The Reactivity–Selectivity Principle: Redefinition and Reexamination on an Experimental Basis*

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The Reactivity–Selectivity Principle (RSP) has been redefined with more precision for several cases, all restricted to rate constants but with different variable factors. This principle is formulated in terms of simple mathematical expressions, involving only rate constants and avoiding any σ constants, equilibrium constants or other parameters. With a given reaction series four types of behaviour are possible: (i) a valid RSP when the selectivity decreases with reactivity; (ii) anti-RSP when the reverse is true; (iii) indifferent behaviour when the change in selectivity is negligible; (iv) a cross-over when RSP is valid in one part of the series and invalid in the other. All four cases have been observed in the available experimental data. A statistical examination has been carried out on two sets, each containing 100 reaction series. In a set concerning the original narrow definition – two reagents reacting with one series of similar substrates – RSP is evidently an invalid rule: the numbers of positive and negative cases is approximately equal. In the second set, where temperature is the variable factor, RSP holds but not without exceptions (five convincingly documented exceptions from 100 cases): generally a reagent is less selective at a higher temperature. Some relations to the Hammond postulate are mentioned.

The inverse relationship between increasing reactivity of a reagent and its selectivity, called the Reactivity–Selectivity Principle (RSP), has been the object of several recent reviews,[1] of one special issue of *Isr. J. Chem.*,[2] and of numerous further papers.[3–6] In still more papers it is just mentioned as a well-known rule, but it is difficult to trace back to its inventor: probably the first clear formulation is in the book by Leffler and Grunwald.[3] The literature has given great attention to the theoretical corollaries[2,4] but relatively less to the proper experimental background. Mostly it is accepted that RSP has been sufficiently proven. Positive examples are mentioned as further proofs of a well known law. When opposing cases are encountered, they are quoted as interesting cases, 'the exception proving the rule'. Nevertheless, it has been pointed out that the exceptions seem to be too many;[4f,g,5] even the extreme opinions that RSP is 'virtually useless in practice' or 'absent as a general rule' have been offered.[6] To the best of our knowledge no attempt has been made to evaluate the experimental evidence quantitatively in a broader extent. In the most important approach seventeen reactions were evaluated[4c] which could be correlated with σ constants: the number of valid and invalid cases was not given explicitly and different definitions of RSP were mixed together. We want here to evaluate a greater number of examples extending beyond the validity of any linear free energy relationship. For this reason it is necessary to define RSP with more precision and to formulate it in terms of simple mathematical expressions. Our point of view is almost purely empirical: the agreement with experiments is the only criterion.

Definitions of RSP

A. In the original, most narrow conception[3] two similar reagents can react in analogous reactions with various substrates of a given set. The reagent which reacts faster should show smaller differences in reaction rates within this set, *i.e.* lower selectivity. [A quantitative measure of these differences is log k, see later eqns. (1) and (2).] Our formulation seems to be in accord with the common feeling: intuitively one expects more by-products in a vigorous reaction, and in the extreme case the most reactive reagent will react with every substrate at every collision (in solution at the diffusion rate). The heart of the problem is in the definition of similarity. When RSP fails, one could say that the two reagents (or the substrates) are not sufficiently similar, or that the reaction mechanism has changed. Let us mention that in our opinion the substrates within the set should also be similar to each other, in fact even more than the reagents are.

B. According to a modified definition a reagent can react with two similar sets of substrates, in which case the set reacting faster should exhibit smaller differences between individual rates. The examples according to this definition are less numerous, since it is not easy to find two similar sets of substrates with some common inner arrangement to be strictly comparable. (A good example may be the reaction of trifluoroacetic anhydride with 5-substituted thiophenes on the one hand and with 5-substituted furans on the other hand.[6h]) In addition, the difference in reactivity between the sets should be larger than within the sets. If this is not the case,[4c,d] the substrates may be said to be doubly substituted and the problem is better treated in terms of substituent effect additivity than in terms of selectivity. Another limiting case is when the two sets form two parts of a longer series in which the reactivity depends on some external factor (σ constant, equilibrium constant). Then RSP requires that this dependence is actually curved with a decreasing slope. Experimentally this requirement was not supported,[1a] except possibly in some long Brønsted plots which are partly under diffusion control.

C. Further extensions of RSP are possible in which the two reagents are replaced by one reagent in two different solvents or under different conditions, or both the reagents and conditions are varied. These extensions are mostly ill defined and not well supported by experiments.

