109. Statistical Differentiation between Various Reaction Mechanisms: The Case of Heterolytic Dediazoniations of Arenediazonium Ions[1]

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Dedicated to two masters of using models in chemistry,
A. Dreiding (Zurich) and *P.B. Weisz* (Princeton) on the occasion of their 60th birthdays

(30.X.78)

1. Introduction. - The majority of present-day papers dealing with reactions of organic compounds contain information, hypotheses or speculations concerning the mechanism of the reactions discussed. Sometimes, such information can be classed with that referred to by *Bunnett* [2] when he quotes a colloquium speaker who said: 'We've written this mechanism down so many times, therefore, we're sure it's right.' In this paper we discuss a more reliable method for the elucidation of reaction mechanisms, namely kinetic investigations. They are among the most important methods for the mechanistic evaluation of a chemical reaction.

In a large number of research papers the consistency of the experimental results with a certain mechanism is often stressed. There are, however, only very few papers in which a rigorous differential treatment of the data for two or more potential mechanisms is given, resulting in verifications and/or falsifications [3] of the mechanisms under discussion. The purpose of the present paper is to demonstrate that a reliable differentiation is possible even between complex mechanistic alternatives if the experimental data are subjected to the appropriate statistical treatment.

The use of modelling techniques in the analysis and solution of problems in chemistry is widespread and has come under intensive scrutiny in recent years as shown by *Suckling et al.* [4]. For a comparison of physical and mathematical models, we refer to a chapter on models in a monograph written by one of us [5]. In this paper a method for differentiating mathematical models will be discussed with the help of the mechanism of heterolytic dediazoniation of arenediazonium ions.

2. Kinetics of the solvolysis of arenediazonium salts. - Dediazoniations of arenediazonium ions are considered the only examples of a nucleophilic aromatic substitution proceeding *via* an aryl cation [6] [7]. Inconsistencies with a slow, rate-limiting aryl cation formation followed by a fast reaction with the solvent were ra-

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[1] Dediazoniation of Arenediazonium Ions in Homogeneous Solution, Part XIII. Part XII see [1].

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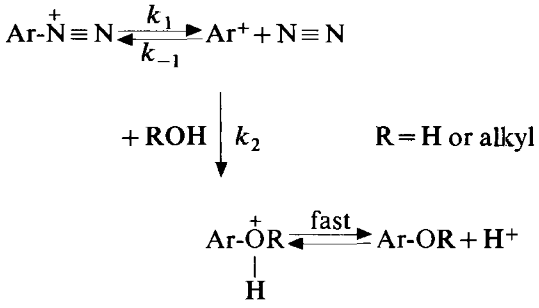
tionalized by the discovery [7] [8] that the back reaction of the first step can take place to a considerable extent. This mechanism (1) yields the usual steady state equation (2). Equation (1) also fits the observation [9] that, in arenediazonium ions, the *α* and *β* N-atoms rearrange.



$$\mathrm{Ar\text{-}\overset{+}{N}{\equiv}N} \underset{k_{-1}}{\overset{k_1}{\longleftrightarrow}} \mathrm{Ar^+ + N{\equiv}N} \qquad (1)^{2)}$$

$$\Big\downarrow k_2 \ \ +\mathrm{ROH} \qquad \mathrm{R = H \text{ or alkyl}}$$

$$\mathrm{Ar\text{-}\underset{H}{\overset{+}{O}}R} \xleftrightarrow{\text{fast}} \mathrm{Ar\text{-}OR + H^+}$$

$$v = [\mathrm{Ar\text{-}N_2^+}] \frac{k_1 k_2 [\mathrm{ROH}]}{k_{-1}[\mathrm{N_2}] + k_2[\mathrm{ROH}]} = k_s [\mathrm{Ar\text{-}N_2^+}] \qquad (2)$$

Equation (2) predicts a nonlinear decrease of the rate of dediazoniation (v) with increasing concentration of molecular nitrogen in the solution. At infinite concentration of N_2 no reaction should take place.

The solubility of N_2 in all suitable solvents is limited even under relatively high pressures. Therefore the function $v = f[N_2]$ can only be followed experimentally over a limited concentration range of N_2.

