SUMMARY

We describe a new process of preparation of 1,2,4-triazol-5-ones substituted in position 3, by condensing ureides with phenylhydrazine, with or without solvent. The characteristics of 11 substances are given, as well as 3 infra-red spectra.

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131. Organo-metal Substitutions[1])

by **C. K. Ingold**

(11. IV. 64)

This lecture is on mechanism, but it is connected with the present "eruption" of preparative activity in the area of overlap between organic and inorganic chemistry. The recent accretion of knowledge in this area has washed out the boundary between inorganic and organic chemistry, the last of the traditional internal frontiers in chemistry to have retained some degree of definiteness. Today, and for the future, if one is an organic chemist, every metal in the periodic table is of potential interest; and if one is an inorganic chemist, so is every type of organic structure.

Some of us can remember the time, some 30 years ago, when various stoichiometrically different general reactions, up to then regarded as belonging to quite unrelated departments of organic chemistry, were accepted as members of a single great family of reactions, which were named "nucleophilic aliphatic substitutions". These general reactions, despite their different fields of application, were bound into one family by common mechanisms. Even at that time one felt that a counterpart family, which might be named "electrophilic aliphatic substitutions", must exist; but it is only within recent years that such a family has been shown to exist and that work to establish its common mechanistic pattern has been begun.

In nucleophilic substitution, the groups that enter or leave a substrate carry their bond-electrons with them; and commonly they are anions, such as halide ions or

[1]) PARACELSUS Lecture delivered before the Swiss Chemical Society on February 22nd, 1964, at the Winter Meeting of the Society in Fribourg, on the occasion of the award of the PARACELSUS Medal. The material presented was also incorporated into a lecture delivered on April 22nd, 1964, under the title "Electrophilic Aliphatic Substitutions" in the "Frontiers in Chemistry" lecture series at Wayne State University, Detroit, Michigan. – Published here by special permission of the Editorial Board. The same subject matter will appear in "Record of Chemical Progress" (Wayne State University).

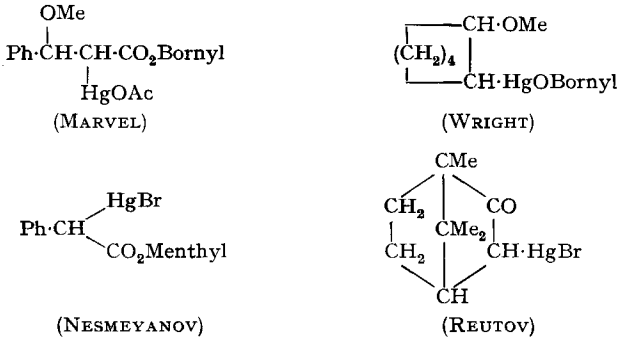
various oxy-anions. In electrophilic substitution, the groups come and go without their bond electrons; and commonly they are cations such as hydrogen ions and various metal ions. Because so many of the simplest cations are metallic, we expect electrophilic aliphatic substitution to occupy a central place in organo-metal chemistry, just as nucleophilic aliphatic substitution occupies a central place in what, for contrast, I may call organo-non-metal chemistry.

In any study of reactions, stoichiometry comes before mechanism. One must know what happens before one can even ask how it happens. Our knowledge of the occurrence and stoichiometry of reactions in the organo-non-metal field was well filled in when the study of their mechanism was undertaken 30 years ago. In contrast, our knowledge merely of what organo-metal reactions exist is, even today, very much more fragmentary. And so the discovery of new general reactions, which are, or may be, electrophilic aliphatic substitutions, has to be pursued concurrently with the investigations which are necessary to establish mechanism, and perhaps the common mechanistic forms which characterise electrophilic aliphatic substitution.

When, in the middle of the last decade, the late Professor E. D. HUGHES, with H. B. CHARMAN and me, set out to establish the mechanisms of electrophilic aliphatic substitution, in its central area of metal-for-metal substitutions, nothing substantial had been done on the kinetics of such reactions. There had been a substantial amount of work on the stereochemical course of some mercury-for-mercury substitutions. Our first difficulty with this was, and is, that it starts at the wrong end. The stereochemical course of a reaction is a property of its mechanism, not of its stoichiometry; and so, to determine stereochemical course apart from mechanism is like finding a lost hat without finding the owner. There was no proof even that the stereochemically studied substitutions were electrophilic. A kinetic study should come first.

Our second difficulty with the earlier work was that it did not fully prove stereochemical course, because the mercury-bearing atom was only one of several asymmetric atoms in the optically active molecules employed, which were those formulated in *Chart 1*. In each example the seat of substitution was under the permanent asymmetric influence of the other centres of optical activity in these molecules.