D. One well defined case of changing reaction conditions is when only the temperature is variable. A reaction at a higher temperature is faster, and should, according to the RSP, be less selective. This requirement is parallel, but not strictly equivalent,[7] to the statement of the Compensation Law[8] (CL) according to which the activation enthalpy in a series of related

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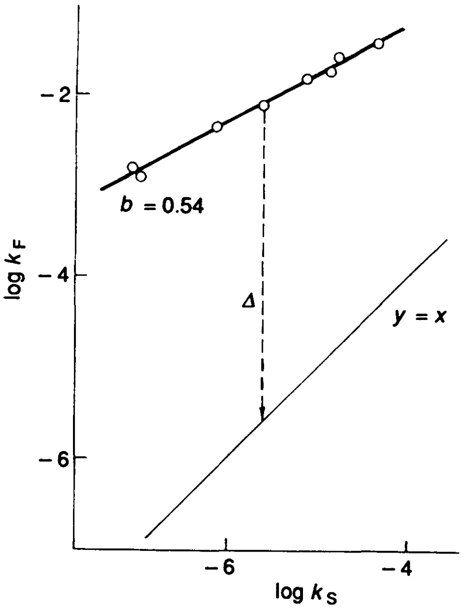

Fig. 1 An RSP plot according to eqn. (3) when the principle is valid, RSP(+): oxidation of *meta*- and *para*-substituted benzyl alcohols by ethyl chlorocarbamate on the one hand and by pyridinium chlorochromate on the other; experimental data from ref. 11. Shown are the slope of the regression line b and the mean difference in reactivity of the two reagents Δ.

reactions should be proportional to the activation entropy. Most reaction series obey both principles, but using more sophisticated statistics[7] cases were discovered where RSP is valid but CL not; in a few examples the reverse is true.[9] All the cases can be well distinguished and characterized in terms of a more general phenomenon, the Isokinetic Relationship (IKR).[7] The deciding factor is the value of the isokinetic temperature β, an extrapolated value of temperature at which all the reactions of the series should proceed at the same rate.

Mathematical Formulation

The mathematical formulae are formally equal for all the definitions: we shall use the terms of definition A. Although the formulae are very simple, they have not yet been stated exactly.

(a) The simplest possible formulation[10] is based only on four rate constants: two reagents (slow S and fast F) reacting with two substrates (1 and 2). The notation is chosen so that F reacts faster than S (with 1) and 2 reacts faster than 1 (with S); the choice of reagent is made so that the difference between reagents is larger than between substrates. In order to get reasonable

$$\log k_{F1} > \log k_{S1}$$

$$\log k_{S2} > \log k_{S1}$$

$$\log k_{F1} - \log k_{S1} > \log k_{S2} - \log k_{S1}$$

results, interpretable in terms of common theories, one must restrict the considerations to cases where the sequence of reactivity is not reversed [eqn. (1)]. Then the requirement of RSP reads as in eqn. (2). The use of logarithms of rate constants

$$\log k_{F2} > \log k_{S2} \qquad (1)$$

$$\log k_{F2} - \log k_{F1} < \log k_{S2} - \log k_{S1} \qquad (2)$$

in these relationships is of advantage for a comparison with the formulations in the succeeding paragraphs. The two inequalities, eqns. (1) and (2), give two limits for k_{F2} in order to meet the RSP. If k_{F2} is greater than defined by eqn. (2), the reverse of RSP is valid: the faster reagent is more selective. If k_{F2} is smaller than defined by eqn. (1), the reactivity is reversed and the validity of RSP cannot be examined: in terms of the above definition one can say that the reactions are not 'similar'.

The verification of RSP based on four rate constants is simple and unambiguous, but not very efficient from the statistical point of view. On the one hand, the result may be easily affected by experimental error, on the other hand there is little possibility of testing whether the two reactions are sufficiently similar (for instance a possible change of reaction mechanism). Eqn. (1) is certainly a necessary but not a sufficient condition.

(b) A better experimental basis is a set of rate constants when two reagents (fast F and slow S) can react with a series of similar substrates ($i = 1, 2, \ldots, n$). Then the similarity of the reactions requires an approximate, more or less precise, linear relationship between the two series, as in eqn. (3) where ε_i is a

$$\log k_{Fi} = a + b \log k_{Si} + \varepsilon_i \qquad (3)$$

$$0 > b > 1 \qquad (4)$$

random variable with zero mean value [the error of eqn. (3)]. The RSP then requires eqn. (4). By the same token as in method (a), the slope b must be positive, otherwise the reactions are not similar. The condition of similarity may be further tested by the precision of eqn. (3) (correlation coefficient and standard deviation from the regression line). The validity of RSP is judged according to eqn. (4). If a larger set of data is available, b can be calculated together with its confidence interval, and the validity of eqn. (4) can be given a confidence level. If eqn. (3) is not valid with a sufficient precision, no conclusions about the RSP are possible. (When the relationship is not linear, certain pairs of points may correspond to RSP, certain others to its reversal.) Some difficulty may arise with the choice of the reagent and the substrate. When the experiments are planned, the choice should be made in such a way that the differences between reagents are greater than between substrates. When literature data are processed, any choice is often impossible since the model requires a greater number of substrates, but is satisfied with two reagents. In some cases it may be that the greatest difference in reactivity within the substrate set is greater than between the reagents: then a 'crossing' of RSP behaviour may be observed (see later Fig. 4). Since the difference between reagents is variable along the series of substrates, it is advisable to define the mean difference Δ as in eqn. (5).

$$\Delta = \left(\sum_i \log k_{Fi} - \sum_i \log k_{Si}\right) \Big/ N \qquad (5)$$