A series of 41 kinetic runs in 2,2,2-trifluoroethanol (TFE) at a constant total pressure of 300 atm. of mixed N_2/Ar gas, but at 8 different ratios of N_2 and Ar (thus resulting in concentrations of N_2 from 0.00 to 3.03 M) yielded the results [10] shown in the *Figure*. The 3 sets of points refer to mean values of 7, 4 and 3 measurements, with the corresponding standard deviation. The three curves in the *Figure* are three possible interpretations of the results. However, by visual inspection, when the standard deviations are taken into account, it can be concluded that all three curves fit the data in a satisfactory manner.

The dotted line is straight and it demonstrates that even a linear relationship $v = a - b[N_2]$ might fit the experimental data. Such a linear relationship, however, is not consistent with any mechanism we can think of for the reaction conditions used. The dashed line is the best fit[3] for the relationship

$$k_s = \frac{a_1}{b_1[N_2] + c_1} \qquad (3)$$

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[2] The intermediate(s) may also react with other nucleophiles but the solvent. For simplicity the consequent proton release in the reactions of X^+ and Y^+ with ROH is not written separately in (4) and the following mechanisms.

[3] Individual experimental measurements, and not the mean values, were used in all curve fitting processes. The *Figure* contains only the mean values for reasons of simplicity.

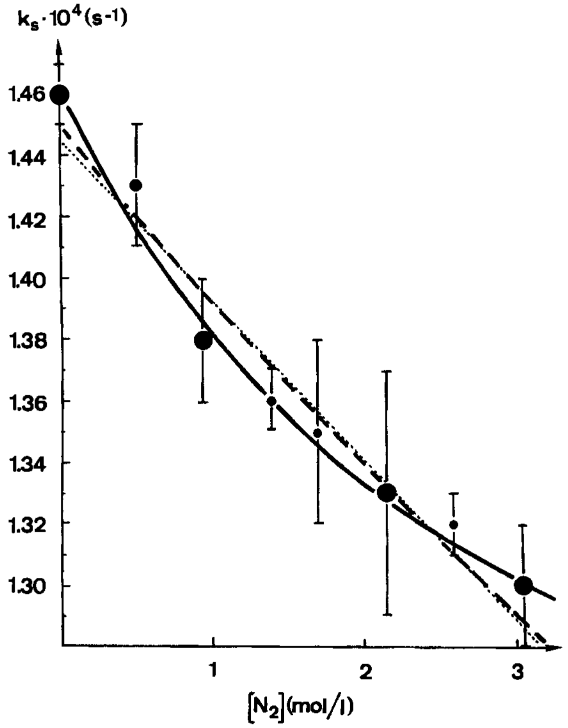
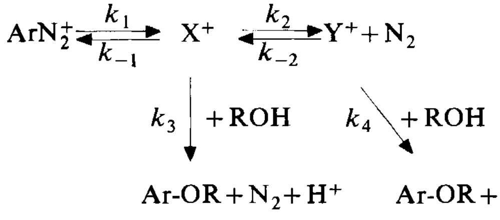


Figure. *Experimental values (with standard deviations) and calculated curves for the dependence of the dediazoniation rate* (k_s) *for 2,4,6-trimethylbenzenediazonium tetrafluoroborate on N_2-concentration (TFE, 300 atm., 25°).* Best fit obtained for a straight line (dotted line) and by using formula 3 (dashed line) and 6 (full line), respectively. The experimental points are mean values of 7 (large dots), 4 (medium dots) and 3 (small dots) measurements, respectively.

which is the mathematical model for the rate equation (2) of the two-step mechanism (1) with the aryl cation as steady state intermediate. It is recognized that this non-linear relationship between v and $[N_2]$ fits the experimental data somewhat better than a linear one. However, it seems that the deviations of the experimental points from the curve are not random, but systematic. At low and at high concentrations of N_2, the experimental rate values are higher than predicted by equation (2) and at medium N_2-concentrations they are lower. Therefore a more 'curved' line would fit the data better.

