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Chemistry. — "*On the velocity of substitutions in the benzene nucleus.*" By Dr. F. E. C. SCHEFFER. (Communicated by Prof. A. F. HOULEMAN).

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1. In the preceding paper the dependence of the velocity constant on the temperature was represented by the equations;

$$\frac{d \ln k}{dT} = \frac{\epsilon_t - \epsilon}{RT^2} \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and

$$\ln k = \frac{\epsilon - \epsilon_t}{RT} - B \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and it was shown that the greater part of the experimental data allows the substitution of a constant value for $\epsilon - \epsilon_t$. According to the considerations of the preceding paper this value furnishes a pretty accurate measure for the energy difference between the reacting substances and the intermediate state during the reaction, at least if the velocities have been measured with sufficient accuracy, and the value of the energy difference is not too small.

In order to arrive at an opinion about the efficiency of these considerations and the equations 1 and 2 derived from them, I have tried to apply the latter to the experimental data. I have for this purpose tried to find those examples where we may expect the simplest behaviour, and in my opinion they are to be found in the department of organic chemistry.

If we imagine a reaction which is indicated by the equation of reaction $A + B = \dots$ and if we determine the reaction velocities at different temperatures, the above mentioned energy value can be calculated. If we then replace the molecule A by another A' , we can find the required quantity of energy also for the reaction of this molecule A' with B , and in this way obtain an insight into what influence a substitution of A' for A exercises on the differences of energy with the intermediate state.

Let us e. g. suppose that the molecule benzene is nitrated; we might then calculate from measurements of the nitration velocity at different temperatures what quantity of energy is required to force the nitric acid molecule into the sphere of action of one of the hydrogen atoms in the benzene nucleus. If we then replace the molecule benzene e. g. by chloric benzene, we can calculate the quantity of energy required for this reaction also by measurement of the ni-

tration velocity, and obtain an insight in this way into what influence the chlorine atom in the benzene has on the required quantity of energy for the substitution. In this way a value can then be found which can quantitatively be expressed for that which is generally expressed by the intensity of the binding of the atoms which are liable to substitution.

Such calculations, however, cannot be carried out in the absence of the required material of facts. Determinations of velocity of substitutions as mentioned above have been hardly carried out as yet; though Prof. HOLLEMAN and his pupils have collected a considerable number of data on the relative velocity of the substitution of the different hydrogen atoms in the same aromatic molecule. All these measurements refer to simultaneous reactions, and it is just for this kind of reactions that the application of the above mentioned equations is very simple.

When we expose the molecule toluene to the action of nitric acid, three substitutions appear simultaneously. In the toluene three different kinds of hydrogen atoms liable to substitution occur, two on the ortho-, two on the meta-, and one on the para-place with respect to the chlorine atom. So we have here three reactions proceeding simultaneously, each with a definite velocity constant. If we now want to apply the above equations we must first of all bear in mind that the velocity constant is determined by the energy and entropy difference required for the substitution, and that accordingly if these quantities were equal for the ortho-, meta-, and para-substitution, there would yet be formed twice as many ortho- and metadisubstitution products as paraproducts, because in a definite quantity of toluene there are twice as many ortho- and metahydrogen atoms liable to substitution, as para-hydrogen atoms. If therefore the velocity constants for ortho-, meta-, and para-substitution are represented by k_o , k_m , and k_p , the substitution velocities v_o , v_m and v_p are represented by the equations:

$$v_o = 2k_o c_{C_6H_5Cl} c_{HNO_3}, \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad (2a)$$

$$v_m = 2k_m c_{C_6H_5Cl} c_{HNO_3} \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad (2b)$$

and

$$v_p = k_p c_{C_6H_5Cl} c_{HNO_3} \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad \cdot \quad (2c)$$

The ratio of the quantities ortho, meta-, and para-products, which are formed in the unity of time, therefore, amounts to $2k_o : 2k_m : k_p$; hence it is independent of the time. If therefore the reaction is allowed to proceed regularly to its close, or if it is stopped at an arbitrary moment, the ratio of the obtained substitution products is

at the same time the required ratio of the velocity constants¹⁾.

Not the velocity constants themselves, therefore, only their mutual ratio is to be derived from the measurements collected by Prof. HOLLEMAN.