When a data set is treated according to this model, results of four types can be obtained. They are best seen in a graphical representation when $\log k_{Fi}$ values are plotted against $\log k_{Si}$ according to eqn. (3). (i) The RSP is valid when the slope b is significantly less than unity and Δ is not too small (say greater than the range of $\log k_{Fi}$), Fig. 1, the case RSP(+) according to the notation suggested.[4c] (ii) When b is greater than unity, the reversal of RSP takes place, Fig. 2, RSP(−). (iii) No decision is possible when the slope b is not significantly different from unity, Fig. 3. The reason may be either equal selectivity of the two reagents or an insufficiently precise linearity (experimental error, great chemical differences between substrates). Since the two reasons cannot always be distinguished, we denote this case by RSP(?). (iv) When Δ is too small, it may be that the regression line intersects the straight line $y = x$. Then the validity of RSP is changed since the terms fast reagent and slow reagent will

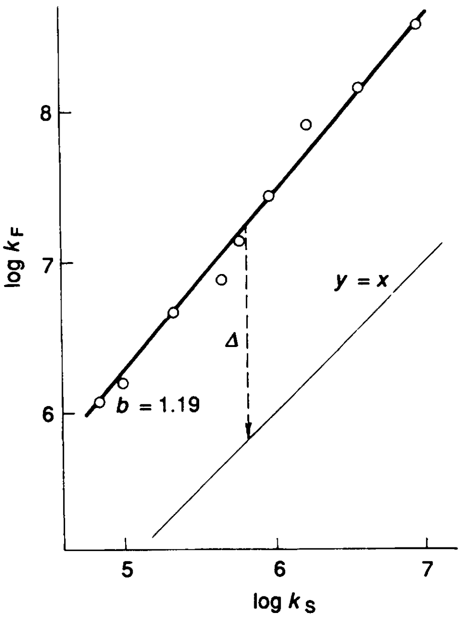

Fig. 2 An RSP plot contradictory to the principle, RSP(−): group transfer reactions of the radicals $Re(CO)_4L^{\cdot}$ (with various ligands) with trimethylsilyl methyl sulfide or with dibutyldisulfide; experimental data from ref. 12

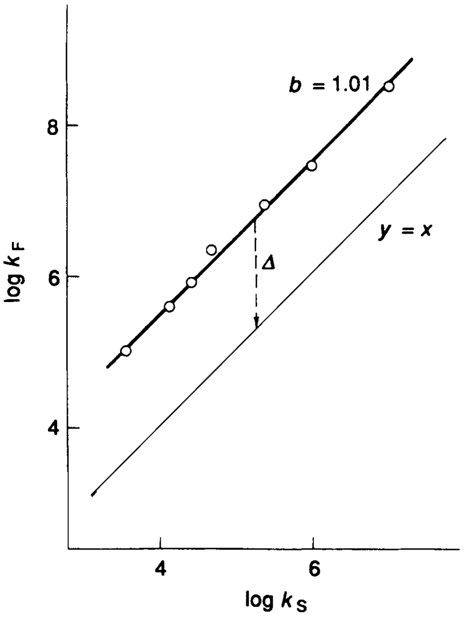

Fig. 3 An RSP plot showing indifferent behaviour, *i.e.* no change of selectivity, RSP(?): coupling of *meta-* and *para*-substituted phenyldiazonium ions with 2-hydroxynaphthalene-6-sulfonic acid or with 2-naphthol; experimental data from ref. 13

exchange. In Fig. 4 RSP is invalid in the main area of the graph but would be valid to the left of the point of intersection. We denote this case RSP(±). In fact this type of behaviour could be observed very often if the set of substrates were sufficiently extended (to the right in Fig. 1, to the left in Fig. 2). In most cases, however, such an extension is physically impossible: it would be necessary to include substrates of quite divergent structures, sometimes even impossible. For instance, Fig. 1 should be extended up to benzylacohols bearing substituents with σ constants of approximately -3.5 while the lowest possible value is about -1. We can say that when the RSP(±) behaviour is encountered, the reason is an insufficient difference in reactivities of the two reagents.

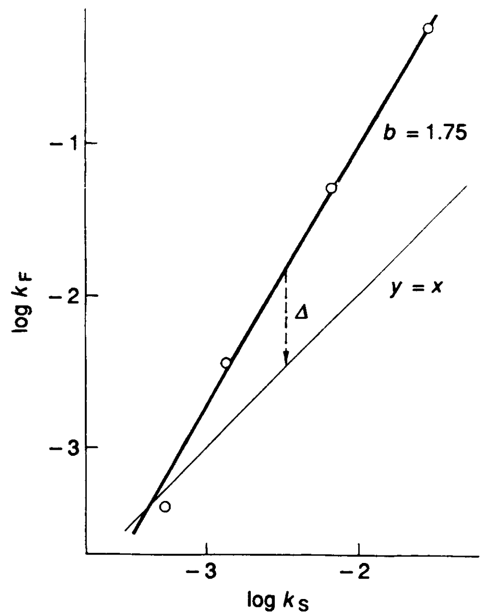

Fig. 4 A RSP plot when the validity is reversed within the range of accessible values, RSP(±): lactonization of *N*-(2′,2′,2′-trifluoroethyl)-6-hydroxybicyclo[2.2.1]heptane-2-carboxamide or of *N*-propyl-6-hydroxybicyclo[2.2.1]heptanecarboxamide by various bases, experimental data ref. 14. RSP holds on the left of the point of intersection, but does not hold on the right. The choice of the terms reagent and substrate is in this example reversed compared to the usual meaning.