Kinetic equations can be written for mechanisms with more than one intermediate, *e.g.* mechanism (4) in which the first intermediate X^+ still contains nitrogen and in which N_2 molecules become free only in the two second steps, namely in forming the second intermediate Y^+ or by reaction with the nucleophile (solvent). Y^+ may also react with the solvent. The kinetics of mechanism (4) are described by equation (5). Its mathematical model for $v = f[N_2]$ is equation (6).


$$\begin{tikzcd} ArN_2^+ \arrow[r, shift left, "k_1"] & X^+ \arrow[l, shift left, "k_{-1}"] \arrow[r, shift left, "k_2"] \arrow[d, "k_3"', "+ROH"] & Y^+ + N_2 \arrow[l, shift left, "k_{-2}"] \arrow[d, "k_4"', "+ROH"] \\ & Ar\text{-}OR + N_2 + H^+ & Ar\text{-}OR + H^+ \end{tikzcd}$$

(4)[2]

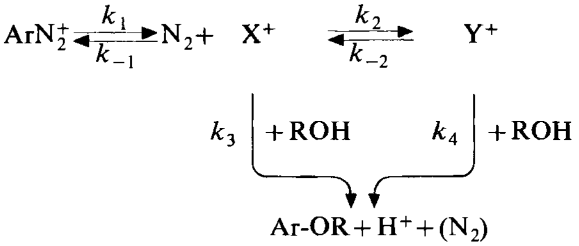
$$\mathrm{v}=[\mathrm{ArN}_2^+]\frac{k_1k_{-2}k_3[\mathrm{ROH}][\mathrm{N}_2]+k_1(k_2k_4[\mathrm{ROH}]+k_3k_4[\mathrm{ROH}]^2)}{(k_{-1}k_{-2}+k_{-2}k_3[\mathrm{ROH}])[\mathrm{N}_2]+k_{-1}k_4[\mathrm{ROH}]+k_2k_4[\mathrm{ROH}]+k_3k_4[\mathrm{ROH}]^2} \tag{5}$$

$$k_s=\frac{a_2[\mathrm{N}_2]+b_2}{c_2[\mathrm{N}_2]+d_2} \tag{6}$$

The application of the mathematical model (6), *i.e.* mechanism (4) to the experimental values of the rate constants yields the solid curve in the *Figure*. In contrast to the dashed curve there seems to be no systematic order in the sign of the deviations of the mean values.

Most chemists will probably stop their evaluation at this point and claim that mechanism (4) fits experimental data best[4]). This is incorrect for two reasons: 1) It is clear that a mathematical relationship such as (6) which has one independent parameter more than equation (3) will fit the experimental data better; 2) if one considers one mechanism with two intermediates, one has to check if alternative mechanisms, also involving two intermediates, are possible. In this section we will discuss the second question, which is a chemical problem. In section 3 of this paper we will evaluate the first question which has to be treated statistically.

Another mechanism with two consecutive intermediates is (7) where in the formation of the first intermediate X^+ N_2 is already split off; X^+ rearranges in some way to a second intermediate Y^+; X^+ and Y^+ form products with nucleophiles. The corresponding kinetic equation is (8). It corresponds to the mathematical model (3). As this relationship between k_s and $[N_2]$ is the same as that for the one-intermediate mechanism (1), we can not differentiate (1) from (7) by evaluating the function $k_s = f[N_2]$.



(7)[2])

$$\mathrm{v}=[\mathrm{ArN}_2^+]\frac{k_1(k_{-2}k_3+k_2k_4+k_3k_4[\mathrm{ROH}])[\mathrm{ROH}]}{(k_{-1}k_{-2}+k_{-1}k_4[\mathrm{ROH}])[\mathrm{N}_2]+(k_2k_4+k_{-2}k_3+k_3k_4[\mathrm{ROH}])[\mathrm{ROH}]} \tag{8}$$

Instead of two consecutive intermediates we may visualize two competitive pathways each with one intermediate. Here again, N_2 is split off during the formation of either one or both of these intermediates. These two alternatives correspond to mechanisms (9) and (12) with the rate equations (10) and (13), respectively. The

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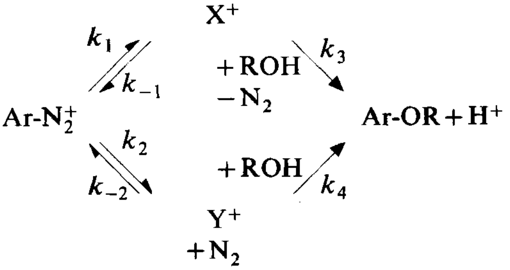
[4]) A few chemists will even say that (4) is the only correct mechanism. This claim is basically wrong in all cases.

mathematical model for (10) is the same as for equation (5), *i.e.* (6). Therefore, mechanisms (4) and (9) cannot be differentiated by statistical analysis. Rate equation (13) of mechanism (12) corresponds to a new mathematical model, namely (14).

