ABSTRACT

The interpretation of transition state theory via reaction energy profiles is problematical, as it remains unclear whether the energy being represented is the Gibbs energy or the potential energy. Although transition state theory is formally an extension of classical equilibrium theory, employing the Gibbs energy can lead to ambiguities in explaining reactivity trends and differences. Thus, the differential reactivity of the carbonyl group in carboxylic esters and carboxylic acid chlorides, when present in the same molecule, can only be explained by invoking transition state effects because of the common ground state. The said transition state effects, however, apparently need implausible assumptions.

It is argued herein that these ambiguities can be avoided by employing potential energy. In particular, by invoking the "localized" potential energy at a reactive center, ground state effects can be brought into play. This is likely to be largely vibrational potential energy, as this is closely involved in bond breaking and making. It appears, therefore, that transition state theory is best viewed in a qualitative sense for it to be practically meaningful.

These arguments, in fact, have intriguing implications for catalysis, particularly the theory of enzyme catalysis. Thus, enzymes apparently possess large negative Gibbs energies of formation, hence their reactivity cannot be explained by ground state effects. However, if the "localized" potential energy...
energy of the reactive groups in the active site is considered, the phenomenal reactivity of enzymes becomes comprehensible, in an alternative to the Pauling hypothesis of transition state stabilization. This generally implies that the action of catalysts needs to take into account the ground state potential energy of the catalyst, which is almost always ignored in current theoretical treatments.

Keywords: Catalysis; enzymes; gibbs energy; potential energy; proteins; transition state theory.

1. INTRODUCTION

The representation of chemical reactions in terms of energy profiles is based in transition state theory, and offers an at-a-glance correlation of reactivity and molecular structure. Key to this approach is the idea that reactivity can be related to an “activation energy”, particularly of the rate-determining step, a concept that dates back to the Arrhenius equation (1890) [1,2].

The experimentally-derived Arrhenius equation was the basis of transition state theory (1935), a brilliantly-conceived generalized treatment of chemical reactivity [3]. Transition state theory is itself based in classical equilibrium theory [4], and intriguingly relates rates to an equilibrium constant. Transition state theory proposes that reactions must occur via a key species called the transition state (TS, Fig. 1), which represents the highest energy point in the profile that reactant species must surmount to form the product ground state. Transition state theory thus relates the rate constant (k) of the reaction to the equilibrium constant (K) between the reactants and the transition state (Eq. 1 and Fig. 1). This ultimately leads to the Eyring equation (Eq. 2), a rigorous quantitative relationship that is a cornerstone of modern physical organic chemistry [1,2]. Despite its broad scope and approach, however, transition state theory apparently fails to provide convincing leads to certain intricate problems in chemical reactivity.

An intriguing problem in the qualitative application of transition state theory concerns the exact definition of the activation energy [3,6,7]. Whilst the Arrhenius law apparently led to the enthalpy of activation (the entropy part being...
subsumed in the “pre-exponential factor”), transition state theory has often been interpreted in terms of the Gibbs energy of activation. This is believed to be the difference between the Gibbs energy of the transition state and that of the reactants ground state. The resulting energy profiles, therefore, refer to the Gibbs energy changes occurring during the reaction.

The transition state itself is believed to occupy a “saddle point” in the energy profiles [3], implying a narrowly defined “col” (relative to the ground state) in a three-dimensional profile. The resulting surfaces, however, are often interpreted in terms of potential energy, as they apparently plot energy changes in a hypothetical single molecule (of each reactant). These ambiguities have led to a conundrum of sorts: although unresolved, it has apparently led to the view that Gibbs energy profiles refer to molecular ensembles, whereas potential energy surfaces represent a collection of individual trajectories.

Although the said conundrum is of little concern generally, the inherent ambiguities can become manifest in certain cases, so cannot be brushed aside. These can lead to critical insights, however, so are worth pursuing in exploring the limits of transition state theory, which remain a continuing concern [8-12]. In particular, transition state theory is apparently focused on the transition state, hence ground state effects are generally difficult to pin down.

In fact, an intriguing case concerns the exceptional reactivity of compounds that apparently possess enormous thermodynamic stability (e.g., enzymes). A simplistic interpretation of transition state theory is apparently ruled out in these cases, as ground state effects cannot be invoked. These clearly represent challenges to transition state theory, or at least its phenomenological interpretation. The discussion below is directed at defining the problem in the hope of finding a meaningful resolution, although within the framework of transition state theory itself.

2. DISCUSSION

2.1 Current Status of Transition State Theory

The formulation of transition state theory and its interpretation apparently represent an intriguing dichotomy. Thus, transition state theory was based on the classical concept of chemical equilibrium, with the equilibrium constant being ingeniously transformed into a rate constant. This was achieved by introducing the revolutionary idea that the transition state collapses to the products at every vibration of the bonds undergoing change, the putative vibrations becoming translations along the reaction coordinate. The rate of this collapse was set at a constant value of \( k_0T/\hbar \), with the burden of accounting for differential rates falling entirely on the equilibrium constant for the formation of the transition state from the reactants (Fig. 1, Eq. 1).