(c) Strong RSP. The RSP has been always formulated as a qualitative principle, using the terms 'more' and 'less'. Nevertheless, some quantitative aspects cannot be completely avoided. At least when the difference in reactivity is almost zero, one must expect that the difference in selectivity is also almost zero. A similar statement could also hold for very large differences. In these comparisons different data sets were involved. A comparison within one data set comes into consideration when measurements with more than two reagents and the same set of substrates are available. Then, original RSP requires only a reversed sequence of reactivity and selectivity. However, one can go a step further and suppose a linear relationship between the slope b of eqn. (3) and Δ as defined in eqn. (5). In the graphical representation this assumption is equivalent to a family of straight lines, intersecting at one point (Fig. 5). The corresponding mathematical expression is the equation we shall call 'strong RSP' [eqn. (6)]. Here b_i and x_j are

$$\log k_{ij} = y_o + b_i x_j \qquad (6)$$

empirical parameters for the reagent and substrate, respectively. Equations of this mathematical form have several times been established[17] and also mathematically analysed.[17a] Attention was focused on the constant y_o, the 'magic point':[17b] its value is independent[17a] of any arbitrariness in the values of b_i and x_j. In the field of RSP this point represents some limiting value of reactivity in which, for a particular substrate, the reaction rate is independent of the reagent and *vice versa*. When RSP holds, this point should be situated on the side of high reactivity [Fig. 6(*a*)], but a reverse pattern was also observed [Fig. 6(*b*)]. One can assume that the magic point is just a product of extrapolation and not experimentally accessible. This is not always true, see *e.g.* Fig. 6(*b*) where this point could be approximately reached with 3-nitroaniline or with 4-dimethylaminobenzyl fluoride. No good experimental evidence is available. Strong RSP could be very important for sensitive and convincing tests, but the available data are somewhat monotonous and restricted mostly to compounds of the Hammett type. Generally it is difficult to realize small and systematic structural changes in both reactants.

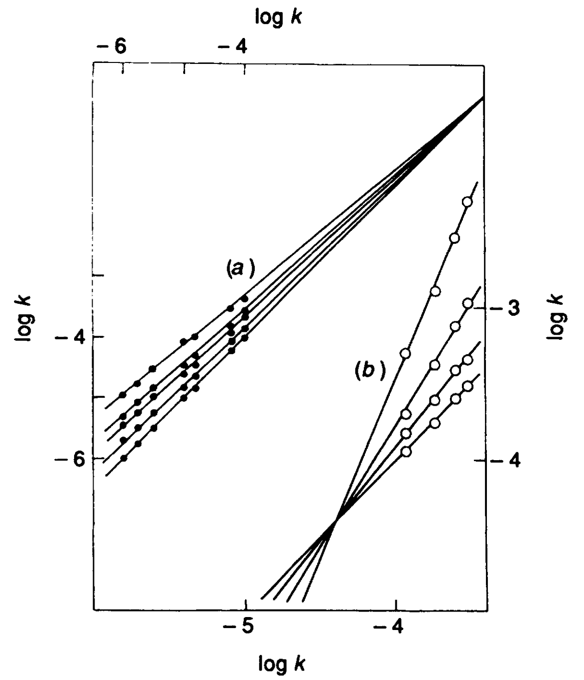

Fig. 5 Strong RSP, plots according to eqn. (6): (*a*) solvolysis of various *meta*- and *para*-substituted allyl benzenesulfonates with various alcohols; data from ref. 15; (*b*) acylation of various substituted anilines with substituted toluene-*x*-sulfofluorides; data ref. 16

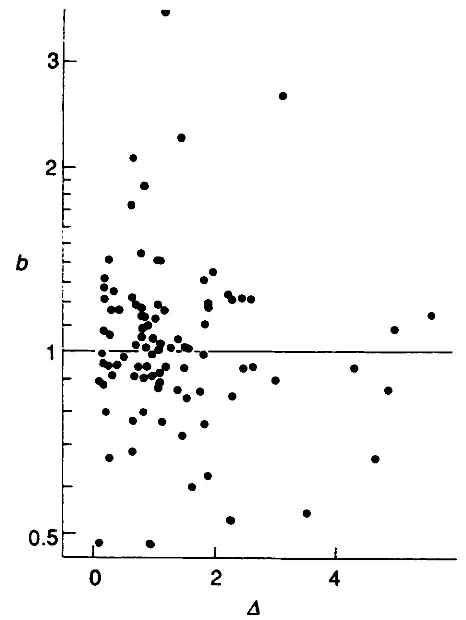

Fig. 6 A statistical test of RSP according to the narrow definition (two reagents with a group of substrates): the slope *b* of eqn. (3) plotted *vs.* Δ according to eqn. (5). RSP holds in the cases situated below the straight line.