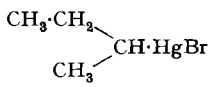
Chart 1. *Substrates in early stereochemical studies of mercury exchanges*



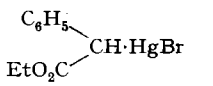
Given the background of prior work, the obvious first task was to apply the kinetic method to metal-for-metal substitutions. We saw that we might make a second methodological contribution if we could command stable optical activity in a mol-

ecule containing a single asymmetric centre bearing a metal. This was provided in the examples shown in *Chart 2.* CHARMAN produced the first of them by optically resolving *s*-butylmercuric bromide. As we afterwards found out, REUTOV in Moscow and JENSEN in Berkeley were doing the same, or almost the same thing, contemporaneously. Subsequently R. M. G. ROBERTS optically resolved α-carbethoxybenzylmercuric bromide.

Chart 2. *Optically resolved mercury compounds*



$[\alpha]_D = 24°$ in acetone
(H. C. CHARMAN)

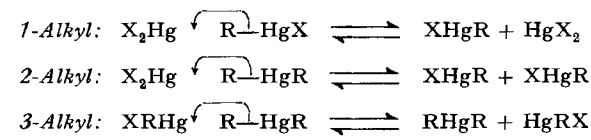


$[\alpha]_D = 14°$ in acetone
(R. M. G. ROBERTS)

This fairly easy optical resolution of organic mercury compounds determined that our first attack on the kinetics of metal-for-metal substitutions would be made with mercury compounds. Moreover, it was obvious to begin with mercury-for-mercury substitutions, with the use of some form of labelling, including isotopic labelling, when necessary. For in that way we avoided having to determine the relation of sign of rotation with configuration, as is necessary when a different element is being introduced by the substitution.

On the assumption that mercury-alkyl redistributions, as they are traditionally called, would prove to be electrophilic substitutions, we predicted the three stoichiometrically different reactions shown in *Chart 3.* We call them the 1-, 2- and 3-alkyl mercury exchanges. All mercury-alkyl redistributions known at that time were of the 2-alkyl type. We looked for, and found, the other 3-alkyl and 1-alkyl reactions. This illustrates the remark made earlier that, in the organo-metal field, one has to discover new reactions as well as to determine the mechanisms of reactions old and new.

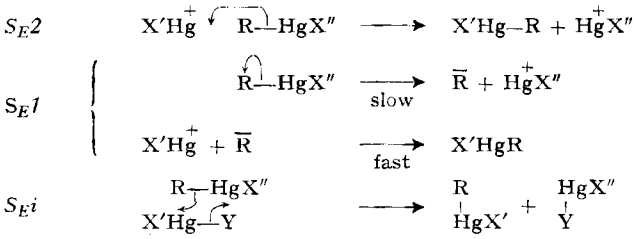
Chart 3. *Electrophilic mercury exchanges*



As an aid to planning, it is necessary to have some preconception (whether right or wrong is unimportant) as to what electrophilic mechanisms might be operative. Our preconception, based on the best guide we had, namely the known mechanisms of nucleophilic substitution, contemplated three basic mechanisms, called bimolecular, unimolecular and internal, and labelled S_E1, S_E2 and S_Ei, which are formulated in *Chart 4.* We may note their observable characteristics.

The bimolecular mechanism, S_E2, requires second-order kinetics. Unlike the nucleophilic mechanism S_N2, it is not limited by the PAULI principle to producing inversion of configuration, because there is no excess of electrons in competition for the transferred bonding orbital in the transition state, the circumstance which in nucleophilic substitution keeps the exchanging groups apart. In bimolecular electrophilic substitution, any stereochemical result might be expected *a priori.* The uni-

Chart 4. *Basic mechanisms of electrophilic aliphatic substitution illustrated for 1-alkyl mercury exchange*



molecular mechanism, S_E1, which depends on the rate-controlling formation of a carbanion, requires limiting first-order kinetics; and extensive or complete racemisation would be expected to accompany substitution. The internal mechanism, S_Ei, requires second-order kinetics; and now substitution must occur with total retention of configuration. Kinetic distinctions can be drawn between the two second-order mechanisms S_E2 and S_Ei. The simplest follows from the consideration that, as the potential anion, written as Y, is so varied that it becomes more and more ionic until in the end it is completely dissociated, so rate by mechanism S_Ei should diminish, finally to zero, whilst rate by mechanism S_E2, which relies on the positivity of the substituting agent, should increase continuously.

