a molecule of the undissociated acid. The fact that *the basicity of the anion is inversely proportional to the acidity of the acid* provides an obvious explanation of the fact that the oldoide ion has no marked catalytic activity, such as is possessed by the acetate ion in virtue of the weakness of the acid from which it is derived. It is of interest to notice that, whilst ammonia is a *base* in virtue of its ability to accept a proton from an acid, the resulting ammonium ion is an *acid* (just like an oxonium ion) in virtue of its ability to give up a proton, *e.g.*, when the ammonium salt is dissociated into the free acid and base,  $\text{NH}_4\text{Cl} \rightleftharpoons \text{NH}_3 + \text{HCl}$ . In the case of ammonium acetate or pyridinium phenoxide, there is a similar reversal of function on the two sides of the equation :



On the other hand, a metallic ion, which can neither give nor accept a proton, possesses no acid or basic properties of any kind, and cannot act as a catalyst for mutarotation.

#### *Applications of the Electrolytic Theory of Catalysis.*

(a) *The Dual and Quadruple Theories of Acid Catalysis.*—The “dual theory” of acid catalysis met with a good deal of passive resistance merely because it was not easy to see how an acid could

\* The ionisation of water cannot give rise to a free proton, and must therefore be written as  $2\text{H}_2\text{O} \rightleftharpoons \text{OH}_3^+ + \text{OH}^-$ , instead of  $\text{H}_2\text{O} \rightleftharpoons \text{H}^+ + \text{OH}^-$ .

act as a catalyst apart from its acidity, *i.e.*, its ability to liberate hydrogen ions. This difficulty no longer exists, however, if we admit that  $HX$  and  $OH_3^+$  can both act as proton donators, and so contribute to the catalytic activity of the system, although only the ion is able to contribute directly to its electrical conductivity. Dawson's "quadruple theory" of catalysis presents even greater difficulties, since no hint is given to suggest why the *anions* of a salt should be catalytically active, but not the *kations*. The distinction thus made between anions and kations has, however, been shown to be fictitious, in that it only applies to metallic kations, which cannot take any part in a catalysis which depends on giving or receiving a proton; on the other hand, our own experiments have shown that the ammonium and pyridinium ions, which can give but not receive a proton, both act as catalysts for the mutarotation of a sugar in aqueous solutions. It is also clear that the catalytic activity of an anion depends on the weakness of the acid from which it is derived, and should therefore disappear, as experiment has proved (*e.g.*, in the case of the chlorides), when the anion is derived from a strong mineral acid. If, then, we admit that the kations of a weak base and the anions of a weak acid possess similar catalytic functions to the hydrogen and hydroxyl ions, since they must also be classed as acids and bases in terms of the modern definitions, all the coefficients in Dawson's equation for the catalysis of acetone are then seen to refer to molecules or ions which possess acid or basic functions, thus :

$$v = k_H[H^+] + k_a[A^-] + k_{OH}[OH^-] + k_m[HA].$$

On the other hand, those molecules and ions which cannot act as acids or bases are omitted from the equation, since they are not able to influence the course of the change.

(b) *Catalysis by Neutral Water*.—A similar difficulty to that encountered in connexion with the dual theory of acid catalysis is presented by the constant term in Hudson's equation for the velocity of mutarotation of glucose, which we may write as :

$$k_1 + k_2 = 0.258[\overset{+}{H}] + 9750[\bar{O}H] + 0.0096.$$

The constant term, which accounts for practically the whole of the velocity at the isoelectric point, and for 92% of the velocity in neutral water, was regarded by Kuhn and Jacob as a measure of the velocity of isomeric change in *neutral molecules of sugar*, and by Euler as representing the *isomeric change of a "zwitterion"* derived from the sugar; but it can be explained much more naturally by regarding it as a measure of the catalytic activity of *neutral molecules of water*. It was, however, very difficult to see how water could

