IX.—*Optical Activity and the Polarity of Substituent Groups. Part VI. Optically Active Acids and Bases.*

By HAROLD GORDON RULE.

IN the first paper of this series (J., 1924, **125**, 1121), it was shown, from a consideration of the relative directive effects of a number of substituents on benzene substitution, that the substituents could be arranged in a *polar series* representing a gradual transition from those of high positive polarity through the comparatively non-polar groups to those of high negative polarity. This series was also found to correspond with the influence of the same substituents on the rotatory powers of certain aliphatic and aromatic compounds, special reference being made to the menthyl esters of ortho-substituted benzoic acids. A theoretical justification for this series was based on the views of Sir J. J. Thomson on the nature of substitution in organic compounds (*Phil. Mag.*, 1923, **46**, 497).

In the main, these conclusions have been supported by further experiments with the menthyl and *sec.*-β-octyl esters of *o*-substituted benzoic acids (Rule and Smith, J., 1926, 553; Rule and Numbers, *ibid.*, 2116), although where the substituents are separated from the asymmetric atom by a longer non-conjugated chain their influence on the rotatory power is more closely related to their *general effect* as deduced from data referring to the dissociation constants of acids. Under the latter heading may be mentioned the derivatives of active bases investigated by Betti (*Gazzetta*, 1923, **53**, 417) and the menthyl and *sec.*-β-octyl esters of monosubstituted acetic acids (Rule and Smith, J., 1925, **127**, 2188; Rule and Mitchell, J., 1926, 3202). The deductions previously drawn from Thomson's views on *m*- and *p*-disubstituted benzenes have not been confirmed, however, and from an investigation on the inductive capacities of *o*-, *m*-, and *p*-disubstituted benzenes recently carried out in these laboratories, Kerr (*Phil. Mag.*, in the press) concludes that Thomson's suggestions only hold in their original simplicity for compounds of this type in which the two substituents are identical.

Now if the properties of compounds are affected in the manner indicated above by the polarity of substituent groups, it would be anticipated that changes of an even more pronounced character would follow the introduction into the molecule of ionisable complexes which are capable of assuming an actual electrical charge. It is an accepted fact that an ionised complex exerts a powerful influence on substitution in the benzene nucleus, and that the course of this reaction varies with the sign of the charge. For example, although aniline under ordinary conditions substitutes in the *o*-, *p*-positions, it may be nitrated in the *m*-position by using it in the form of aniline sulphate dissolved in a large excess of sulphuric acid. The positively charged ionic complex $\cdot NH_3^+$ thus behaves as a positive or *m*-directive substituent. On the other hand, benzoic acid, which brominates slowly in the *m*-position, may be rapidly converted into the *o*- and *p*-derivatives by chlorinating the sodium salt in aqueous solution (Lossen, D.R.-P. 146174). Here the negatively charged complex $\cdot CO\cdot O^-$ ranges itself with the negative or *o*-, *p*-directive substituents. The parallel between the influence of substituents on the nitration of a mono-substituted benzene and on the optical activity of esters of *o*-substituted benzoic acids is illustrated in the following table, where (*a*) represents the percentage of *m*-compound formed, (*b*) percentage of *p*-compound, (*c*) molecular rotations of the menthyl esters, and (*d*) molecular rotations of the *sec.*-β-octyl esters, in so far as these values have been determined.

Table of Substituent Influence.

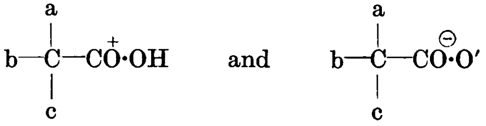
	NH_3^+.	NO_2.	CO_2H.	COMe.	H.	Me.	I.
a	Chiefly meta	93	76	55	—	3·1	—
b		0·4	1·2	—	—	41	66
c	—	381°	332°	261°	239°	231°	237°
d	—	122°	(90—117°*)	—	78°	—	—

	Br.	Cl.	F.	$CO\cdot O^-$.	OMe.	NMe_2.
a	0·3	—	0·2			
b	62	70	87	(Chiefly para and ortho.)		
c	205°	195°	194°	180°	148°	101°
d	—	47°*	—	—	33°	—

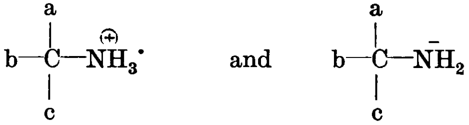
* Rule, Numbers, and Paterson, unpublished results.