We began kinetic work with the well known reaction of 2-alkyl mercury exchange (*Chart 3*), using *s*-butyl as the alkyl group, because we could have it in optically active form when required, and using bromide, acetate and nitrate as alternative anionic groups. In ethanol, and in acetone, the kinetics were of second order. When the potential anion in the substituting agent was made progressively more ionic, by replacing original bromide successively by acetate, nitrate and perchlorate, the absolute rate increased markedly. The factor of increase from bromide to nitrate, the range of anions over which the kinetic form could be controlled, was 10^4. With nitrate as anion, the rate was so high that it had to be measured at $-50°$. The reaction with perchlorate as the anion could not be kinetically controlled because it was instantaneous, even at $-50°$. These results and others convinced us that mechanism S_E2 was under observation.

We then showed that this mechanism retains configuration. The method is explained in *Chart 5*. Optically active *s*-butylmercuric bromide was converted by means of a (necessarily racemic) *s*-butyl GRIGNARD compound into a di-*s*-butylmercury, which was then labelled by optical activity in one only of its two otherwise equivalent alkyl groups. The degree sign denotes the optical label. This material then became the substrate for the 2-alkyl mercury exchange. On treatment with mercuric bromide, it must give, as the equations show, *s*-butylmercuric bromide with one-half of the optical activity of that substances as employed originally – one-half, provided that the label of optical activity sticks firmly to its alkyl group while the mercury atom attached to it is being replaced by a different one, or, in other words, provided that configuration is fully retained in the substitution. One can similarly see that, if the substitution led to racemisation at the atom substituted, the final optical activity would be one-quarter of the original; and that, if the substitution inverted configuration, the final activity would be zero.

Chart 5. *Stereochemistry of S_E2 mechanism of 2-alkyl mercury exchange. – Method*

$$s\text{-}\overset{\circ}{\text{Bu}}\text{HgBr} + s\text{-BuMgCl} \xrightarrow[\text{GRIGNARD}]{} s\text{-}\overset{\circ}{\text{Bu}}\text{HgBu-}s$$

$$s\text{-}\overset{\circ}{\text{Bu}}\text{HgBu-}s + \text{HgBr}_2 \xrightarrow[S_E2]{} s\text{-}\overset{\circ}{\text{Bu}}\text{HgBr} + s\text{-BuHgBr}$$

Substitution with:	Retention	Racemisation	Inversion
$\alpha_{final}/\alpha_{initial}$	$^1/_2$	$^1/_4$	0

The results for the three anionic groups, bromide, acetate and nitrate, for which we have kinetic proof of mechanism, are given in *Chart 6*. All rotations of products, taken with *s*-butylmercuric bromide, prepared by a final anion exchange when necessary, were one-half of the original rotation, so showing that configuration is quantitatively retained in this mechanism of 2-alkyl exchange.

Chart 6. *Stereochemistry of S_E2 mechanism of 2-alkyl mercury exchange. – Results*
Initial *s*-BuHgBr: $[\alpha] = -15.2°$

Substituting agent	Solvent	Final $[\alpha]$
$HgBr_2$	EtOH	-7.6^8
$HgBr_2$ + 3LiBr	EtOH	−7.8
$Hg(OAc)_2$	EtOH	−7.5
$Hg(NO_3)_2$	EtOH	−7.8
$Hg(NO_3)_2 + HNO_3$	1:1 aq.-EtOH	−7.2
	Mean	−7.6

One of the expected, but previously undiscovered electrophilic mercury exchanges was the 3-alkyl exchange (*Chart 3*). We found that, when optically active *s*-butylmercuric bromide was mixed in a solvent with inactive di-*s*-butylmercury, the label of optical activity became transferred from the former to the latter. We also found that, when *s*-butylmercuric bromide containing radioactive mercury-203 was mixed with ordinary di-*s*-butylmercury, the label of radioactivity became similarly transferred. These label transfers are represented, as consequences of the anticipated 3-alkyl exchange, in *Chart 7*, in which an asterisk represents a label of radioactivity and the degree sign one of optical activity. In this representation of the label transfers, the stoichiometry is such that one alkyl group is transferred, when one mercury atom is transferred from one chemical type of compound to the other. Thus if we measure the rate of transfer of the optical label, and also the rate of transfer of the radioactive label, the two rates should be the same.