If we now apply equations 1 and 2 to these examples, it appears that the application becomes so very simple in this case in consequence of the equality of the energy ϵ of the reacting substances for all the three reactions that take place simultaneously, and that therefore the difference in velocity of substitution at an ortho- and metaplace e.g. is different only in consequence of this that the quantity of energy (and entropy) to replace the ortho-hydrogen differs from the energy required to cause the substitution at the meta-place.

The objection that these reactions do not take place in dilute solution cannot be advanced against the application of the two equations, for in these substitutions a great excess (molecular) of the substituting substance is generally present. In nitrations e.g. the substance that is to be nitrated is added in drops to a large quantity of nitric acid, and the nitration is practically completed before the following drop is added.

Moreover I pointed out already in the preceding paper that the objection of higher concentrations cannot be serious, since it is self-evident that the splitting up of the energy values must always be carried out in essentially the same manner. It has, moreover, repeatedly appeared in these substitutions that different ratio of the reacting substances has no appreciable influence on the mutual ratio of the reaction products.

If we now represent the energy of the intermediate states for the three substitutions by ϵ_{t_o} , ϵ_{t_m} , and ϵ_{t_p} , then equation 1 gives:

$$\frac{d \ln \frac{k_o}{k_m}}{dT} = \frac{\epsilon_{t_o} - \epsilon_{t_m}}{RT^2} \quad . \quad . \quad . \quad . \quad . \quad (3a)$$

$$\frac{d \ln \frac{k_o}{k_p}}{dT} = \frac{\epsilon_{t_o} - \epsilon_{t_p}}{RT^2} \quad . \quad . \quad . \quad . \quad . \quad (3b)$$

$$\frac{d \ln \frac{k_m}{k_p}}{dT} = \frac{\epsilon_{t_m} - \epsilon_{t_p}}{RT^2} \quad . \quad . \quad . \quad . \quad . \quad (3c)$$

Here the third equation is of course dependent on the two others.

¹⁾ HOLLEMAN, Die direkte Einführung von Substituenten in den Benzolkern, p. 72. We also refer to this work for the experimental data occurring in this paper.

These equations enable us to calculate the differences of the required substitution energies from measurements of the velocity, at least for so far as they have been performed at different temperatures.

If we now also apply equation 2, we get:

$$\ln \frac{k_o}{k_m} = \frac{\epsilon_{t_m} - \epsilon_{t_o}}{RT} + B_m - B_o \quad . \quad . \quad . \quad . \quad . \quad (4a)$$

$$\ln \frac{k_o}{k_p} = \frac{\epsilon_{t_p} - \epsilon_{t_o}}{RT} + B_p - B_o \quad . \quad . \quad . \quad . \quad . \quad (4b)$$

$$\ln \frac{k_m}{k_p} = \frac{\epsilon_{t_p} - \epsilon_{t_m}}{RT} + B_p - B_m \quad . \quad . \quad . \quad . \quad . \quad (4c)$$

With respect to the constants B from the equation 4 we know that each of them consists of the required entropy difference and of constants which do not depend on the nature of the reacting substances. These latter disappear therefore in equation 4, where always differences between two B -values occur, so that the value $B_m - B_o$ of equation 4a can be replaced by $\eta_{t_m} - \eta_{t_o}$, and just so for the other equations.

So we see that the difference of the substitution energies and entropies can be directly calculated for these reactions from the experimental determinations. The accuracy with which these calculations can be carried out, is of course determined by the value of the errors of observation.

When I applied equations 4 to the data, it soon appeared that the values for $\eta_{t_m} - \eta_{t_o}$ etc. in general possess small amounts, and sometimes differ very little from zero. I have therefore examined whether it is possible to account for the observations *only* by a difference of energy, hence by assuming that *the difference in substitution-entropy would be zero for the different hydrogen atoms*. Mathematically this comes to this that every substitution might be represented by the aid of *one* constant, which would then have the meaning of the difference in substitution-energy. On this hypothesis the equations 4 are transformed into:

$$\ln \frac{k_o}{k_m} = \frac{\epsilon_{t_m} - \epsilon_{t_o}}{RT} \quad . \quad . \quad . \quad . \quad . \quad (5a)$$

$$\ln \frac{k_o}{k_p} = \frac{\epsilon_{t_p} - \epsilon_{t_o}}{RT} \quad . \quad . \quad . \quad . \quad . \quad (5b)$$

$$\ln \frac{k_m}{k_p} = \frac{\epsilon_{t_p} - \epsilon_{t_m}}{RT} \quad . \quad . \quad . \quad . \quad . \quad (5c)$$

To show that the material of facts really admits of such a hypothesis. I subjoin the values which must be assigned to the differences of energy of the equation 5, expressed in calories.