Therefore, these ideas essentially merge a macroscopic ensemble idea (equilibrium) with the intricate details of bonding changes in individual molecules. In fact, the idea of an equilibrium between the reactants and the transition state is itself questionable, as the subsequent collapse of the transition state is set at the rate of a bond vibration!

Despite this critique, however, transition state theory remains an invaluable part of chemical theory overall. At the very least, transition state theory offers a viable explanation for the Arrhenius equation, indeed transforming it into a more rigorous analog (Eq. 2). Transition state theory also offers an additional ground state effects for explaining reactivity (via transition state effects). In its intricate details, however, transition state theory apparently raises more questions than it answers!

Clearly, if transition state theory is to be a useful tool in a quintessentially experimental science, its meaningful interpretation—although without flouting accepted laws—becomes paramount. A qualitative approach to transition state theory is attempted below keeping in mind the above apparent lacunae in the exact theory, particularly as they bear upon contradictions in explaining experimental observations.

Indeed, the question about transition state theory is not so much “Is it valid?” as “What is its most useful formulation?”, a subtle but noteworthy difference!

2.2 Problematic Structure–Reactivity Trends

An intriguing case that possibly indicates the limits of transition state theory lies in the functional group selectivity that would obtain in \( \text{trans-4-ethoxycarbonylcyclohexanecarboxylic} \) acid chloride (1, Figs. 2 and 3). In this, the acid...
chloride group would be far more reactive towards nucleophiles than the ester group. However, ground state effects cannot be invoked to explain this selectivity, as the ground state is common to the two groups.

Transition state effects, however, lead to interesting contradictions. Thus, nucleophilic attack at the two carbonyl centers would occur via tetrahedral intermediates (Ia and Ib, for the ester and acid chloride respectively), with the rate determining step being different in the two cases. In the ester case, the collapse of Ia to product is likely to be rate determining, whereas in the acid chloride case, the formation of Ib is likely to be rate determining. (This is because chloride ion is a better leaving group than ethoxide ion, and the slow step would be rate determining.)

Furthermore, the greater reactivity of the acid chloride now implies that the transition state (TS₂) for the formation of Ib would be lower in energy than that (TS₁) for the collapse of Ia. However, this is apparently implausible as in TS₂ there is a partial positive charge (δ⁺) adjacent to a more electron-withdrawing group (Cl, relative to OEt in TS₁)! Despite the greater Pauling electronegativity of oxygen (3.5) relative to chlorine (3.0), the Hammett σ values indicate [2,4] that OEt (+0.015) is less electron-withdrawing than Cl (+0.373).

These comparisons, of course, are based on assumptions about the rate-determining transition state in the two cases. However, it is noteworthy that the proposed electronic effects would apply in general, as all the four possible transition states involved have rather similar charge distribution patterns. Therefore, it is difficult to avoid the conclusion that transition state theory leads to ambiguous results in certain cases.

This raises the question of how best to formulate transition state theory in order to deal with such ambiguities, bearing in mind the above critique that the original exact formulation of the theory is itself ambiguous (if not contradictory).

2.3 Towards an “Empirical Transition State Theory”

2.3.1 General considerations

The above brief discussion indicates that—in certain cases at least—conventional transition state theory leads to ambiguities, essentially derived from problems in involving the reactant ground state in a meaningful way. The problem is particularly manifest if the profiles are based on Gibbs energy changes, as then two reactive centers in a molecule would perforce possess a common ground state.

![Fig. 2. Nucleophilic reactivity of the ester-acid chloride 1 via tetrahedral intermediates Ia and Ib, and key transition states TS₁ and TS₂ respectively. Canonical forms IIa and IIb contribute to the ground state potential energy](image-url)
An interesting alternative approach would involve potential energy changes at the different reactive centers. In fact, transition state theory was originally based on trajectories obtained by plotting potential energy changes [3,6,7]. The leap to Gibbs energy profiles was apparently a tacit extension, noting that two-dimensional profiles must be potential energy plots. Attempts were indeed made to resolve this controversy, although the outcome is unclear.

However, if it may be assumed that potential energy changes may be employed in interpreting transition state theory, it paves the way for a fundamental reappraisal of the manner of depicting structure-reactivity trends in complex molecules. For, now, the localized potential energy at a reactive center—particularly derived from the vibrations of the bonds undergoing change—can be defined as the reactant ground state.