(d) Mathematical formulation of RSP is somewhat simplified when the reactivity depends, with some approximation, on an external factor like the Hammett constant, solvent permittivity *etc.*, and can be expressed as a kind of Linear Free Energy Relationship (LFER). In the case of two reagents the two LFER have the form of eqns. (7) and (8) where σ stands for an external

$$\log k_{Fi} = \log k_{F0} + \rho_F\sigma \qquad (7)$$

$$\log k_{Si} = \log k_{S0} + \rho_S\sigma \qquad (8)$$

parameter of any kind. The RSP then requires that the proportionality constants ρ_F and ρ_S are of the same sign, and ρ_S greater in absolute value. The two conditions can be expressed by one inequality [eqn. (9)]. In the case of more reagents the

$$\rho_S\rho_F > \rho_F^2 \qquad (9)$$

general form of a LFER reads:[18]

$$\log k_{ij} = \log k_{00} + \rho_1\sigma_i + \rho_2\sigma_j + \rho_{12}\sigma_i\sigma_j \qquad (10)$$

The magic point is reached at $\sigma_i = -\rho_2/\rho_{12}$ and $\sigma_j = -\rho_1/\rho_{12}$. The RSP requires such a combination of signs that the magic point is situated on the side of high reactivity:[10]

$$\rho_1\rho_2\rho_{12} < 0 \qquad (11)$$

Using this principle the validity of RSP was investigated on several reaction series.[4cd] The treatment based on external factors suffers on the one hand from introducing an additional source of inaccuracy, and, on the other hand, from being restricted to a narrow class of compounds, mostly to derivatives of the Hammett type.

Statistical Testing

For the following testing of RSP we have chosen the mathematical description as given in the method (b) of the preceding section. The reasons for this choice are as already sketched: while the formulation of method (a) is too general (cannot distinguish good and bad examples), methods (c) or (d) are too particular (would restrict the experimental material too much). These reasons are also connected with the practical consequences: it would be hardly possible to find a sufficient number of examples for the models (c) or (d), while for the model (a) there would be too many and their choice would be difficult. Concerning the proper chemical definition of RSP we have chosen two possibilities: model A as described above (two reagents with the same set of substrates) and model D (one reagent at two different temperatures). Only for these two models was it possible to find a sufficient number of examples. Note that for model D the available data usually concern more than two temperatures and could be treated according to eqn. (6), using more sophisticated statistics[7] and the results of the examples already calculated.[9] However, we preferred simpler treatment in terms of eqn. (3) in order to compare the two models, A and D, under strictly comparable conditions.

Data Choice.—Two sets were selected for model A (two reagents) and model D (two temperatures), respectively, each containing 100 examples. The necessary conditions were: (i) All measurements made in one laboratory under comparable conditions, mostly in the same solvent (exceptionally in different solvents when the solvent was identical with the reagent). (ii) The minimum number of substrates was four, provided the relationship according to eqn. (3) was actually linear with a good accuracy. In larger sets, with six points or more, one deviating point was eliminated if necessary. The criteria for elimination were in fact arbitrary since there is no efficient statistic for sets with 4–6 points. All problematic examples were better disregarded. (iii) If data for more than two reagents (or more than two temperatures) were available, only two were chosen, usually the fastest and the slowest. The data sets with at least four reagents were treated separately according to eqn. (6) (strong RSP). (iv) In the case of two reagents attention was paid to the reaction mechanism which should be closely similar, at least in the statement of the original authors. In any case rate constants of the same order must be compared. (These conditions are considered as fulfilled in all the cases of the model D.)

The examples for the model A were partly those mentioned already in the literature,[1,4] mostly they were found by a more

Table 1 Results of a statistical evaluation of RSP

	Model A (two reagents)		Model D (two temperatures)
	eqns. (3) and (4)	eqn. (6) (strong RSP)	eqns. (3) and (4)
All cases examined	100	14	100
RSP(+)	27	4	68
RSP(−)	36	7	5
RSP(?)	22	2	27
RSP(±)	15	1	0
All cases with $b < 1$	46	5	79
$b > 1$	54	9	21
Differences in reactivity, Δ	0.09–5.84	—	0.16–2.40
Mean value of Δ	1.33	—	0.73
Differences in temperature $\Delta T/K$	—	—	9–200
Mean value of $\Delta T/K$	—	—	26
Number of substrates, N	4–16	15–56[a]	4–57
Mean value of N	6.1	28.4	9.8
Number of deleted points (mean)	0.2	0.5	0.5

[a] Number of all experimental rate constants.