Nitration of chlorobenzene.

$\epsilon_{t_0} - \epsilon_{t_p} = 825$				
	$t = 0$		$t = -30$	
	found	calc.	found	calc.
ortho	30.1	30.4	26.9	26.6
para	69.9	69.6	73.1	73.4

Nitration of bromobenzene.

$\epsilon_{t_0} - \epsilon_{t_p} = 647$				
	$t = 0$		$t = -30$	
	found	calc.	found	calc.
ortho	37.7	37.7	34.4	34.3
para	62.3	62.3	65.6	65.7

Bromation of toluene.

$\epsilon_{t_0} - \epsilon_{t_p} = 658$						
	$t = 25$		$t = 50$		$t = 75$	
	found	calc.	found	calc.	found	calc.
ortho	35.5	35.5	23.5	23.5	6.2	6.0
para	53.9	53.9	32.8	32.8	7.5	7.7

Nitration of benzoic acid.

$\epsilon_{t_0} - \epsilon_{t_m} = 800$						
	$t = -30$		$t = 0$		$t = 30$	
	found	calc.	found	calc.	found	calc.
ortho	14.4	15.9	18.5	18.4	22.3	20.7
meta	85.0	83.5	80.2	80.3	76.5	78.1

Nitration of ethyl-benzoate.

$\epsilon_{t_0} - \epsilon_{t_m} = 500$						
	$t = -40$		$t = 0$		$t = 30$	
	found	calc.	found	calc.	found	calc.
ortho	25.5	25.0	28.3	27.5	27.7	28.5
meta	73.2	73.7	68.4	69.2	66.4	65.6

Nitration of toluene.

$\tau_b - \tau_p = 135$; $\tau_m - \tau_0 = 1490$								
	$t = -30$		$t = 0$		$t = 30$		$t = 60$	
	found	calc.	found	calc.	found	calc.	found	calc.
para	39.3	38.7	38.1	37.6	26.8	36.6	35.3	35.7
ortho	57.2	58.6	58.0	58.6	58.8	58.5	59.6	58.2
meta	3.5	2.7	3.9	3.8	4.4	4.9	5.1	6.1

If we extend the investigation to the introduction of a third substituent in the twice substituted benzene, we get:

Nitration of m-chlor-benzoic acid.¹⁾

$\tau_b - \tau_a = 1290$				
	$t = -30$		$t = 0$	
	found	calc.	found	calc.
<i>a</i> (1, 3, 6)	93	93.5	92	91.5
<i>b</i> (1, 3, 2)	7	6.5	8	8.5

Nitration of m-brom-benzoic acid.

$\tau_b - \tau_a = 1020$				
	$t = -30$		$t = 0$	
	found	calc.	found	calc.
<i>a</i> (1, 3, 6)	89	89.2	87	86.8
<i>b</i> (1, 3, 2)	11	10.8	13	13.2

Nitration of m-dichlor-benzene.

$\tau_b - \tau_a = 1400$				
	$t = -30$		$t = 0$	
	found	calc.	found	calc.
<i>a</i> (1, 3, 6)	97.4	97.3	96.2	96.4
<i>b</i> (1, 3, 2)	2.6	2.7	3.8	3.6

¹⁾ In these tables the place of carboxyle is indicated by 1.

Nitration of o-dichlor-benzene.

$\epsilon_b - \epsilon_a = 1400$				
	$t = -30$		$t = 0$	
	found	calc.	found	calc.
α (1, 2, 4)	94.8	94.8	92.8	93.0
b (1, 2, 3)	5.2	5.2	7.2	7.0

Nitration of o-chlor-benzoic acid.

$\epsilon_b - \epsilon_a = 890$				
	$t = -30$		$t = 0$	
	found	calc.	found	calc.
α (1, 2, 5)	86	86.4	84	83.8
b (1, 2, 3)	14	13.6	16	16.2

Nitration of o-brom-benzoic acid.

$\epsilon_b - \epsilon_a = 760$				
	$t = -30$		$t = 0$	
	found	calc.	found	calc.
α (1, 2, 5)	82.9	82.9	80.3	80.3
b (1, 2, 3)	17.1	17.1	19.7	19.7

When we now pass in review the results of the above tables, it appears that the harmony between the found and the calculated values is very satisfactory in general. In the majority of the examples the deviations very certainly remain within the errors of observation. Only in the nitration of benzoic acid an appreciable deviation between the found values and the calculated ones occurs. This nitration, however, is according to Prof HOLLEMAN one of the first carried out examples, in which the "method of extraction" was applied, which was later replaced by more accurate analysis methods.

