

EVIDENCE IN FAVOUR OF EXNER ISOKINETIC METHOD TO DETERMINE ACTIVATION PARAMETERS

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Exner method to ascertain the isokinetic relationship (IKR) and obtain isokinetic activation parameters in a reaction series, although well known, is relatively little applied: A great many chemists do not appear to be convinced of the superiority of isokinetic activation parameters over conventional ones, and the IKR itself is still a controversial matter. From our kinetic results on the decarboxylation of a series of 4-substituted-2,6-dinitrobenzoate ions in aqueous solution, activation parameters were calculated, both by Exner method and by a conventional one. The obtained isokinetic activation enthalpies correlate much better ($r = 0.998$, 5 points) than the conventional ones ($r = 0.97$, 5 points), with the energies (calculated at the STO-3G *ab initio* level) for the formation of substituted aryl anions, the latter being a process expected to be energetically related to the decarboxylation reaction. This is the first example of non-statistical evidence in favour of Exner method to determine activation parameters, a method that we strongly advocate.

Mechanistic information obtained from the influence of temperature on the rate constant of a reaction in solution is usually discussed in terms of activation enthalpy ΔH^\ddagger and activation entropy ΔS^\ddagger . There are two conventional methods to estimate these activation parameters for a given reaction (regardless of whether it belongs to a reaction series or not): a direct method and an indirect one.

According to the direct method, it is assumed that the dependence of rate constant on temperature is given by the thermodynamic expression of the Eyring equation (Eq. (1)). The linear regression (preferably with appropriate weighting¹) of $\ln(k/T)$ over T^{-1} allows the calculation of both ΔH^\ddagger and ΔS^\ddagger , these two parameters being temperature-independent by hypothesis (or model),

$$k = (k_B T/h) \exp(\Delta S^\ddagger/R) \exp(-\Delta H^\ddagger/RT). \quad (1)$$

According to the indirect method, it is assumed that the dependence of k on T is given by the Arrhenius Law (Eq. (2)), E_a and A being temperature-independent. The Arrhenius parameters are estimated by linear regression, and then the Eyring parameters are calculated from the former according to Eqs (3) and (4). These two equa-

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tions show that both ΔH^\ddagger and ΔS^\ddagger are temperature-dependent; however, their variations with T are usually smaller than the experimental uncertainty and they are often neglected. Usually the choice between the direct and the indirect method is a matter of taste, because both results are not statistically distinguishable;

$$k = A \exp(-E_a/RT) \quad (2)$$

$$\Delta H^\ddagger = E_a - RT \quad (3)$$

$$\Delta S^\ddagger = R[\ln A - \ln(k_B T/h) - 1]. \quad (4)$$

On the other hand, there are also two non-conventional methods to determine activation parameters which apply in special circumstances. The first method is used for one reaction and a single kinetic run during which the reaction temperature is continuously increased^{2,3}. The second one (Exner method) applies to a reaction series, *i.e.* to a set of closely related reactions (typically, with a change of substituent or solvent). This paper illustrates that, for the frequent situation in which the isokinetic relationship holds, the application of Exner method to a reaction series as a whole gives better (more accurate) activation parameters than the application of any conventional method separately to each reaction of the series.

Exner has developed a statistical method to ascertain if the isokinetic relationship (IKR) holds for a given reaction series⁴⁻⁷. As side-products of this analysis, the values of the isokinetic temperature (β) and the isokinetic activation parameters ($\Delta H_{\text{iso}}^\ddagger$ and $\Delta S_{\text{iso}}^\ddagger$) are also obtained. In Exner method it is assumed that every reaction of the series follows the Arrhenius law; then, the IKR is taken as hypothesis to be tested; *i.e.*, it is assumed that all the Arrhenius plots have a common point of intersection corresponding to β^{-1} , and this point is calculated by a least squares method. The hypothesis of the IKR is to be accepted if the standard deviation (s_{00}) of the free regression lines is larger than the standard deviation (s_0) of the constrained regression lines. If s_{00} is smaller than s_0 , a quantitative statistical test can be used to estimate the significance level of the IKR^{7,8}.

Many controversies and misunderstandings have arisen in the past in connection with the IKR, and there are still many chemists who consider this relationship as being accidental⁹. What can be said beyond any doubt is that the classical isokinetic plots (*i.e.* ΔH^\ddagger) are unsuitable to ascertain the IKR^{10,11}. In fact, the use of these plots has become a typical example of misuse of correlation analysis¹². Undoubtedly, when the purpose is to ascertain the IKR in a reaction series, Exner method should be applied. Examples of such applications have appeared in the literature: Exner himself analyzed 100 reaction series, finding 78 cases in which the IKR was valid and 14 in which it remained undecided¹³; Schmid and Sapunov found some other examples of IKR in their own work^{14,15}.