Chart 7. *Establishment of 3-alkyl mercury exchange: Label transfers in 3-alkyl exchange*

$$\text{RHgR} + \overset{\circ}{\text{R}}\text{HgBr} \longrightarrow \overset{\circ}{\text{R}}\text{HgR} + \text{RHgBr}$$

$$\text{RHgR} + \text{RH}\overset{*}{\text{g}}\text{Br} \longrightarrow \text{RH}\overset{*}{\text{g}}\text{R} + \text{RHgBr}$$

$$\overset{\circ}{\text{R}}\text{-transfer}/\text{H}\overset{*}{\text{g}}\text{-transfer} = 1$$

This is an important point, because the label transfers might be interpreted in another way, namely as a consequence of two successive steps of the already studied

2-alkyl exchange; and if that had been the true interpretation of the observed label transfers, we should have lost interest. How the label transfers could thus arise is shown in *Chart 8*. It is here assumed that a mercuric salt is formed in the first step, but is destroyed so rapidly in the second step that one does not see it. And enough is known about rates in 2-alkyl mercury exchanges to make it certain that, if a mercuric salt were thus formed in the first step, it would be consumed in the second so rapidly that one would not see it. So the interpretation is entirely possible. However, according to this interpretation two alkyl groups would be transferred, while one mercury atom is being transferred, from one chemical type of compound to the other. And so, if we measure the rate of transfer of the optical label, and that of the radioactive label, the first rate should be twice the second.

Chart 8. *Establishment of 3-alkyl mercury exchange: Label transfers in a sequence of 2-alkyl exchanges*

$$2\overset{\circ}{R}HgBr \longrightarrow \overset{\circ}{R}Hg\overset{\circ}{R} + HgBr_2$$
$$R_2Hg + HgBr_2 \longrightarrow 2RHgBr$$
$$2R\overset{*}{H}gBr \longrightarrow RHgR + \overset{*}{H}gBr_2$$
$$R_2Hg + \overset{*}{H}gBr_2 \longrightarrow RHgBr + R\overset{*}{H}gBr$$
$$\overset{\circ}{R}\text{-transfer}/\overset{*}{H}\text{g-transfer} = 2$$

Thus we have to determine whether the rates of optical and of radioactive label transfer are in a ratio of 1 or of 2; and we can do this either by double labelling in a single experiment, or by alternative labelling in parallel experiments. Some results, obtained by both methods, with *s*-butyl as the alkyl group, bromide as the anion, and ethanol as solvent, are in *Chart 9*. The two rates of label transfer are evidently equal; and thus we can conclude that our expected 3-alkyl reaction is indeed here under observation.

Chart 9. *Establishment of 3-alkyl mercury exchange: Comparison of optical and radioactive rates*

s-Bu_2Hg + *s*-BuHgBr in ethanol at 25°

Optical rates		Radioactive rates	
Run	10^{-7} M/s	Run	10^{-7} M/s
1	4.6	1	4.4
3	4.7	54	4.9
4	4.8	57	4.4
Mean	4.7	Mean	4.6

In the course of the work which provided these conclusions, two further findings emerged. They were that the substitution is kinetically of second order, and that it entails no loss of optical rotation. The latter conclusion was made inevitable as soon as it was noticed that the final irreducible rotation of *s*-butylmercuric bromide recovered from long-period runs, so-called "complete" runs, in which equimolar amounts of optically active *s*-butylmercuric bromide and optically inactive di-*s*-butylmercury had undergone exchange, was one-third of the original rotation of that substance. One-third is the fraction in which its optical activity would be retained

if the labels of optical activity became distributed equally among the three alkyl groups concerned in the exchange, without any loss of labels during the process of distribution, or, in other words, provided that configuration is totally preserved when one mercury atom is replaced by another on the optically active alkyl group.

On changing the anionic group from bromide to acetate, and thence to nitrate, the rate rose progressively, as in the previous example, by an over-all factor above 10^4. We may conclude that the 3-alkyl substitution in ethanol uses the S_E2 mechanism, which proceeds with total retention of configuration.

The other expected stoichiometrically distinct form of electrophilic mercury-for-mercury substitution, the 1-alkyl exchange (*Chart 3*), is another reaction that cannot be established by a simple observation of label transfer. We can observe the transfer of labelled mercury between an alkyl-mercuric salt and an inorganic mercuric salt. But such a transfer might arise either from the anticipated 1-alkyl exchange or from a sequence of steps of the familiar 2-alkyl exchange, as shown in *Chart 10*. The latter interpretation assumes that a dialkylmercury is formed in the first step of 2-alkyl exchange, and then is destroyed in the second step so rapidly that it is not observed. And we know enough about the rates of 2-alkyl exchanges to be sure that, if the dialkylmercury were indeed produced in the first step, it would be destroyed so rapidly in the second that it would not be observed.