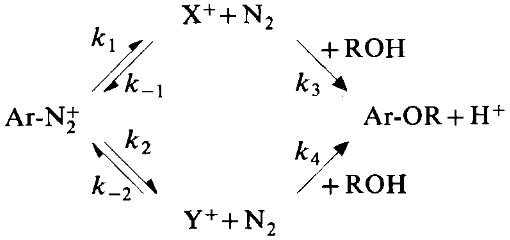


(9)[2]

$$v=[\text{Ar-N}_2^+]\left(\frac{k_2k_4[\text{ROH}]}{k_{-2}[\text{N}_2]+k_4[\text{ROH}]}+\frac{k_1k_3[\text{ROH}]}{k_{-1}+k_3[\text{ROH}]}\right) \tag{10}$$

$$k_s=\frac{a_3}{b_3[\text{N}_2]+c_3}+d_3 \tag{11}$$

(11) is equivalent to (6) when $k_s = f[n_2]$ is considered.



(12)[2]

$$v=[\text{Ar-N}_2]\left(\frac{k_1k_3[\text{ROH}]}{k_{-1}[\text{N}_2]+k_3[\text{ROH}]}+\frac{k_2k_4[\text{ROH}]}{k_{-2}[\text{N}_2]+k_4[\text{ROH}]}\right) \tag{13}$$

$$k_s=\frac{a_4}{b_4[\text{N}_2]+c_4}+\frac{d_4}{e_4[\text{N}_2]+f_4}\equiv k_s=\frac{a_5[\text{N}_2]+b_5}{c_5[\text{N}_2]^2+d_5[\text{N}_2]+e_5} \tag{14}$$

Possible mechanistic alternatives with one and two reaction intermediates[5] having been considered, a check has to be made if one or more of them can be excluded on the basis of the available experimental data (in this case dediazoniation rates at

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[5] Obviously even more variations are possible (each of them fitting one of the mathematical models already presented) *e.g.* assuming some rate constant much larger than the other and thus making one or the other step irreversible, *etc.*

different N_2-concentrations). Two approaches will be used: (i) A rigorous statistical evaluation and comparison of the best fits obtained with mathematical models (3) and (6)[6]) in the hope that one of them fits the data better; (ii) if approach (i) is successful, chemical considerations will enable a decision to be made concerning which mechanism from the remaining pairs (1) or (7), or (4) or (9) is the most suitable (Part 4).

From the above reasoning it is obvious that in the best case only one mechanism remains that is still in accordance with the available experimental data. It does not mean that it is the correct mechanism. More 'complicated'[7]) ones can always be written to fit the data at least as well. As the available knowledge about a specific reaction increases, it may become necessary to alter or expand a hitherto accepted mechanism. Therefore it is only possible to exclude and disapprove a mechanism definitely, but never to 'prove' it [3].

3. Statistical evaluation of the mathematical models. - The functional relations (3), (6) and (14) are mathematically equivalent to the relations (3'), (6') and (14'), respectively (replacing $[N_2]$ by x).

$$k_s = \frac{1}{a + \beta x} \tag{3'}$$

$$k_s = \frac{1}{a + \beta x} + \frac{1}{\gamma} \tag{6'}$$

$$k_s = \frac{1}{a + \beta x} + \frac{1}{\gamma + \delta x} \tag{14'}$$

Whereas the parameters in the old models cannot be estimated uniquely from the results of a controlled experiment the parameters a, β, γ and δ can. The representation above shows in addition that (3') is a submodel of (6'), which in its turn is a submodel of (14').

Polynomial models of the type $k_s = b_0 + b_1x + b_2x^2 + b_3x^3$ are referred to as linear, quadratic or cubic depending on their degree. The polynomial models are of course linear in the unknown parameters whereas models 3, 6 and 14 are intrinsically nonlinear and therefore more difficult to deal with numerically as well as statistically.

It has already been stated that the linear model is not admissible over the whole range of theoretically possible values of $x = [N_2]$ and this is even more true of the polynomial models of higher degree. However, locally, *i.e.* in the interval of the given eight values, they might fit to the experimental data equally as well as the

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[6]) Model (14) has one characteristic in common with model (3), *i.e.* at $[N_2] = \infty$ the rate approaches zero, in contrast to model (6) where it approaches a constant value greater than zero.