or less random search in recent journals. Particular attention was given to the *Journal of the Chemical Society, Perkin Transactions 2* and *Inorganic Chemistry*, but the examples from inorganic chemistry are much less numerous than from organic chemistry. Care was paid not to repeat the same or very similar reactions, but some types of reactions were always more studied than the others. Our set certainly cannot be considered as a random sample of all the reactions but it is reasonably representative for the reactions which have been kinetically studied. Some properties of the statistical sample are given in Table 1, all the reactions and references are listed in supplementary Table I.*

In the search for the model D we used our previous collection of examples of the isokinetic relationship[9] and took those which concerned kinetics, where the structure of the substrate was the variable factor, and where at least four substrates could be found investigated at two temperatures. The two temperatures chosen were as different as possible. (In some examples the temperatures were so diverse for individual substrates that it was not possible to find the four required points.) When the linear dependence, eqn. (3), was not sufficiently precise, the example was disregarded. According to all the criteria there remained 47 examples of the original 100. They were complemented by 53 additional examples chosen arbitrarily from the recent literature. Some properties of the statistical sample are given in Table 1, the individual reactions are not listed.

Results

With the original definition, model A (two reagents with the same set of substrates), all the four anticipated types of behaviour were found: valid RSP (Fig. 1), the opposite of RSP (Fig. 2), indifferent behaviour (Fig. 3), and crossing (Fig. 4). The number of individual cases cannot be given exactly unless we decide which values of the slope b are statistically different from unity (distinguishing Fig. 3 from Figs. 1 or 2) and what extension of the structural variation of the substrate is still possible (distinguishing Fig. 4 from Figs. 1 and 2). Since efficient tests are not possible on the small number of data, we used quite arbitrary standards: the values of the slope b between 0.95 and 1.05 were taken as effectively unity, a crossing was considered as possible when it would require a 50% extension of the scale of substrates. With these standards we obtained the values listed in Table 1, first column. More objective may be the task of distinguishing only two classes: $b < 1$ compatible with RSP; $b > 1$ incompatible with RSP. The cases of crossing, or of b near to unity are not separated in this case, but it is assumed that they occur with the same probability in the two classes. The results in Table 1 confirm the previous ones: RSP is valid or invalid with the same probability. The best survey is obtained from the graphical representation when b is plotted *vs.* Δ (Fig. 6). Not only are the same number of points situated below and above the line $b = 1$, but there is no trace of any functional dependence. If RSP were valid, at least as a limiting law in extreme cases, there should be a trend with a negative slope (numerous small values of b for greater values of Δ). We believe that we can also reject the hypothesis that RSP is valid in most cases, say for simple reactions, and that it can fail in some exceptions, say for more complex mechanisms: the number of examples (100) should be sufficient to reveal the rule and separate it from the 'exceptions'. We tried also to test whether RSP is possibly valid only as a limiting rule for slow (or fast) reactions. When the values of b were plotted (not shown) *vs.* the mean values of $\log k$, covering 15 orders of magnitude, no sign of a functional dependence was detected.

The above results can be confirmed on a smaller subset of strong RSP (Fig. 5). There are only 14 examples but the statistical weight of one of them is much higher, see the number of substrates (Table 1). Similar criteria as in the first set were applied. The number of indifferent cases, RSP(?), was somewhat reduced since a decision was possible even when the differences in slopes were small but systematic. As a result only two indifferent cases were observed (they would correspond to parallel lines in Fig. 5) and only one case was classified as crossing, RSP(±), that of Fig. 5(*b*). In several cases the strong RSP is fulfilled with a surprising accuracy, which means that the straight lines actually intersect at one point (Fig. 5). The reason may be that all the examples are restricted to compounds of the Hammett type. As mentioned, this fact devalues the results obtained with strong RSP.

With the model D (one reagent at two temperatures) we used the same procedure as for model A, although usually data were available at more than two temperatures and more sophisticated statistics[7] could be applied. This statistic was referred to only for a decision as to whether the slope b is statistically significantly different from unity. (If $b = 1$ the reaction enthalpy

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* Supplementary material available. Table of reactions used for statistical testing the RSP with basic statistics (7 pages) and the pertinent references (5 pages) may be obtained from British Library Document Supply Centre, Boston Spa, Wetherby, West Yorkshire, UK, LS23 7BQ. Supp. Pub. No. 56935 (12 pages), see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 2*, 1993, issue 1.

Table 2 Reaction series showing a reversed RSP behaviour when followed kinetically at two temperatures with a common reagent

	Graphical treatment, eqn. (3)				Statistical treatment, ref. 9			
Reaction	T_1, T_2/ K	N^a	b	Δ	N^b	β^c/ K	s_o (s_{00})^d (log u)	ψ^e
Recombination of aryldiantipyryl cations with OH^- [g]	293 308	4	1.27	0.38	39	220	0.014 (0.014)	0.056
Recombination of aryldiantipyryl cations with CN^- [h]	284.5 313	6	1.32	0.72	30	220	0.013 (0.013)	0.046
Esterification of substituted benzoate anions with 4-nitrobenzyl bromide [i]	308 318	10 (2)	1.16	0.36	36	269 [f]	0.013 [f] (0.016)	0.14
Decarbonylation of 4-aroyltetrahydrofuran-2,3-diones [j]	503 528	4 (1)	1.41	0.53	15	432	0.032 (0.026)	0.21
Oxidation of substituted fluorenes with Ce^{IV} nitrate [k]	323 338	6	1.40	0.66	18	292	0.080 (0.071)	0.13