Chart 10. *Establishment of 1-alkyl mercury exchange:*

(A) *Label-transfer by 1-alkyl exchange:*

$$RHgX + H\overset{*}{g}X_2 \longrightarrow R\overset{*}{H}gX + HgX_2$$

(B) *Label-transfer by a sequence of 2-alkyl exchanges:*

$$RHgX + RHgX \longrightarrow R_2Hg + HgX_2$$

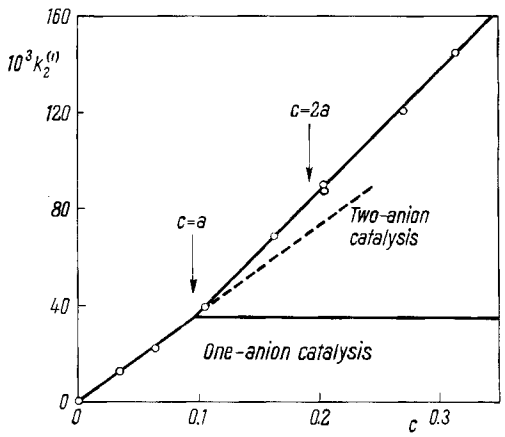
$$H\overset{*}{g}X_2 + R_2Hg \longrightarrow R\overset{*}{H}gX + RHgX$$

(over-all stoichiometry as in A)

In this case, the alternative interpretations cannot be distinguished by double labelling. But they can be distinguished by a kinetic study; for the kinetics of the 1-alkyl process (A), whatever its mechanism, can never be the same as those of the 2-alkyl sequence (B). F. G. THORPE and H. C. VOLGER have studied the kinetics of radiomercury transfer between an alkylmercuric salt and a mercuric salt, with methyl, *s*-butyl, and several other alkyl groups, and with halides, acetate and nitrate as anionic groups, in ethanol as solvent. Their results demonstrate that the predicted 1-alkyl mercury exchange is indeed the reaction which is responsible for the observed transfers of labelled mercury. The same results show that this substitution has second-order kinetics throughout. They also show that, as the anionic group is changed from bromide to acetate, and thence to nitrate, the absolute rate progressively rises by an over-all factor above 10^5. Finally, they show that, with *s*-butyl as the alkyl group, no loss of optical activity accompanies the radioactive label transfer. We may therefore conclude that this 1-alkyl mercury-for-mercury substitution, like the 2-alkyl and 3-alkyl exchanges mentioned earlier, employs the S_E2 mechanism in solvent ethanol, and that, in this mechanism of substitution, configuration is quantitatively retained.

During this kinetic study of mercury exchange between alkylmercuric and mercuric salts, a catalysis by anions was observed, which appeared to be connected with the co-ordinating power of the anions for mercury; for the order of effectiveness of the catalytic anions was $I^- > Br^- > Cl^- > OAc^- > NO_3^-$, the last of these being ineffective. This is the inverse of the order of ionicity of mercuric salts and of alkylmercuric salts involving these anions. The form of the catalysis is illustrated in *Chart 11* for the exchange between methylmercuric bromide and mercuric bromide under catalysis by lithium bromide, in acetone. The rate rises linearly with the concentration of lithium bromide, until this is equal to the concentration of mercuric bromide, when the curve suddenly takes a new direction, and then continues linearly with increasing lithium bromide to the limit of the measurements. The slope after the change of direction is not in all cases greater than before. With neopentyl as the alkyl group and with bromide as catalyst, the second slope is less steep, as shown in *Chart 12*. With s-butyl as the alkyl group, the second slope is steeper than the first when the catalytic anion is a halide ion, but much less steep than the first when the catalyst is an acetate ion. But the break in the curve is always present, and is always at the point of 1:1 equivalence; and no other break has ever been observed.

Chart 11. *Effect of LiBr (c) on second-order substitution rate of MeHgBr + $HgBr_2^*$ (each 0.095 M) in ethanol at 60°* [a])



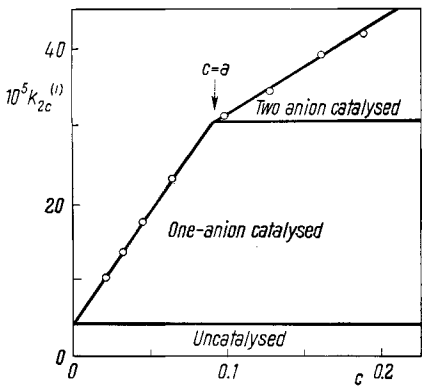
[a]) J. chem. Soc. *1961*, 2361.

This peculiar kinetic character has a perfectly clear meaning. We have two catalytic processes. At the lower catalyst concentrations, one catalytic anion, added to a reactant in pre-equilibrium, is thereby carried into the transition state of the mercury exchange. At the higher catalyst concentrations, a second anion, taken up by one of the reactants in pre-equilibrium, is likewise carried into the transition state. We call these two catalytic processes, the one having one and the other having two extra anions in its transition state, the 1-anion and 2-anion catalyses of 1-alkyl exchange.