[7]) If several mechanisms fit the experiment equally well, according to *Occam*'s razor, the simplest still satisfying one is chosen.

other models. In fact, the best fit (in the sense of minimizing the sum of squared deviations) of the simplest of the 'reasonable models', namely (3')[8]) is, in the interval of observation, hardly distinguishable from the fit of the linear model (see *Figure*).

The reason for this can be seen from an expansion of function (3') into a polynomial series (15).

$$k_s=\frac{1}{a+\beta x}=\frac{1}{a}\left(\frac{1}{1+\frac{\beta x}{a}}\right)=\frac{1}{a}-\frac{\beta}{a^2}x+\frac{\beta^2}{a^3}x^2-\frac{\beta^3}{a^4}x^3+\cdots \qquad (15)$$

The parameters in model (3') can be estimated: $\hat{a}=0.690$ and $\hat{\beta}=0.0282$, and hence the expansion of the fitted curve is (15').

$$\hat{k}_s=1.449-0.059\,x+0.0024\,x^2-0.0001\,x^3+\cdots \qquad (15')$$

The magnitude of the coefficient $b_2=\beta^2/a^3$ is determined essentially by

$$b_0=\frac{1}{a} \quad \text{and} \quad b_1=\frac{\beta}{a_2} \qquad b_2=b_1^2/b_0$$

If the slope b_1 is very small then b_2 and the higher coefficients can be neglected for the given interval of observation, *i.e.* $1/(a+\beta x)$ is approximately linear in that interval. It is therefore not surprising that the best fit of the 'linear' model is $\hat{k}_s=1.446-0.052\,x$.

The improvement of the linear model over the constant model $k_s=b_0$ is of course most significant (F = 188). The more difficult question to answer is whether the data supports the hypothesis of a systematic deviation from linearity or from model (3').

The standard way to approach this question is to use an F-test to compare the variance within the experimental values (an estimate of the pure error) and the sum of squared deviations of the means from the fitted regression line (as an estimate of the lack of fit). The respective ANOVA table is (using standard terminology) [11]:

Source	D.f.	SS	MS	F-ratio
Total (corr.)	40	0.1464		
Linear Regr.	1	0.1213	0.12132	188
Residual	39	0.0251	0.00064	
Lack of fit	6 = (8–2)	0.0059	0.00098	1.7
Pure error	33 = (41–8)	0.0192	0.00058	not significant at $a=0.1$

The test indicates no deviation from linearity or from model (3'). However, the above test has an important drawback that has scarcely been mentioned in the

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[8]) The fitting of the nonlinear models (3') and (6') has been accomplished by means of the NL WOOD program originally written by *D.A. Meeter*, Univ. of Wisconsin; revised at American Oil by *F.S. Wood*.

literature *i.e.* it is exclusively based on the magnitude of the deviations from the model and completely insensitive to a systematic order in the signs of the deviations (as exhibited by the mean values in the *Figure*). A nonparametric test that evaluates the number of equal signs on a row, the 'runs-test', on the other hand, does not make use of the magnitude of the deviations. Furthermore, in the case of residuals of a regression the distribution of its test statistics is only known (approximately) for large numbers of measurements.

In our case an F-test of the fit of the quadratic model *versus* the linear model essentially measures both types of deviations and it is not surprisingly highly significant:

Source	D.f.	SS	MS	F-ratio
Resid. Lin.	39	0.0251		
Resid. Quad.	38	0.0197		
Lin.-Quad.	1	0.0054	0.0054	10.38
Residual	38	0.0197	0.00052	significant at $\alpha = 0.001$

Locally, *i.e.* in the range of observations, the quadratic model fits the data significantly better than the pure linear model.

We now show that the quadratic model can be replaced by the model (6′) which is admissible over the whole range of values. Whereas the fit of model (3′) is very close to a straight line (a fact that is corroborated by the closeness of its residual sum of squares, 0.0235, *versus* 0.0251 of the linear model), the fit of model (6′) is very close to that of the quadratic model (with residual sum of squares 0.0196 *versus* 0.0197). The reason for this is that the coefficient of the quadratic term in the expansion of model (6′), *i.e.* in (16), can be chosen independent of the linear and

$$k_s = \frac{1}{\alpha+\beta x} + \frac{1}{\gamma} = \frac{1}{\alpha} + \frac{1}{\gamma} - \frac{\beta}{\alpha^2}x + \frac{\beta^2}{\alpha^3}x^2 - \frac{\beta^3}{\alpha^4}x^3 + \cdots \tag{16}$$

constant term coefficients β/α^2 and $(1/\alpha + 1/\gamma)$, respectively, because of the additional degree of freedom introduced by the parameter γ. The fitted coefficients of model (6′) are $\hat{\alpha} = 3.175$, $\hat{\beta} = 1.105$ and $\hat{\gamma} = 0.872$ which yields (16′).