[a] Number of reactions investigated at the temperatures T_1 and T_2. [b] Number of all reactions investigated at all temperatures. [c] Isokinetic temperature: a reversed RSP with $b > 1$ corresponds to β lower than the experimental temperatures. [d] Standard deviations from the Arrhenius lines: s_o with a common point of intersection (as in Fig. 5), s_{oo} unconstrained, the hypothesis of a common point of intersection is accepted if s_o is not much greater than s_{oo}, ref. 7. [e] Characteristic of the fit related to the differences of reactivity between the reactions of the series: for a good empirical relationship ψ is usually less than 0.1. [f] The hypothesis of an isoenthalpic series ($\beta = \infty$) cannot be rejected with certainty. [g] V. V. Sinev, O. F. Ginzburg and E. I. Kvyat, *Zh. Obshch. Khim.*, 1968, **38**, 112. [h] T. A. Nikolova and V. V. Sinev, *Org. React.* (*Tartu*), 1982, **19**, 36. [i] C. Gnanasekaran, J. Chandrasekharan and N. Rajasekaran, *Ind. J. Chem. Sect. B*, 1982, **21**, 426. [j] Yu. S. Andrejchikov, L. I. Varkentin and A. P. Kozlov, *Zh. Org. Khim.*, 1980, **16**, 785. [k] S. Narasimhan and N. Venkatasubramanian, *Ind. J. Chem. Sect. A*, 1976, **16**, 349.

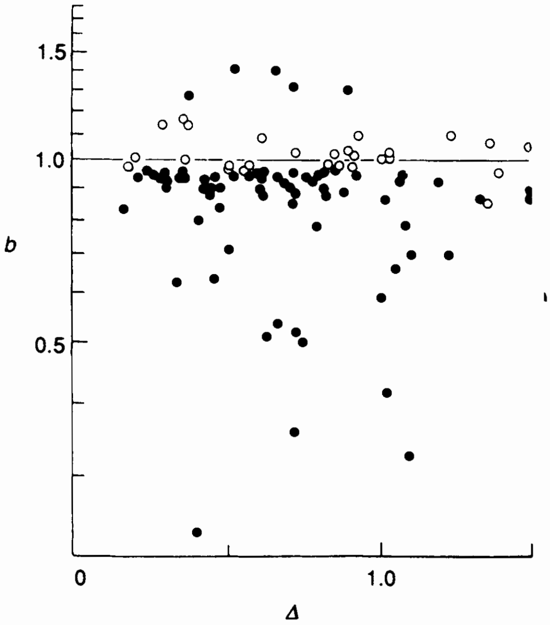

Fig. 7 A statistical test of RSP when temperature is the only variable factor (the same reagent at two temperatures): the slope b of eqn. (3) plotted *vs.* Δ according to eqn. (5); ○ series in which the hypothesis b = 1 cannot be rejected on the basis of broader experimental data, ● the other series

is constant for all the substrates and the series is classified as isoenthalpic.[7]) This means b was determined by a simple plot at two temperatures (as in Figs. 1–4) but its possible equality or non-equality to unity was decided according to statistical tests[7] based on the whole picture (as in Fig. 5). In this way the procedure is more cautious and a greater number of indifferent cases, RSP(?), can be obtained. The results shown in Table 1 are quite different from the model A: RSP is generally valid and only five actual exceptions were found. These are listed in Table 2 together with some statistical characteristics, but no common feature can be discovered. The fundamental difference between the two models is evident from a comparison of Fig. 6 and Fig. 7. One can understand that two reactions differing only in temperature are much more similar to each other than two reactions with two different (even 'similar') reagents. The validity of RSP at variable temperatures is also in accord with the common feeling: reactions at low temperatures are believed to be more selective.

Discussion

Theoretical Corollaries.—Most of the theoretical treatments of RSP have started from the assumption that it is valid, *i.e.* at least generally, or in typical cases. They then explained the validity in terms of various theories.[2–4] When RSP does not hold generally, it would be more justified to predict in which reactions it holds and in which the reverse is true. Here we shall only comment on the classical theoretical treatment of Leffler and Grunwald,[3] based on the Hammond postulate[19] and on the reasoning of the correlation analysis. As in most treatments of this subject,[3,4g,6b] let us consider first a reaction with a single maximum on the reaction coordinate and with the equilibrium shifted towards products ($\Delta G^\circ < 0$). In the reaction with a faster reagent ($\Delta G^{\ddagger}_{F} < \Delta G^{\ddagger}_{S}$) the equilibrium may also be displaced. Most probably it is displaced towards the products ($\Delta G^\circ_F < \Delta G^\circ_S$) in accordance with the Polanyi principle,[3,20] some exceptions are possible for particular reactions.[4g] It is not decisive whether the energy difference in the product state ($\Delta G^\circ_F - \Delta G^\circ_S$) is greater than in the transition state, as assumed by Leffler and Grunwald[3] and by Clementi and Marino,[6b] and as shown in Fig. 8, or whether it is equal as assumed by Argile and Ruasse,[4g] or whether it is still smaller (it can even be zero if the two reagents yield the same product). In all these cases the fast reaction should have an earlier TS, eqn. (12) in accordance