The parallel is a very complete one, and particular attention may be directed to the difference in the behaviour of the positive carboxyl group and the negatively charged $\cdot CO\cdot O^-$ complex. The value of 180° is quoted for the rotation of the sodium salt of menthyl hydrogen phthalate in 5% aqueous solution (Kenyon and Pickard, J., 1915, **107**, 58), but it is probable that this falls to a still lower limiting value at greater dilutions. No figures are yet available for the rotation of menthyl *o*-dimethylaminobenzoate in acid solution. It may, however, be predicted that this will be higher than that for the free basic ester, and probably higher than the value for the unsubstituted menthyl benzoate, if the hydrochloride is sufficiently ionised under the conditions of experiment.

The influence of an ionisable group should also be recognisable in a simple type of compound in which the remaining three groups attached to the asymmetric atom are of a comparatively non-polar character. In this connexion, it is common knowledge among workers with optically active substances that the rotations of simple active acids and bases often diminish in magnitude and frequently undergo a reversal of sign when the compounds are converted into the ionised state. This is precisely what might be expected, particularly if the acidic or basic group is the only group of high polar character in the molecule.

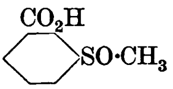


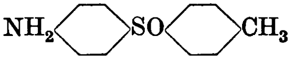
$$b\text{—}\overset{a}{\underset{c}{C}}\text{—}\overset{+}{C}O\cdot OH \quad \text{and} \quad b\text{—}\overset{a}{\underset{c}{C}}\text{—}\overset{\ominus}{C}O\cdot O'$$



$$b\text{—}\overset{a}{\underset{c}{C}}\text{—}\overset{\oplus}{N}H_3^{\cdot} \quad \text{and} \quad b\text{—}\overset{a}{\underset{c}{C}}\text{—}\overset{-}{N}H_2$$

Among optically active acids undergoing a reversal of this kind may be mentioned the lactic, glyceric, and methoxysuccinic acids. Phenylpropylacetic acid (Pickard and Yates, J., 1909, **95**, 1011), having a molecular rotation of $[M]_D = 140{\cdot}7°$ in benzene and 104·7° in chloroform, gives a sodium salt of $[M]_D = 5{\cdot}0°$ in water. Benzylmethylacetic acid increases somewhat in rotation on being converted into its sodium salt. Numerous salts of *d*-valeric acid are described in the literature, but no mention is made of their rotatory power. A specimen of commercial valeric acid in the author's possession, however, had a specific rotation almost exactly double that of the corresponding sodium salt, when both were examined in a 10% solution in aqueous alcohol. The tendency in this case is therefore towards a reversal of sign. The interesting optically active sulphoxides prepared by Harrison, Kenyon, and Phillips (J., 1926, 2079), in which the ionisable groups are separated from the asymmetric sulphur atom by a benzene nucleus, behave in the same manner. *d*-*m*-Carboxyphenyl methyl sulphoxide has a lower rotation in the form of its sodium salt, and *l*-4′-amino-4-methyldiphenyl sulphoxide suffers a reversal of the sign of rotation in hydrochloric acid solution.





Other typical optically active bases which show a reversal of sign on being converted into their hydrochlorides are lævorotatory amylamine and *l*-nicotine. On the other hand, *d*-butyl*iso*butylacetic acid is recorded as having a specific rotation of + 6·3° in xylene, + 6·0° in alcohol, and + 7·1° in an equivalent amount of aqueous sodium hydroxide (Fischer, Holzapfel, and Gwinner, *Ber.*, 1912, **45**, 250). No figures are available for the salt and the acid in the same solvent.

In the majority of cases, the ionisation of an active carboxylic acid appears to lead to a smaller change in rotatory power than the ionisation of an active base. Probably one factor contributing towards the weaker effect of the electrolytically dissociated carboxyl group is that the atom bearing the charge is one remove further away from the asymmetric centre than that in the corresponding base.

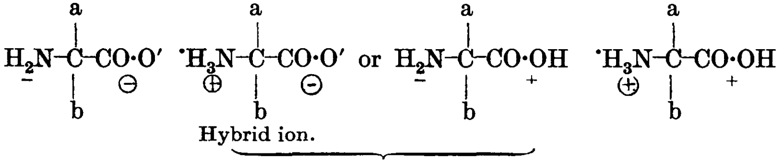
A more definite example of the change in the polar influence of the amino-group on ionisation is to be found in the rotatory powers of derivatives of active amyl alcohol, although it is doubtful if some of these have yet been obtained in a state of optical purity.

Molecular Rotations of Amyl Derivatives, $C_5H_{11}X$.

