An Anti-traditional Interpretation of the LFER Mechanistic Message*

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In the core of the linear free energy relationship paradigm, lies the ‘boundedness’ assumption. That is, the nature of the transition state is intermediate between that of the reactants and products. An outcome of this assumption is that the fraction of the effect of a perturbation on the kinetics relative to its effect on the equilibrium of the reaction corresponds to the fraction by which the transition state has progressed along the reaction coordinate. Using computational results for the homolysis of MeX and applying the curve-crossing model to the Michael addition reaction it is shown that the ‘boundedness’ assumption may, in certain cases, be both quantitatively as well as qualitatively wrong.

Unlike other stationary points along a reaction profile, the transition state (TS) structure cannot usually be directly determined (we refer to information gathered from X-ray analysis etc. as a direct determination). Nevertheless, because it governs the kinetics of chemical reactions, deciphering its structure has been a focal point in physical organic chemistry from its early beginning. The major probe for TS structure determination is linear free energy relationships (LFERs) in their various forms. The basic assumption employed is that the TS has a structure intermediate between that of the reactants and products. A related assumption is that essential features, such as partial charges, etc. vary gradually between reactants and products and hence are limited to the region bounded by these species. The ratio of the kinetic to the thermodynamic effects of a given perturbation (e.g. substituent variation) corresponds, therefore, to the position of the TS along the reaction coordinate. We will refer to this as the ‘boundedness assumption’.

Already by the first half of the century, the LFER method was well established. However, with time, anomalies and inconsistencies started to appear. These were usually glossed over by modifications of the model or simply ignored. As is common in the natural evolution of paradigms, when the number of flaws becomes too large, the need for a new theory emerges. However, ‘the decision to reject one paradigm is always simultaneously the decision to accept another’.

In this review article, it is not our intention to present a well rounded new substitute for the LFER theory. Rather we intend to pinpoint a weak link in the LFER paradigm which is a source for some of the failure of this theory and to suggest a lead for an alternative approach.

A major weakness in this field is, of course, our inability to determine directly the TS structure and therefore to confirm the LFER inferred structure by virtue of comparison.

It is clear that ab initio calculations could very well be a reasonable substitute for LFER in determining TS structure. Although both methods suffer from the same limitation, namely, the inability to check inferred results against a directly determined structure of TS, this method has the advantage of being capable of calculating other features which are TS related. Thus a successful prediction of kinetic isotope effects, energy of activation, etc. lends credibility to the computed TS structure even in the absence of a direct way of confirming this structure. However, at present, and in light of the difficulty of incorporating solvation effects into the calculations, this method will have to await further development of theory and hardware before being conveniently put to use.

We believe that within the LFER paradigm the boundedness assumption may, in certain cases, prove to be correct. But under no circumstances can it be taken for granted. The following two examples demonstrate this point.

In the first example we use computational results for the homolysis of MeX [X being more electronegative than Me, e.g. OH, N₃, F, etc. eqn. (1)] to show that variations in atomic (or group) charges are not bound to the region defined by the reactants and the products. The calculations show the following:

\[ \delta^+ \delta^- \]

\[ \text{Me–X} \rightarrow \text{Me}^+ + \text{X}^- \]  \hspace{1cm} (1)
culations were performed using the ab initio multi-configura-
tion self-consistent field (MCSCF) method.

Partial charges on X as well as on the methyl group were
calculated by several methods for different Me–X separa-
tions. It was found for a series of nine Xs that the partial
positive charges on the methyl group (and the comple-
mentary negative ones on X) first increase to a maximum
and only later on decrease to the neutrality of the products
(Fig. 1). The explanation to this seemingly unusual result it
rather simple. As shown in Fig. 2, using the valence bond
(VB) approach, the bond between the Me and X is con-
structed from the ionic and the covalent VB configurations.

The ionicity in the ground state is incurred by the mixing of
the ionic configuration into the covalent one. The degree
of mixing is inversely proportional to the energy gap between
the two configurations. As can be seen in Fig. 2 the energy
gap is much smaller at Me–X distances longer than that of
the equilibrium geometry. Therefore, as the Me–X bond is
stretched, the ionic configuration mixes to a greater extent
into the covalent one inducing polarization of the ground
state. At even larger distances, owing to the gradual de-
crease in the overlap, configuration mixing is decreased
and hence also the partial charges which are eventually
nullified.

Fig. 1. A schematic diagram for the variation of charge on the
methyl group of MeX as a function of the Me–X distance in a
homolytic dissociation.

Fig. 2. Ionic and covalent VB configurations for MeX.