$$\alpha_F < \alpha_S \tag{12}$$

with the Hammond postulate,[19] or more exactly with its 'corollary'[21] (or extension). Now, when similar substrates undergo the reaction, it is assumed that the position of the TS is practically unchanged,[3,4g] in agreement with our definition that the differences between substrates (denoted here through the operator δ) should exert smaller effects on the reaction rates than the changes in the reagent (denoted by the subscripts F and S). The selectivity is defined by the change of the activation Gibbs energy ($\delta\Delta G^{\ddagger}$) which is related to the reaction Gibbs energy, $\delta\Delta G^\circ$, by the empirical Leffler postulate,[3] eqn. (13).

$$\delta\Delta G^{\ddagger} = \alpha\delta\Delta G^\circ \tag{13}$$

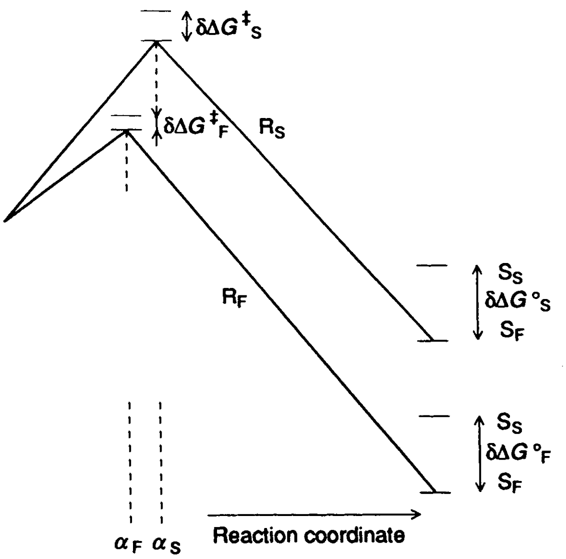

Fig. 8 Energy plot for a typical reaction obeying Polanyi principle, Hammond postulate and RSP: reactions with two reagents are denoted F (fast) and S (slow), reactions with various substrates are shown by parallel lines and denoted by the operator δ

Leffler and Grunwald[3] assumed that $\delta\Delta G^{\circ}$ are approximately equal for the two reagents, or better that $\delta\Delta G^{\circ}_{F}$ is not larger, eqn. (14). Then the earlier TS is decisive and RSP holds, eqn. (15).

$$\delta\Delta G^{\circ}_{F} \leqslant \delta\Delta G^{\circ}_{S} \tag{14}$$

$$\delta\Delta G^{\ddagger}_{F} < \delta\Delta G^{\ddagger}_{S} \tag{15}$$

The three premises, eqns. (12)–(14), thus yield a conclusion, eqn. (15), which has been empirically disproved. Hence at least one of the premises must also be wrong. Eqn. (14) is somewhat less important than the others: $\delta\Delta G^{\circ}_{F}$ may even be a little larger than $\delta\Delta G^{\circ}_{S}$ if α_F is sufficiently smaller than α_S. In our opinion the Leffler postulate, eqn. (13), is the most suspicious. It is evidently not valid for symmetrical and near-to-symmetrical reactions, but these do not occur often among the reactions investigated in connection with RSP. Eqn. (13) may also be valid less exactly when the TS and product state are less similar, i.e. for small α as in Fig. 8.

A different picture is obtained when a reaction is followed from the slow side (the equilibrium shifted towards the reactants). This can occur in practice when an unstable intermediate is formed in the rate-determining step. This case was analysed by Farcasiu[21] who stressed a possible case when the faster reaction has a later TS [eqn. (12) with reversed inequality]. This can occur when $\delta\Delta G^{\circ}_{F}$ and $\delta\Delta G^{\circ}_{S}$ are nearly equal (*e.g.* the same product for both reagents) and mainly the position of TS is shifted: then the RSP is violated. On the other hand eqn. (13) could be more accurately valid in this case, since TS and product state are more similar. It is thus difficult to assess whether RSP is violated more easily in simple reactions or in reactions with an intermediate. No statistical evidence was obtained. In our opinion it would be necessary to know better the reaction mechanisms: also the knowledge of both rates and equilibria for some reaction series would be advisable.

Conclusions

Although RSP was evidently disproved as a general rule, we do not consider the results of this study to be completely negative. Analysis of a series of examples revealed that even very similar reactions can behave differently with respect to the RSP criterion. Therefore, investigations of selectivity and its relation to reactivity should be continued and used possibly to characterize a certain type of reaction or a certain mechanism. Particular attention should be given to reactions with a well known mechanism.

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