X.	·NH_3^+.	CO_2H.	I.	Et.	Br.	Cl.	OMe.	OH.	NH_2.
[*M*]	+11·20°	+10·5°	+11·17°	+6·2°	+5·6°	+1·8°	+0·41°	−5·1°	−5·2°

An examination of the figures reveals a close analogy with those relating to the menthyl benzoates and to benzene substitution. Here again the substituents arrange themselves into the polar series, having at the one end the positively charged ionic complex ·NH_3^+ and the carboxyl group, and at the other end the negative amino- and hydroxyl groups. The value quoted for the carboxylic compound is certainly too low (compare J., 1924, **125**, 1121) and possibly the rotation of the amine hydrochloride would also be increased under conditions leading to more complete ionisation. These figures illustrating the reversal in the influence of the amino-group when ionised supplement those recorded above for the carboxyl group in the menthyl benzoates.

Additional support for this explanation of the behaviour of optically active acids and bases may be found in the variations undergone by the rotatory powers of active amino-acids in alkaline, neutral and acid solution. An amino-acid in aqueous solution is in only a very slightly ionised state. On making such a solution alkaline, the result, on the whole, is to convert the positive carboxyl group more or less completely into the negatively charged complex ·CO·O′. On the other hand, the addition of hydrochloric acid to the aqueous solution results in the more complete ionisation of the amino-group, transforming it from a negative substituent into one of positive polarity. These changes go hand in hand with alterations in rotatory power, as may be seen from the following figures referring to the specific rotations of aspartic acid and asparagine. In the formulæ an encircled positive or negative sign represents an ionised complex.



$$\underset{-}{H_2N}\text{-}\overset{a}{\underset{b}{C}}\text{-}\underset{\ominus}{CO\cdot O'} \qquad \underset{\oplus}{{}^{\cdot}H_3N}\text{-}\overset{a}{\underset{b}{C}}\text{-}\underset{\ominus}{CO\cdot O'} \text{ or } \underset{-}{H_2N}\text{-}\overset{a}{\underset{b}{C}}\text{-}\underset{+}{CO\cdot OH} \qquad \underset{\oplus}{{}^{\cdot}H_3N}\text{-}\overset{a}{\underset{b}{C}}\text{-}\underset{+}{CO\cdot OH}$$

	Alkaline solution.	Aqueous solution.	Acid solution.
d-Aspartic acid.	−9·02° (1 mol. NH_3)	+4·36°	+30·0° (1 mol. HCl)
l-Asparagine.	−8·64° (1 mol. NaOH)	−5·30°	+26·4° (1 mol. HCl)

Exceptional behaviour is shown by *l*-leucine, which is recorded as being lævorotatory in aqueous solution and dextrorotatory in both acid and alkaline solutions. Taken in conjunction with the case of *d*-butyl*iso*butylacetic acid already mentioned, this suggests that there is a disturbing factor in the rotatory powers of these two acids, due to the critical length of the butyl chain.

It is evident that the presence or absence of groups of marked polarity is one of the main factors governing the rotatory power of an optically active compound, and already it seems possible to discern at least three ways in which their influence may be brought to bear on the asymmetric atom. The polar influence may be intramolecular and transmitted either through the chain of atoms or through space, as in the case of the menthyl benzoates and amyl derivatives quoted. A second effect, studied by Frankland, Pickard and Kenyon, Hilditch, and others, may lead to a sudden change in activity as the chain attached to the asymmetric centre attains a length of 5, 10, or 15 atoms. This effect is apparently due to the end of the chain coming into close proximity to the asymmetric atom and is therefore intramolecular and transmitted through space. In addition, it is probable that polar groups, whether present in the asymmetric compound or in the solvent, also exert an influence on neighbouring molecules, leading to corresponding changes in rotatory power. Some evidence on this point is provided by the fact that the substituents of the series $H < Me < OMe < Cl < Br < I$ exert a graded influence in the sense indicated on the molecular rotations of the *sec.*-β-octyl acetates, $CH_2X\cdot CO\cdot O\cdot C_8H_{17}$, and that the influence of the solvents C_6H_5X on each of these esters is given by practically the same sequence, *viz.*, $Me < H < OEt < Cl < Br < I$ (Rule and Mitchell, J., 1926, 3202).

Summary.

1. It has previously been shown that substituents may be arranged into a polar series representing a gradual transition from high positive, through neutral, to high negative polarity, and that this series corresponds to the relative influence of the substituents on

benzene substitution and the rotatory power of a number of optically active compounds.

2. It is now pointed out that the positively charged ionic complex $-NH_3^{\cdot}$ ranges itself with the positive substituents and the negatively charged complex $-CO\cdot O'$ with the negative substituents in their influence on rotatory power and benzene substitution.

3. This extension of the original theory is shown to explain the behaviour of a number of optically active bases, acids, and amino-acids on ionisation.

4. Three ways are suggested by which the polar effect may be transmitted to the asymmetric atom.

UNIVERSITY OF EDINBURGH. [*Received, November* 27*th,* 1926.]