The impact of these results on the boundedness assump-
tion is rather obvious. The traditional expectation is that
the partial charges will vary along a line such as the dashed
line in Fig. 1. Nevertheless, the actual charges strongly
deviate from the limits of the bounded region. Thus, in a
case of a similar reaction, having a TS in which a substi-
tuent or solvent effect based LFER is used to monitor
the TS location, almost any conclusion reached in the tradi-
tional way will be erroneous.

The second example is the Michael addition reaction
[MAR, eqn. (2)]. Using this reaction we will try to illumi-
nate the same issue from a different angle. In order to
analyze the electronic structure of the MAR TS let us first
describe the construction of a reaction profile for the solvo-
ysis of R–X [eqn. (3)] by the potential surface crossing
technique. This method was introduced by Bell, Evans
and Polanyi more than fifty years ago. With certain variations
it was used by other investigators such as Marcus, Wood-
ward and Hoffmann, Warshel etc. Here we will use the
Shaiik and Pross generalized curve-crossing model which
incorporates both the insight of local orbital symmetry as
well as VB structures. It is based on the crossing of the
potential surfaces emanating from the reactants and the
products. These potential surfaces could correspond either
to states or to VB configurations. The TS is achieved at the
avoided crossing region of the two curves. Owing to reso-
nance between the two structures the TS will be located
below the formal crossing point of the two curves.

R–X ⇌ R⁺ + X⁻

Fig. 3 depicts the potential energy curves for the covalent
and the ionic states of R–X in the gas phase. According to
this schematic diagram, heating R–X will lead to its homolytic dissociation. In solution, however, the major change will be a drastic lowering of the right-hand side of the ionic curve due to solvation. As a result, the two curves will cross. R–X will dissociate into ions by a motion first along the covalent surface and then by crossing over to the ionic one. A motion in the opposite direction, that is from right to left, corresponds to a nucleophilic attack on R⁺.

The two lower curves in Fig. 3 differ in a one-electron transfer (electron shift) from X to R. Since the reactants in a nucleophilic reaction are on the ionic surface and the products are on the covalent one, it is clear that an electron transfer from the nucleophile to R⁺ has occurred in the course of the reaction. As was pointed out by Shaik and Fross, for the simple case of two configuration interaction, Half an electron has been transferred as the system has reached the TS.¹³ This seemingly surprising conclusion is based on simple quantum mechanical considerations. At the crossing point, the two structures are of the same energy. Therefore they contribute equally to the overall electronic configuration of the TS. Since the reactants are 100% ionic and at the TS the ionicity is reduced to only 50%, the conclusion regarding the half electron transfer seems to be unavoidable. On the other hand, the traditional assumption that as the nucleophile gets closer to the substrate it transfers more of its charge, to the best of our knowledge, has no theoretical support whatsoever. One can easily see however, the intuitive justification for the this assumption. As the nucleophile approaches the substrate, the energy gap between the ionic and the covalent configuration decreases and the overlap increases. According to the previous discussion, this will result in an enhanced mixing of the two configurations. That is, as the nucleophile approaches the substrate toward the TS it transfers more of its charge to the substrate. However, at the TS itself, because of the energy equality of the crossing curves, as mentioned above, only half an electron is transferred.

It should be stressed that the half-electron transfer concept is an approximation of the real situation. In reality, this can be somewhat changed owing to a skewing effect or the intervention of other configurations. In addition it should be pointed out that going from the TS to the products does not involve the transfer of the other half of the electron since, in the final covalent state, R–X is polarized and X retains some of its original charge. Thus, for the reaction in the reverse direction – the solvolysis of R–X – the amount of charge shifted from R to X upon to the TS, is likely to be significantly smaller than half and will depend on the polarizability of R–X in its ground state.

In Fig. 4 the construction of the reaction profile for MAR from the relevant potential curves is demonstrated.¹⁴ Going from left to right, first along curve I and then crossing to II corresponds to a normal β-elimination process. Continuation of the motion along curve I without crossing over corresponds to an unusual β-elimination reaction in which the lone pair of the internal nucleophile expels the leaving group as a radical and not as an anion. It is worthwhile pointing out that this seemingly imaginary process may, under suitable conditions, correspond to ‘real chemistry’. This may occur when the relative energy of the two states is equalized or reversed. An example of this effect may be found in Cram’s work aimed at generating carbocations in a β-eliminating process [eqn. (4)].¹⁵ In this case the neighboring oxygen atom is responsible for both; the destabilization of the carbocation by virtue of pair–pair repulsion and the stabilization of the spin density in the radicaloid species by virtue of the three-electron two-orbital interaction.¹⁶ In addition, the radical anions of diaryl ketones are highly stable. Therefore, the energy gap between the two states is diminished to the extent that it enables this unusual reaction to occur side by side with the normal β-elimination process.