If, according to Exner method, the IKR appears as statistically significant and it is adopted as being true, the use of the isokinetic activation parameters is statistically logical, for any discussion of the dependence of k parameters are expected to be better than the unconstrained ones for statistical reasons. In practice, however, although Exner method is reasonably well known*, it has been little applied: it seems that many chemists, interested mainly in the values of activation parameters themselves, prefer to use a conventional method, without considering the hypothesis of the IKR. An important reason for the relatively low use of Exner method could be that a great many chemists are not convinced of the superiority of isokinetic activation parameters over unconstrained ones. This lack of conviction is understandable because, to our knowledge, no examples have been published in which isokinetic parameters appear as a better description of the dependence of k on T , except for the fact that (by model) they strictly follow the IKR. As both types of activation parameters are calculated from the same kinetic data, in order to establish meaningful comparisons between them, they should be correlated separately with a third quantity which is independent of those kinetic data. We describe below the first example of such a comparison.

RESULTS AND DISCUSSION

In the course of our research on substituent effects in aryl anion intermediates, we have determined the kinetics of decarboxylation (in aqueous solution, at several temperatures) of a series of 4-substituted-2,6-dinitrobenzoic acids, the substituents being H, Cl, Br, I, NO_2 and OCH_3 (ref.¹⁶). The reactions were first order at the low concentration employed (*c.a.* $10^{-4} \text{ mol l}^{-1}$) at which the acids are fully dissociated. The rate constants were determined at four different temperatures, with duplicate runs at the two extremes of the temperature range, obtaining very significant Eyring and Arrhenius plots. From the Eyring plots (we verified that the results were virtually the same from the Arrhenius plots), by weighted least squares regressions¹ which in all cases had correlation coefficients greater than 0.9997 (6 points), the unconstrained activation parameters, ΔH^\ddagger and ΔS^\ddagger , were calculated. Their values and standard errors are shown in the Table I. An Exner analysis of the type called "special case"⁴ (all reactions followed at corresponding temperatures) was carried out with the $\log k$ values shown in the Table I, processing the data with a programmable calculator, according to described guidelines⁷; the isokinetic activation parameters, $\Delta H_{\text{iso}}^\ddagger$ and $\Delta S_{\text{iso}}^\ddagger$ shown in the Table I, were obtained. The values of s_{00} and s_0 were 0.0104 and 0.0109 respectively (F value of 1.10), which means that the isokinetic hypothesis cannot be rejected. As s_{00} is not significantly larger than 0.0102 (the average standard

* According to the on-line version of Science Citation Index, the review article of ref.⁷ has been cited more than 90 times; even the method has been included in a recent textbook (ref.¹⁴).

TABLE I

Unconstrained and isokinetic activation parameters, and kinetic data used in the calculation of the later (values with asterisk are extrapolated). ΔE Calculated energies for the transformation of YC_6H_5 into $p-YC_6H_4$ ($^-$) (ref. 17)

Y	Unconstrained ^a				Isokinetic ^d				ΔE^b a.u.
	ΔH^\ddagger kcal mol ⁻¹	ΔS^\ddagger cal K ⁻¹ mol ⁻¹	$T^{-1}/10^{-3}$ K ⁻¹	$-\log(k/s^{-1})$	ΔH^\ddagger_{iso} kcal mol ⁻¹	ΔS^\ddagger_{iso} cal K ⁻¹ mol ⁻¹	ΔS^\ddagger		
H	41.03 ± 0.28	25.35 ± 0.75	2.68	2.60	2.54	2.46	2.46	26.80	0.8242
Cl	39.64 ± 0.10	26.47 ± 0.27	4.5413	3.8464	3.3025	2.5991	39.16	25.29	0.8044
Br	39.45 ± 0.36	26.02 ± 0.96	4.5225	3.8433	3.3005	2.6101	39.15	25.29	0.8044 ^c
I	38.81 ± 0.41	23.95 ± 1.06	4.6175	3.9052	3.3797	2.7103	39.35	25.41	—
NO ₂	35.62 ± 0.47	22.51 ± 1.27	3.0698	2.4098	1.941*	1.303*	35.86	23.18	0.7825
OCH ₃	42.17 ± 0.50	27.43 ± 1.21	5.812*	5.062*	4.4985	3.7474	42.02	27.13	0.8264

^a 1 cal = 10⁻³ kcal = 4.1868 J; ^b 1 a.u. = 2625.46 kJ mol⁻¹; ^c value assumed equal to the one Cl (see text).

error of $\log k$) the applicability of the Arrhenius equation is *a posteriori* statistically legitimated.