Probably the deviation remains within the errors of observation also here. This supposition seems not too hazardous when the results are considered which were obtained in the nitration of the methyl ester of benzoic acid, where very probably in the nitration an error occurs at 0° , which is greater than the above deviations. Prof. HOLLMAN informed me that he too considered the agreement in the tables as very satisfactory.

The above test, therefore, really leads to the conclusion that the substitutions in the benzene nucleus can be satisfactorily accounted for up to now by one single constant, the difference of energy for substitution at the different places in the nucleus. If there were only one example known where the errors of observation were undoubtedly smaller than the deviation from the theoretically calculated value, the originally proposed hypothesis would have to be rejected; so it will have to appear from the continued investigation whether really all the examples without exception conform to the rule, for which no exceptions have been found as yet.

Equations 3 and 5 accordingly, account for the facts which are known up to now. If we now compare the two equations, we come to the following conclusion: The second members of the two equations have always opposed signs; if therefore in equation 5a $k_o < k_m$, i.e. if on substitution more meta- than orthoderivative is formed, then $\epsilon_m - \epsilon_o$ is negative.

It then follows from equation 3a that the value of $\frac{d \ln \frac{k_o}{k_m}}{dT}$ is positive. We can express this generally as follows:

The quantity of the product which is formed to a smaller degree, increases relatively on rise of temperature.

In this we should bear in mind that to decide whether a product is formed in a smaller quantity, it is necessary to divide the quantities formed by the value that indicates the number of equivalent places in the nucleus. Thus the nitration of toluene furnishes *seemingly* an exception, as *seemingly* the quantity of ortho is greater than the quantity of para-nitrotoluene. If however, it is borne in mind that in this substitution there are two ortho-places available to one para-place, and that therefore para and *not* ortho is the product that is formed in greater quantity, the stated rule appears to be valid also here.

As far as I am aware there are no exceptions to this rule either. Only the nitration of iodo-benzene does not follow it, as here the

quantity of ortho-compound does not increase on rise of temperature, but decrease; this nitration is repeated in Prof. HOTTELMAN's laboratory, because the presence of dinitro-compounds may possibly give rise in this case to comparatively great errors in the analyses. In the case of another example that departs from the rule, the quantity of para-product in the nitration of benzoic acid and its methylester, the changes at varying temperature are so slight that the errors of observation may even have changed the qualitative conduct.

Moreover the above consideration establishes the already known practical rule that in general it is desirable for the preparation of pure substitution products to work at low temperature; for according to the stated rule higher temperature always promotes the formation of by-products.

When we examine what influence the above result exercises on our theoretical considerations, we arrive at the following conclusion:

When a hydrogen atom in the benzene nucleus is replaced by an atom or a group of atoms, an intermediate state makes its appearance, which is caused by exactly the same atoms for the substitutions at all available places in the benzene-nucleus. For instance in the case of a nitration the intermediate state is caused by the coincidence of the "kritische Räume" of the carbon atom of the nucleus at which the substitution takes place, of the hydrogen atom, and of the OH and NO₂ group of the nitric acid molecule, at least when in an analogous way as BOLTZMANN ascribes a "kritische Raum" to the NO₂ molecule, we do so for the groups in question. Then the above conclusion would involve that the volumes of the Räume which cover each other, do not differ, or only very little for the substitutions at the different places, but that the different velocity of substitution is caused by the fact that the more distant atoms influence in a different way the energy required for the different places.

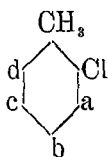
2. An entirely different question, which, however, can be brought in connection with what precedes, is the following: Is it possible when the quantity of the products, which are formed when a second substituent is introduced, is known, to calculate that of the substances which are formed when a third substituent is introduced? In other words is it possible to draw a conclusion from the energies required for the introduction of a second substituent, about the energy required for the introduction of a third? If e. g. we suppose that toluene is nitrated on one side, chlor benzene on the other, we know the relative quantity of the nitroproducts formed; if we now nitrate chlor toluene, it is the question whether the quantity

of the nitroproducts formed in the latter case is to be calculated from the former case. In the first place we should bear in mind that the energy of the substances we start from is different, and now it is true that this energy is cancelled in the determination of the relative quantities, yet the energy of the intermediate states may depend on this energy. To obtain an answer to the given questions we should therefore have to introduce a hypothesis concerning the energy quantities.