A leftward motion corresponds to MAR. Again, the difference between the two structures on the right-hand side of the diagram is in a single electron transfer. Using the two configuration approximation, as the TS has been reached, the nucleophile has transferred half an electron to the substrate. The latter, being neutral at the beginning, has now acquired partial radical anionic character. This radical anionic character is manifested maximally in an early TS (when the two curves in Fig. 4 cross at a large nucleophile – substrate separation). In a late TS, the two radicaloid species, the substrate and the nucleophile, are
highly coupled to form a partial covalent bond. Thus, going down along the Morse curve involves a trade off between the radical–radical anionic character of the system and a more covalent–paired state.

The crucial point in this analysis is that it clearly shows the radical anionic nature of the substrate at the TS\(\text{14}\) (if this is not achieved extremely late). Thus, while the previous example demonstrated that the reaction path may quantitatively exceed the boundaries set by the reactants and products for a given feature i.e., partial charges, this example demonstrates that the TS may have unique electronic features (e.g. radical anionic in the present case) which cannot be found either in the reactants or in the products. Thus, the boundedness assumption is violated both qualitatively and quantitatively. Since the magnitude of the substituent effect, for example, may depend not only on quantitative variations in charge but also on the electronic nature of the TS (i.e., the degree of pairing, as in the present case.) the assignment of TS location without considering these possibilities may be misleading. In other words, there is no reason to assume a priori that if the effect on the kinetics of the reaction is a fraction of that on the equilibrium, this fraction corresponds to the position of the TS along the reaction coordinate.

Finally, we address a more specific question: what is the information that can be retrieved from Hammett type studies regarding the TS structure in MAR? We will confine the analysis to substituents at the α-position [see eqn. (2)]. The case of substituent variation in the β-position is much less amenable to quantitative analysis.

An early TS (curve crossing occurs near the plateau of curve I in Fig. 4) will bear a large resemblance to the radical anion of the substrate with a small degree of bonding to the nucleophile. The charge transferred to the LUMO of the substrate (ca. half an electron: can be delocalized over the whole molecule including the substituents at the α-position thereby inducing a large ψ value. A late TS (curve crossing occurs near the bottom of curve I in Fig. 4) will resemble more the covalent adduct. In the latter case the same amount of charge resides largely on the β-carbon provoking a smaller response from the substituents at the α-position. Thus, in MAR with α-substituents a large ψ value is indicative of an early TS and vice versa.\(\text{14,18}\)

There are quite a few experimental results which are consistent with this outcome (examples are the relative magnitude of ψ in water and DMSO in the reaction of CN\(^-\) with 2-nitro-1,1-diyarylethylene;\(\text{14}\) the dependence of the \(^{13}\)C chemical shift – rate correlation on ψ;\(\text{18}\) the principle of non-synchronicity,\(\text{18}\) etc.). However, a detailed discussion is beyond the scope of this presentation.

In conclusion, the boundedness assumption does not seem to be of general applicability. It might be valid in cases where an additional, low-energy configuration(s), mix(es) into the two basic configurations. This may result in a gradual variation of the amount of charge transferred from the nucleophile to the substrate at the TS and may lead to a result which is in accordance with the traditional understanding. However, the participation of such a configuration(s) should be proved in each case before the traditional approach is employed. In other words, it may be essential to know the electronic distribution along the reaction coordinate of a general reaction before applying the LFER method for the determination of the TS structure of a specific series of reactions. Such a mapping of the potential surface or some relevant cross sections of which, will enable a more enlightened analysis of LFERs data. However, it is clear that if the analysis of each particular case necessitates a rigorous calibration or mapping of the potential surface by quantum mechanical calculations, LFERs will cease to be a probe and may be rendered at most a research objective by itself.

In a recent interview for Scientific American, the noted philosopher of science Thomas Kuhn quipped: ‘the proposer of a new paradigm stands on the shoulder of giants and then bashes them over the head.’\(\text{20}\) There is little doubt that the LFERs paradigm, whether right or wrong, has had a profound stimulatory effect on the field of reaction mechanism. However, the purpose of this lecture has not been to bash the LFERs model. Our primary intent is to create a Hegelian-type dialectic between classical physical organic chemistry and quantum mechanics in the hope of catalyzing a synthesis between the two disciplines.

References


Received October 25, 1991.