Figure 1 is the classical isokinetic plot corresponding to the unconstrained activation parameters (full circles). The poor correlation observed ($r = 0.89$; 6 points; regression line not drawn) illustrates that this plot is unsuitable to ascertain the IKR. As the errors in ΔH^\ddagger and ΔS^\ddagger are mutually dependent, the standard error intervals have been represented with a slope of $T = 400$ K, a central value of the experimental temperature range (similar error intervals can be found in refs⁴⁻⁷). It is evident in Fig. 1 that the apparent straight line connecting the points for Cl, Br and I is purely a consequence of experimental error, the values for Cl and Br being virtually coincident.

The isokinetic activation parameters (open circles) are also shown in Fig. 1; they fall strictly on the straight line corresponding to the isokinetic temperature ($\beta = 1560$ K; dashed line), a consequence of the way they have been calculated.

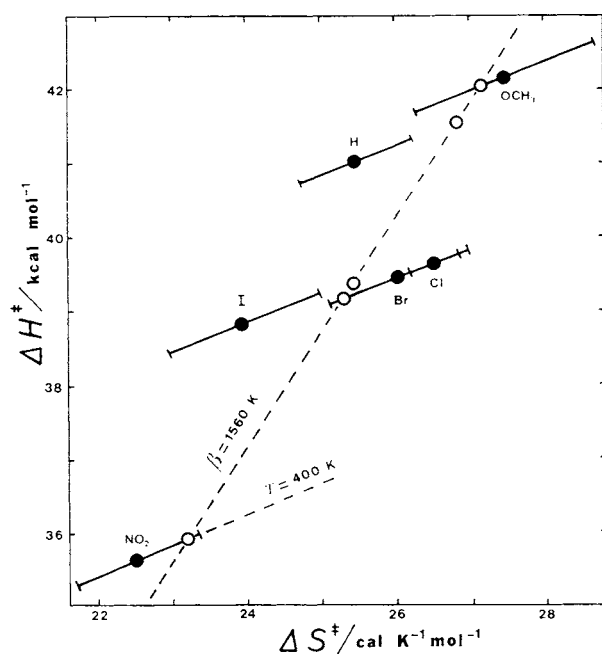
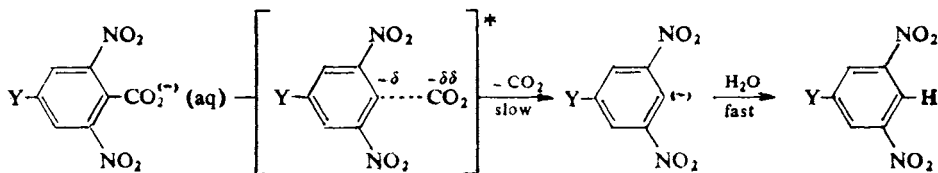


FIG. 1

Isokinetic plot corresponding to unconstrained activation parameters (full circles; regression line not drawn), showing also the isokinetic parameters (open circles) (1 cal = 4.1868 J)



SCHEME 1

Postulated mechanism for the decarboxylation of 4-substituted-2,6-dinitrobenzoates in aqueous solution

All the available data for this decarboxylation reaction support a mechanism (Scheme 1) wherein the substituted benzoate ion loses CO_2 in a rate-determining step, forming a substituted aryl anion which is then rapidly protonated by the solvent¹⁶. The high values of ΔH^\ddagger indicate, according to Hammond postulate, that the transition state of the rate-determining step should be very close to the aryl anion. The positive and very high values of ΔS^\ddagger suggest that much of the strong solvation of the carboxylate group has been lost in the transition state¹⁶.

In search for an independent quantity of correlate with both types of activation parameters, we found that, although aryl anions intermediates had been postulated for few other reactions, no reaction series with a complete set of activation parameters had been published. Fortunately, the energetics of the aryl anion formation was studied theoretically: Eaborn and collaborators¹⁷ calculated the deprotonation energies of *para*-substituted benzenes, *i.e.*, the energy balance ΔE (in atomic units) of the process $\text{YC}_6\text{H}_5 \rightarrow p\text{-YC}_6\text{H}_4^{(-)} + \text{H}^+$, obtaining the values shown in the last column of the Table I. At the level of theory used in the MO calculations (*ab initio*, STO-3G), the energy values for $\text{Y} = \text{Br}$ and $\text{Y} = \text{I}$ are not available; but, considering that the substituent effects of *p*-Br and *p*-Cl are very similar*, the assumption $\Delta E(\text{Br}) \cong \Delta E(\text{Cl})$ seems reasonable.