$$k_s = 1.462 - 0.110x + 0.038x^2 - 0.013x^3 + \cdots \tag{16′}$$

The respective fits for the quadratic and the cubic models are

$$\hat{k}_s = 1.460 - 0.090\,x + 0.012\,x^2 \quad \text{and}$$
$$\hat{k}_s = 1.462 - 0.105\,x + 0.027\,x^2 - 0.003\,x^3.$$

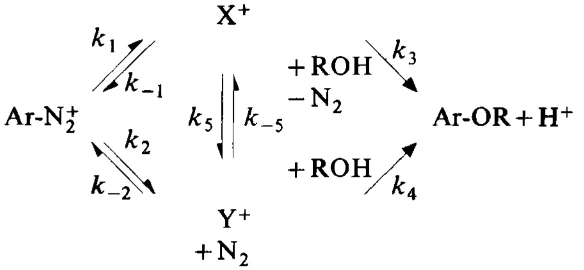
Even though the respective coefficients of the squared term are different, the improvement of the cubic model over the quadratic one has only an F-value of 0.42, *i.e.* is completely insignificant. The seemingly large difference in the coefficients stems from the fact that for the chosen values of x the vectors (x_i^2, i = 1,.. 8) and

(x_i^3, $i=1,..8$) are highly correlated. This shows that model (3′) and model (6′) in the neighbourhood of the fitted parameters are essentially linear in parameter space with 2 and 3 degrees of freedom. An F-test, such as that used above to compare the fit of the two models, is therefore possible.

Source	D.f.	SS	MS	F-ratio
Resid. (3′)	39	0.0235		
Resid. (6′)	38	0.0196		
(3′)-(6′)	1	0.0039	0.0039	7.36
Resid. (6′)	38	0.0196	0.00053	significant at $a=0.01$

Thus, the data provide strong evidence to reject model (3′) in favour of model (6′). A distinction between models (6′) and (14′) is, however, not possible.

4. Chemical evaluation and conclusions. - It follows from Part 3 that model (6) represents a significant improvement when compared with model (3). Therefore, the final question concerns the suitability of mechanism (4) or (9). Each involves two intermediates, one of which contains nitrogen. In mechanism (4) X^+ is formed along the reaction pathway towards Y^+, while in mechanism (9) X^+ and Y^+ are formed competitively in parallel reactions. It must be borne in mind that, based on experiments with β-^{15}N labelled diazonium salts, it was concluded that X^+ was the Ar^+N_2 molecule/ion pair, while Y^+ was the free aryl cation [10]. Thus, necessarily, a direct $X^+ \rightleftharpoons Y^+ + N_2$ pathway (possibly *via* the solvent separated molecule/ion pair) must exist. Inclusion of this pathway into mechanism (9) yields (17). The corresponding kinetic equation also satisfies mathematical model (6), *i.e.*



(17)

it would not improve the best fit of the experimental data. Therefore, it can be concluded that the simplest mechanism that still meets all the requirements imposed by the available experimental results is mechanism (4). The dediazoniation of arenediazonium ions in TFE proceeds *via* two consecutively and reversibly formed intermediates, a nitrogen/aryl cation tight molecule/ion pair and a dissociated, free aryl cation, both of which can react with nucleophiles to give products. In addition to the kinetic data presented above, mechanism (4) enables rationalization of the results obtained with β-^{15}N labelled arenediazonium salts, *i.e.* the N_α-N_β-rearrangement and the exchange of the labelled diazonio group with atmospheric nitrogen (300 atm.) during dediazoniation [10] [12] as well as their dependence on the substituent in the arene nucleus and on the solvent. It must be pointed out that this kind of kinetic investigation gives insight into the stoichiometry of individual intermediates, but not into their structure. Structural information needs additional data: In the reaction discussed here the observation of the N_α-N_β-rearrangement leads, in combination with mechanism (4), to the conclusion that the two N-atoms of X^+ have to be in symmetric positions relative to the aryl part of X^+.

This investigation therefore demonstrates not only the potential, but also the limits of a rigorous evaluation of kinetic data for mechanistic purposes.

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