### 2.3.2 Particular cases

The case of the ester-acid chloride 1 may now be considered. Thus, the greater reactivity of the acid chloride functional center may reasonably be attributed to a higher potential energy content, by invoking the hyperconjugative canonical structure IIb. The greater force constant of the C-O triple bond in IIb (relative to a C-O double bond), in fact, would justify the assumption of a higher potential energy at the acid chloride center. The corresponding canonical form in the ester case (Ila) would be a minor contributor relative to IIb, as the chloride ion is a better nucleofuge than the ethoxide ion (vide supra, 2.2). (Also, vibrational energy is proportional to the square root of the bond force constant [4].)

Although the above arguments concern an electrophilic functional center (a carbonyl group), nucleophilic reactivity may be related to the energy of the HOMO (highest occupied molecular orbital), by invoking frontier orbital effects [2,13]. Thus, a more powerful (soft) nucleophile would possess a correspondingly high-level HOMO, which would reflect a higher potential energy at the nucleophilic center. (Hard nucleophiles would possess a greater charge density, again relating to high potential energy.) Molecules possessed of high bond angle and steric strain would also possess high potential energy, to which may be attributed the facility of bond cleavages and fragmentations that typify these molecules.

### 2.3.3 Catalysis, enzyme reactivity and the Pauling hypothesis

Intriguingly, the theory of catalysis tends to ignore the energy state of the catalyst itself, perhaps in the mistaken belief that this is justified as the catalyst is finally regenerated [1,2]. The
high reactivity of nucleophile catalysts, for example, may possibly be explained conventionally on the basis of the Gibbs energy, essentially because the catalyst generally possesses a single reactive center. However, this simplistic approach would not apply to the case of multifunctional catalysts, for the aforementioned obvious reasons. In these cases, therefore, it would be better to employ the potential energy option.

A particularly important case concerns enzyme catalysis, reaching an understanding of which remains a key focus of chemical biology [14-23]. One problem with explaining enzymic reactivity lies in the fact that the large proteinic enzymes would possess large negative Gibbs energies of formation (derived from the stability of the peptide bond) [21,22]. This precludes invoking a high ground state energy as the origin of their reactivity, although this is without prejudice to the Pauling hypothesis of transition state stabilization. Even so, adapting the Pauling theory is far from simple. (Intriguingly: stabilizing the transition state implies the performance of work, hence the availability of Gibbs energy!)

Furthermore, enzymes differ fundamentally, in their complexity, from simpler catalysts (small molecules, etc.) [15,16]. This is true not only concerning the three-dimensional shape of an enzyme, but also the intricate arrangement of concatenated catalytic groups in its active-site interior. Thus, a case can indeed be made that the active site represents an area of high potential energy that leads to a high ground state energy, hence high reactivity. (The hydrophobic enzyme interior also precludes significant solvation, leading to enhanced reactivity of the catalytic groups, so possibly high potential energy.)

The Pauling hypothesis of transition state stabilization [23], in fact, is predicated on ignoring ground state effects! Indeed, it is noteworthy that the hypothesis was proposed (1948) in the early decades of transition state theory (1935), when the latter was still being explored in terms of scope and limitations. Thus, it now seems opportune to revisit transition state theory, in light of the above critique, particularly in view of the rapidly evolving scenario of chemical biology, in which enzymes will always play a key role.

In fact, the reactivity of even simpler catalysts (say, iodide ion) is rarely the result of a high Gibbs energy, as stable compounds generally possess negative Gibbs energies of formation! Therefore, explaining reactivity is a general problem in the theory of catalysis, and is a particularly significant challenge to transition state theory. Thus, at the very least, an empirical theory of catalysis is urgently needed to deal with the contradictions inherent in current views and approaches.

3. CONCLUSION

Although transition state theory has played a fundamental role in the evolution of modern physical organic chemistry, it is not entirely free of contradictions. These apparently derive from the ambiguities inherent in the original theory itself, and lead to implausible consequences in particular “real life” cases. A serious ambiguity concerns the exact definition of the energy of activation, which may mean either the corresponding Gibbs energy or the potential energy.

Whilst the Gibbs energy of activation appears more formally correct, it is not universally applicable. Thus, explaining selectivity in cases where competing functionalities possess a common ground state demands assumptions about the transition state that may be implausible. In these cases, it seems more reasonable to employ a “localized” potential energy at the reactive center.

These problems concerning transition state theory apparently manifest starkly in the theory of catalysis. Currently, this is entirely based on transition state effects, particularly the Pauling theory of enzymic reactivity. Although the Pauling theory has apparently withstood challenges, it is based in transition state theory, hence vulnerable to the concerns that beset the said theory. It would appear that an empirical approach based on transition state theory as a guiding principle—rather than a rigidly set theory—would be generally beneficial — and still remain within the broad scope of transition state theory.

COMPETING INTERESTS

The author declares no competing interests for this work.

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