The pre-equilibrium in 1-anion catalysis by bromide ion might be as follows:

$$HgBr_2 + Br^- \rightleftharpoons HgBr_3^-$$

Chart 12. *Effect of LiBr (c) on second-order substitution rate of* $Me_3C \cdot CH_2HgBr + \overset{*}{H}gBr_2$ *(each 0.092 M) in ethanol at 100°* [a])



[a]) J. chem. Soc. *1961*, 1144.

The result would be that $HgBr_3^-$ takes the place of $HgBr_2$ as a participant in the transition state of exchange. As to the position of addition equilibrium, we have, as a matter of fact, much independent evidence that this reversible and very rapid addition occurs, and that at our concentrations the equilibrium very strongly favours the adduct. The kinetics themselves confirm this conclusion. For we observe that the rate rises linearly with catalyst concentration, at catalyst concentrations below the point of 1:1 equivalence. Now the thermodynamic equation for the addition is quadratic, and could lead to such a linear catalytic relation only if the equilibrium degree of addition is near one of its limits, that is, either very slight or nearly complete. And the choice between these alternatives is obvious, because, if the degree of addition were slight, nothing would get used up at the point of 1:1 equivalence, and the initial straight line representing rate as a function of catalyst concentration, would continue indefinitely without changing direction. The break at 1:1 equivalence shows that the preliminary addition is substantially stoichiometric, and that only when more than one equivalent of catalyst is added is any left available to engage in a further process.

The further pre-equilibrium involved in a 2-anion catalysis by bromide ion might be as follows:

$$RHgBr + Br^- \rightleftharpoons RHgBr_2^-$$

If $RHgBr_2^-$ takes the place of RHgBr as a component of the transition state of exchange, one more bromide ion is thereby imported. The kinetics show that the degree of addition in this second pre-equilibrium must be only slight. For we observe linear relations between rate and catalyst concentration beyond the break at the point 1:1 equivalence. Therefore the degree of addition in the second pre-equilibrium must be either slight or nearly complete. The choice between these alternatives is as obvious as before: the degree of addition must be only slight because, if it were nearly complete, a second break would appear at the point of 2:1 equivalence; and this is not observed. This conclusion as to the degree of addition agrees with the independent

evidence that alkylmercuric halides do not take up halide ions to any marked degree, and certainly to nothing approaching a stoichiometric extent.

The ways in which the extra anion in 1-anion catalysis, and the two extra anions in 2-anion catalysis, are assumed to be included in the respective transition states are shown in *Chart 13*. The cyclic nature of these transition states is a conclusion drawn from the evidence, and not just a fanciful idea. If we consider the case X = Y = Br, then in the diagram for 1-anion catalysis, Y must, for reasons explained already, be brought in by the lower of the two mercury atoms. One has only to write down the chemical equation for the exchange to see that Y must be carried out by the upper of the two mercury atoms. Therefore, in the transition state, it must be on its way from the one mercury atom to the other; that is, it must be bridging the two mercury atoms. Thus we reach the concept of a cyclic transition state, and a mechanism of the general type of that which, in anticipation, was labelled S_Ei.

Chart 13. *Transition states (S_Ei-type) for 1-anion and 2-anion catalysis of 1-alkyl mercury exchange*

1-Anion 2-Anion

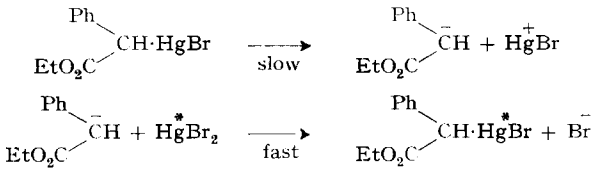
We assume that the second anion added in 2-anion catalysis simply builds up the co-ordination number of the less co-ordinated mercury atom to equivalence with that of the more co-ordinated one. The only evidence for this particular assumption is the absence of any obvious alternative. If it be accepted, we have, in 2-anion catalysis, a further example of the class of mechanism labelled S_Ei.

It is an obvious requirement of these transition states that stereochemical configuration must be retained in the substitutions. The two forms of catalysis can be isolated, the one completely and the other in a nearly pure form, by suitably choosing the conditions; and, with *s*-butyl as the alkyl group, each has been shown quantitatively to retain configuration. One experiment, in which both forms of catalysis contributed substantially to the rate, was run for 200 half-lives of mercury-for-mercury substitution, without any detectable fall of rotatory power.