act as a catalyst, in a process that is catalysed specifically by acids and alkalis, except by dissociation into hydrogen and hydroxyl ions, the activity of which was already allowed for in the equation. On the other hand, since the electrolytic theory of catalysis postulates that prototropic change depends on the combined action of an acid and a base, we may regard the first two terms in the above equation as representing the combined action of (i) a hydrogen (or oxonium) ion acting as a proton donator at one "terminal" of the sugar, with water as proton acceptor at the other, and (ii) a hydroxyl ion acting as proton acceptor at one "terminal" point with water as proton donator at the other. There is then still room for a "neutral water" term to represent (iii) the action of a molecule of water acting as a proton donator (with formation of a hydroxyl ion) at one terminal, with another molecule of water acting as a proton acceptor (with formation of an oxonium ion) at the other terminal. This neutral-water term, which is independent of the acidity and alkalinity of the solution, does not appear in Dawson's equations, perhaps because the enolisation of acetone is too difficult a process to be effected to any appreciable extent by the combined action of two molecules of water and requires the intervention of at least one component with stronger acid or basic properties. Since, however, components of both types are necessary for the effective catalysis of a prototropic change, all the other terms in his equation must be regarded as representing the combined action of the ions or molecules of the catalyst *with neutral molecules of water*, which would be present in an enormous excess in the dilute aqueous solutions with which he worked.

(c) *Hydrolysis*.—Since the analogy between hydrolysis and prototropic change provided the experimental data from which the mechanism now under discussion was first deduced (J., 1925, 127, 1379), it is inevitable that the electrolytic theory of mutarotation should be supplemented by an electrolytic theory of hydrolysis. Thus, when regarded from the point of view which is set out above, the rupture of the ester bond in hydrolysis and its formation in esterification are seen to involve a transfer of valency electrons, which is equivalent to the passage of an electric current; the process therefore again resembles an electrolysis of the organic compound between positive and negative poles provided by the acid and basic components of the solution. Whilst, however, any molecule or ion which is capable of accepting a proton from an organic compound can play the part of the base in promoting prototropic change, this is no longer true of hydrolysis, where the *hydroxyl ion* and the *neutral molecule of water* are the only catalysts which are able to provide the necessary atoms of oxygen and hydrogen. We can

therefore foresee that the acetate ion, which has such a marked effect on the mutarotation of glucose, can exert no *direct* action in promoting hydrolysis. Any effects which it can produce must then result from an indirect process of activating either the pre-existing hydroxyl ions or the ester, or (in some more vague way) the medium in which hydrolysis is proceeding. These effects may be purely apocryphal, although they have been used freely to support the view that catalysis by acids depends exclusively on the concentration of pre-existing hydrogen ions. It is, however, noteworthy that, whilst other workers have suspected that the undissociated acid as well as its ions can act as a catalyst in hydrolytic processes such as the inversion of cane sugar, the inherent activity of the anion of a weak acid was only demonstrated when catalysis was studied by a process depending on prototropic change, and not on hydrolysis. Whilst, therefore, it is quite possible that a physico-chemical analysis may disclose some influence of the anion on esterification or hydrolysis, it appears probable that this indirect effect will be very much smaller than the direct effects which have been observed in the iodination of acetone and in the mutarotation of glucose.

*Summary.*

(a) The catalysis by acids and bases of prototropic change and of hydrolysis is interpreted in terms of an electrolytic theory, according to which a flow of valency electrons through the molecule is produced by bringing a proton donator and a proton acceptor, or a hydroxyl donator, into contact with the two terminals of the labile complex.

(b) An explanation is given of the parts played in the catalysis of isomeric change by (i) neutral water, (ii) the molecules of a strong acid, (iii) the anions of a weak acid, and (iv) the kations of a weak base. The ineffectiveness of metallic kations in isomeric change and of the anions of an acid in hydrolysis are also accounted for.

UNIVERSITY CHEMICAL LABORATORY,  
CAMBRIDGE.

[Received, July 28th, 1927.]

---