In Fig. 2 both $\Delta H_{\text{iso}}^\ddagger$ and ΔH^\ddagger have been plotted against ΔE . It is observed in the Fig. 2 that $\Delta H_{\text{iso}}^\ddagger$ correlates much better ($r = 0.998$; 5 points) than ΔH^\ddagger ($r = 0.97$; 5 points; line not drawn). Using a Leffler-Grunwald operator δ for the change of substituent, the correlation of Figure 2 can be expressed as $\delta(\Delta H_{\text{iso}}^\ddagger) = \text{constant} \cdot \delta(\Delta E)$, and it indicates the existence of a fundamental similitude between the energetics of the decarboxylation reaction and that of the ionization of substituted benzenes (theoretical, hence in absence of solvent). This similitude is understandable considering that on the decarboxylation reaction: *a*) the effect of the two *ortho*-nitro groups (necessary to make the reaction feasible) should be virtually constant along the reaction series; *b*) the difference in solvation between initial and transition states should

* In Charton's recent and very complete compilation¹⁸, the substituent parameters σ , σ^0 , σ_{R} and σ_{I} for *p*-Br and *p*-Cl are the same.

also be virtually constant (only the solvation of the carboxylate group is strongly modified), therefore the substituent effect in solution should parallel the substituent effect in the gas phase; and *c*) the extrapolation of energy to 0 K and the zero-point energy should not change very much along the series (the substituent is little modified in the rate determining step), hence the energetics of the process should be well reproduced by calculation. Besides, it has been known for a long time that MO calculation at STO-3G level reproduce successfully relative values of experimental heats of reactions¹⁹⁻²¹.

CONCLUSION

In summary, we think that Fig. 2 strongly suggest that the $\Delta H_{\text{iso}}^\ddagger$ values of the Table I are more accurate than the corresponding ΔH^\ddagger values; *i.e.*, that in this reaction

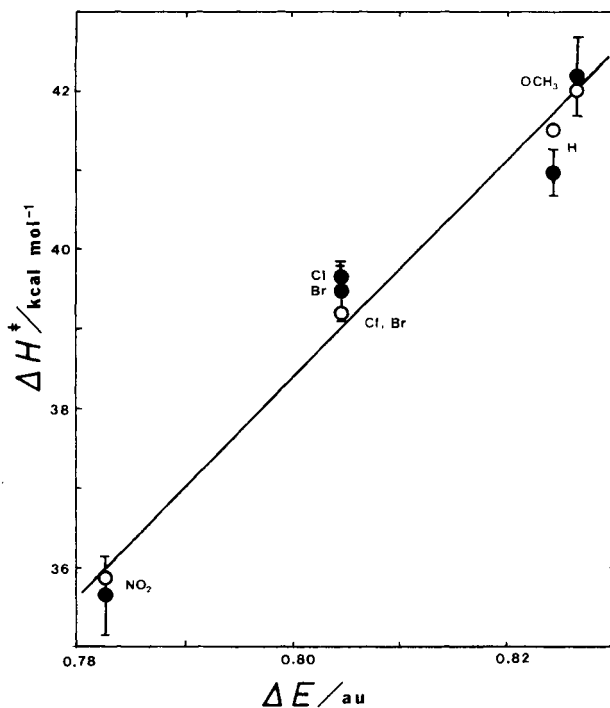


FIG. 2

Comparison between the correlations of unconstrained activation enthalpies (full circles; regression line not drawn) and isokinetic activation enthalpies (open circles), with the calculated energies for the conversion of YC_6H_5 into $p\text{-YC}_6\text{H}_4^{(-)}$ (1 a.u. = 2625.46 kJ mol⁻¹, 1 cal = 4.1868 J)

Exner method is more suitable than any of the two conventional ones. To our knowledge, this is the first example of non-statistical evidence in favour of Exner method to determine activation parameters in a reaction series. Given the general usefulness of this method, we think it should be strongly recommended and introduced in textbooks of Physical Organic Chemistry, as it is being done¹⁴. Obviously, if it happens that a given reaction series does not follow the IKR relationship (as we have found out, for instance, in the decarboxylation of 2-substituted-4,6-dinitrobenzoic acids in analogous conditions¹⁶), Exner method cannot be applied to calculate the corresponding activation parameters.

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