In the work mentioned so far, we do not encounter the unimolecular electrophilic mechanism S_E1, which starts with the rate-controlling formation of a carbanion. In a search for this mechanism, undertaken jointly with R. M. G. ROBERTS, we left the simple alkyl series of mercury compounds, and introduced electron-absorbing substituents into our alkyl groups, hoping thereby to give more stability to the carbanion intermediate. Our leading example was the mercury-for-mercury substitution in α-carbethoxybenzylmercuric salts by radiomercuric salts. Concurrently in Moscow, REUTOV and his collaborators were pursuing the same enquiry with the same example, and we were able to compare results with Professor REUTOV personally in July 1963. There are some points of detail awaiting agreement, but we are agreed, qualitatively and quantitatively, about the fact of main interest; namely that, in

anhydrous dimethylsulphoxide, the substitution in α-carbethoxybenzylmercuric bromide by radiomercuric bromide is of first order in the organo-mercuric salt and of zeroth order in the mercuric salt, and hence must have the S_E1 mechanism formulated in *Chart 14*.

Chart 14. *Example of mechanism S_E1. Solvent Me_2SO*



ROBERTS was able to resolve the mercuri-ester, and therefore we could follow the stereochemical course of the substitution, by comparing its radiometrically measured rate with the rate of change of optical rotation, if any such polarimetric change occurred. Actually the exchange was found to proceed with racemisation; that is, each molecular act of substitution led with equal probability to either enantiomeric form of the substitution product.

This substitution is susceptible to a strong catalysis by bromide ion. This is a catalysis of the rate-controlling formation of the carbanion intermediate of the unimolecular mechanism, and the main point of interest is that it is wholly quadratic in bromide ion. So we label it S_E1-2Br$^-$, and conclude, as illustrated in *Chart 15*, that two bromide ions add successively, each in pre-equilibrium and in small degree, to the carbon-bound mercury atom; and that the instability, necessary for catalysis of the rate-controlling heterolysis that gives the carbanion, arises when a doubled negative charge can be divided in this process to give mutually repelling anionic fragments.

Chart 15. *Nucleophilic catalysis of unimolecular electrophilic substitution*
Mechanism S_E1-2Br

Example: R = Ph·CH·CO_2Et; solvent Me_2SO.

$$RHgBr \underset{\text{fast}}{\overset{Br^-}{\rightleftharpoons}} RHgBr_2^- \underset{\text{fast}}{\overset{Br^-}{\rightleftharpoons}} RHgBr_3^{--}$$

$$RHgBr_3^{--} \xrightarrow[\text{slow}]{} R^- + HgBr_3^-$$

$$R^- + {}^{*}HgBr_2 \xrightarrow[\text{fast}]{} R{}^{*}HgBr + Br^-$$

Our current task is to carry the exploration of electrophilic organo-metal substitutions outside the nursery area of mercury-for-mercury substitutions by the use of other carbon-bound metals, and other cationic substituting agents. We have studied a tin-for-tin substitution and a thallium-for-thallium substitution. The general field involves using unlike entering and leaving groups. In this wider field we have examined a tin-for-mercury, a mercury-for-thallium, and a thallium-for-mercury substitution. The last of these reactions, worked out by C. R. HART, will serve for illustration.

The substitution was by diethylthallic bromide (a highly ionising salt) as substituting agent in di-*s*-butyl-mercury as substrate, the solvent being dimethylformamide. The stoichiometry of the substitution, and our conclusions as to its mechanism, are set out in *Chart 16*. Care had to be taken to eliminate concurrent reactions; but when this was done, the substitution was found to be accurately of first order in the dialkylmercury and of zeroth order in the dialkylthallic salt, results which establish that it employs the unimolecular mechanism, S_E1. This is the first observation of electrophilic substitution by the unimolecular mechanism in an alkyl group which carries no unsaturated or electronegative substituents; that is, it is the first measured rate of formation of a simple alkyl carbanion.

Chart 16. *A non-isotopic electrophilic substitution by mechanism* S_E1

Stoicheiometry: $(Et_2TlBr + s\text{-BuHgBu-}s \rightarrow Et_2Tl \cdot Bu\text{-}s + Br \cdot HgBu\text{-}s$

Mechanism (in dimethylformamide):

$$s\text{-Bu–HgBu-}s \overset{\text{slow}}{\rightleftharpoons} s\text{-Bu}^{\cdot} + s\text{-BuHg}^{+}$$

$$s\text{-Bu}^{-} + Et_2Tl^{+} \xrightarrow{\text{fast}} s\text{-Bu}\cdot TlEt_2$$

$$s\text{-BuHg}^{+} + Br^{-} \xrightarrow{\text{fast}} s\text{-BuHg}\cdot Br$$

The stereochemical course of this reaction is a matter of interest because we know so little about the stereochemical form of alkyl carbanions. They may be flat or pyramidal, and, in the latter case, their inversion frequency may be high or low. Our previous finding, that unimolecular electrophilic substitution in α-carbethoxybenzylmercuric bromide involves total racemisation, hardly constitutes a test case, for the unsaturated phenyl and carbethoxyl substituents, by importing mesomeric character, would tend to flatten the carbanion if it would not otherwise have been flat, and would at least reduce, if not abolish, any finite enantiomeric life it might have had. Simultaneously, the electronegative phenyl and carbethoxyl substituents, by accepting part of the charge of the carbanion, will lengthen its kinetic life as a reaction intermediate. The reduction of enantiomeric life and increase of kinetic life will combine to favour total racemisation, and hence it is not surprising that this was the observed result.