These hypotheses must necessarily be very arbitrary, as analogies with other phenomena are not yet known for them. One of the most plausible hypotheses would in my opinion be the following:

Let us denote the energy required for the substitution of the NO_2 -group for the hydrogen atoms in the benzene molecule by ϵ_1 . Then the energy for substitution of the hydrogen atoms in toluene and chlor benzene resp. may be represented by $\epsilon_1 + \epsilon_{o_1}$, $\epsilon_1 + \epsilon_{m_1}$, $\epsilon_1 + \epsilon_{p_1}$ resp. $\epsilon_1 + \epsilon_{o_2}$, $\epsilon_1 + \epsilon_{m_2}$ and $\epsilon_1 + \epsilon_{p_2}$.

If we now think a substitution carried out in the molecule ortho-chlortoluene, we might assume that the energies required for every substituable place must be added



For substitution at the place a , which is in an ortho-position with respect to chlorine and in metaposition with respect to CH_3 , an energy quantity $\epsilon_1 + \epsilon_{m_1} + \epsilon_{o_2}$ would then be required. Reasoning in an analogous way $\epsilon_1 + \epsilon_{p_1} + \epsilon_{m_2}$ would be required for the place b .

Applying equation 5, we get:

$$\ln \frac{k_b}{k_a} = \frac{\epsilon_a - \epsilon_b}{RT} = \frac{(\epsilon_1 + \epsilon_{m_1} + \epsilon_{o_2}) - (\epsilon_1 + \epsilon_{p_1} + \epsilon_{m_2})}{RT} = \frac{(\epsilon_{m_1} - \epsilon_{p_1}) - (\epsilon_{m_2} - \epsilon_{o_2})}{RT}.$$

When we now consider that the introduction of the second substituent requires:

$$\ln \frac{k_{p_1}}{k_{m_1}} = \frac{\epsilon_{m_1} - \epsilon_{p_1}}{RT} \text{ and } \ln \frac{k_{o_2}}{k_{m_2}} = \frac{\epsilon_{m_2} - \epsilon_{o_2}}{RT},$$

we find easily by combination of the three equations:

$$\ln \frac{k_l}{k_a} = \ln \frac{k_{p_1}}{k_{m_1}} - \ln \frac{k_{o_2}}{k_{m_2}}$$

or

$$\frac{k_b}{k_a} = \frac{k_{p_1}}{k_{m_1}} \frac{k_{m_2}}{k_{o_2}}$$

This is the so-called rule of multiplication, which Prof. HOLLEMAN tried to apply for such calculations already before. This rule appeared to be in pretty close agreement with the observations for the nitration of the ortho-chlor and ortho-brom benzoic acids; in other cases, however, great deviations from the calculations are found.

Afterwards HUISINGA proposed a "rule of summation", but this too presents satisfactory agreement only in some cases. If we examine what relation would have to exist between the energy quantities required for substitution to arrive at a rule of summation, this relation appears to assume such an intricate form that it cannot be accounted for in my opinion from a theoretical point of view. A *general* rule for the calculation of substitution energies at the introduction of a third substituent from the values of energy which are required for the introduction of a second, seems to me impossible to find. It may, however, be possible to find a relation between analogous substitutions, and this relation might possibly be discovered by means of the energy values calculated above. Up to now I have however not made an attempt to do so, because the energy values on which the above tables are founded, can certainly still be modified in the units, and sometimes even in the tens; the extent of these modifications, namely, is in the closest relation with the errors of observation which may be allowed in the determinations.

Moreover I will finally point out that in this paper I only intend to show that the material of facts admits the assumption that the substitution entropies are identical for the different places in the nucleus. That this is really perfectly true has of course not been proved by the test; we can certainly also account for the data by means of equations with two constants (equation 4), in which the second constant in general possesses a small value. It appears in any case that in general the course of this type of reactions is chiefly determined by difference of energy, and the difference of entropy plays only a secondary part. As I showed at the end of § 1 our theoretical considerations about the mechanism of the chemical reactions may be brought into harmony with these results.

In conclusion I gladly express my cordial thanks to Prof. HOLLEMAN for supplying me with the information which I required for the foregoing investigation and for his interest in this work.