It was thus a matter for determination whether, when all electro-polar and unsaturated substituents were absent as in the carbanion of a simple alkyl group, optical activity, centred in the initially combined alkyl group, would be retained in the derived carbanion for long enough to be transferred to the substitution product. The *s*-butyl carbanion is the simplest conceivably asymmetric alkyl carbanion, and therefore a unimolecular electrophilic substitution, depending on the *s*-butyl carbanion, could provide significant evidence concerning the stereochemistry of alkyl carbanions.

When the substitution by diethylthallic bromide in di-*s*-butylmercury, in solvent dimethylformamide, was run with optically active di-*s*-butylmercury, the first-order rate of racemisation of the reaction solution was just equal to the chemically determined first-order rate of the thallium-for-mercury substitution. The substitution, therefore, involved total racemisation. So, either the carbanion is flat, or, if it is not,

its inversion frequency must be so high as to prevent retention of its configuration over the short life it has before being captured by the waiting diethylthallic ions.

This example will illustrate the kind of work currently in progress. We have not yet seriously begun to use the powerful new method, which the inorganic chemists have been developing, for controlling the behaviour of the more exuberant metals by wrapping them up to a suitable degree with selected ligands. With this aid, every metal in the Periodic Table is potentially available for the study of organo-metal reactions. It is obvious that organo-metal chemistry will grow into a major domain of chemistry. At present it is a dark continent with far too few explorers.

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132. Podophyllum-Lignane

4'-Demethyl-desoxypodophyllotoxin-β-D-glucosid, ein neues Glykosid aus *Podophyllum emodi* WALL. und *P. peltatum* L.

16. Mitteilung über mitosehemmende Naturstoffe [1][1])

von **A. von Wartburg, M. Kuhn** und **H. Lichti**

(5. V. 64)

Aus den Wurzeln und Rhizomen von *P. emodi* WALL. und *P. peltatum* L. isolierten wir kürzlich drei weitere zuckerhaltige Lignan-Verbindungen, die wir vorläufig als Lignane F, H und J bezeichneten [2]. Diese Inhaltsstoffe treten nur in geringen Mengen auf; sie lassen sich jedoch neben den bekannten Hauptglykosiden [3] mittels Dünnschichtchromatographie leicht nachweisen und bestimmen. Eine eingehende chemische Untersuchung wurde nur mit der Komponente J durchgeführt, die sich dabei überraschenderweise nicht als Glykosid sondern als Esterderivat, nämlich als Glucosylester der 2:3-*trans*-Desoxypodophyllinsäure [2] erwies. Die vorliegende Arbeit beschreibt nun die Isolierung und Konstitutionsermittlung des zweiten Begleitstoffs, des Lignans H.

Isolierung von Lignan H. Wir verfügten über 60 g Rohglykoside, die nach dem früher beschriebenen Extraktionsverfahren [3] aus *P. emodi* erhalten wurden[2]). Durch mehrfache Chromatographie des Glykosidkomplexes an Silicagel liessen sich rund drei Viertel des dominierenden Podophyllotoxin-glucosids entfernen. Das angereicherte Präparat, das jetzt ca. 10–12% Lignan H enthielt, wurde an feinkörnigem Kieselgel[3]) fraktioniert, wobei eine saubere Abtrennung der Begleitstoffe – vorwiegend Podophyllotoxin-glucosid und wenig Lignan F – erfolgte (Fig. 1). Insgesamt wurden 900 mg (rund 1,5% der Rohglykoside) einheitliches Lignan H in Form eines weissen, amorphen Pulvers vom Smp. 146–158° erhalten; $[\alpha]_D^{20} = -77°$ in Methanol. Aus den Mikroanalysen ergab sich die Bruttoformel $C_{27}H_{30}O_{12}$ mit 2 Methoxylgruppen. Ein

[1]) Die Zahlen in eckigen Klammern verweisen auf das Literaturverzeichnis, S. 1210.

[2]) Lignan H kann auch aus den Rohglykosiden von *P. peltatum* isoliert werden, doch wird die Fraktionierung durch die Anwensenheit von β-Peltatin-glucosid erschwert.

[3]) Zur Methode siehe [4].