Reformulation of activated complex theory

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Abstract

The key assumption of activated complex theory (ACT), that the AC is in thermodynamic equilibrium with the reactants, needs to be reconsidered. This is because the formation of the AC is slower than its collapse to product. However, this can be remedied by assuming that the AC is formed in a rapid pre-equilibrium as a thermally activated species, which collapses to products in a slow step involving the diffusion of another AC molecule (or solvent in the case of a unimolecular reaction). This implies a violation of the principle of microscopic reversibility (PMR), as also the relation between standard free energy change and equilibrium constant ($\Delta G^{o} = -RT\ln K$). However, it may be argued that not only do these not apply to processes performed irreversibly, but also that irreversibility requires the breakdown of the PMR. Accordingly, catalysts may alter equilibrium constants, and enzymes may regulate biochemical processes in hitherto unsuspected ways.

Keywords

Activated complex; catalysts; enzymes; equilibrium constant; irreversibility; Gibbs free energy; microscopic reversibility; transition state

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Introduction

The historical evolution of chemical thermodynamics and kinetics apparently occurred contemporaneously [1,2], the two streams converging with the arrival (1889) of the Arrhenius equation (eqn. 1), relating the rate constant (k) with absolute temperature (T). Interestingly, the earlier van't Hoff relation (eqn. 2) involving the equilibrium constant (K) was the basis of eqn. 1. (The symbols in eqns. 1-3 have their usual significance as mentioned; A is the pre-exponential factor, and R, h and k_B are the gas, Planck's and Boltzmann's constants respectively.)

$$k = A\exp(-E_{act}/RT) \qquad (1)$$

$$(d\ln K)/dT = (\Delta H)/RT^2 \qquad (2)$$

$$k = [(k_B T)/h]\exp(-\Delta G^{\ddagger}/RT) \qquad (3)$$

However, there still remained an important lacuna. Thus, the reaction enthalpy change (ΔH) in the van't Hoff equation (eqn. 2) was a tangible and meaningful quantity, and was the difference between two state properties. The activation energy (E_{act}) of the Arrhenius equation (eqn. 1), however, could not (then) be related to any known state property. It was merely designated as the 'minimum energy that the molecules must acquire for reaction to occur'.

The physical significance of the Arrhenius activation energy was addressed by activated complex theory ('ACT', 1935) [3-6]. ACT proposed that chemical reactions occurred *via* a transitory species of intermediate structure between reactants and products, the 'activated complex' (AC). Furthermore, ACT proposed that the AC existed in thermodynamic equilibrium with the reactants, and decomposed to products at an essentially fixed rate that was independent of the nature of the AC. Most importantly, the equilibrium between reactants

and the AC was expressed in terms of an equilibrium constant that could be related to a corresponding enthalpy of activation, *via* an analog of the van't Hoff equation. Thus, this provided the justification for the analogy between the Arrhenius and van't Hoff equations themselves. (ACT is also termed transition state theory; however, a distinction between 'activated complex' and 'transition state' will be made further below.)

The form of the final Eyring equation (eqn. 3), the key equation of ACT, was again analogous to the Arrhenius equation (eqn. 1), but was expressed in terms of the Gibbs free energy of activation ($\Delta G^{\ddagger}$) [3-6]. Interestingly, therefore, ACT accomplished several conceptual feats in one stroke. In linking the van't Hoff and Arrhenius relations, it gave tangible meaning to the Arrhenius activation energy and, overall, bound chemical thermodynamics and kinetics into a conceptual whole.

The key to this success, in fact, was the introduction of the concepts of statistical thermodynamics. This enabled the expression for the equilibrium constant for the formation of the AC in terms of the partition function, and the isolation of the key vibrational component thereof [3-6]. This was the vibration along the reaction coordinate, and considering this as a translation defined the collapse of the AC to products. This also effectively implied that any AC collapsed to products at the same rate ($= k_B T/h$).

Therefore, the major achievement of ACT was in expressing the rate of a chemical reaction in terms of an equilibrium constant. In the modern context, ACT has played a seminal role in the resurgence of physical organic chemistry [5-7]. Before the introduction of ACT, physical investigations in organic chemistry largely concerned the relation between molecular structure and physical properties, *e.g.* aromaticity, dipole moment, colour, etc. [8]. Reaction mechanisms were explained in terms of (ground state) structures (whenever this was feasible). An interesting example would be the correlation of the selectivity in the Beckmann rearrangement with the geometry of the oxime reactant; another would be the explanation for

the selectivity in aromatic electrophilic substitution in terms of the mesomeric effect in the reactants [9]. ACT, however, not only offered an additional (and alternative) basis for relating structure and reactivity, but also gave tangible meaning to the energy of activation in terms of the structural changes attending the formation of the AC.

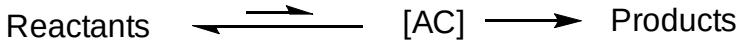
ACT remains the reigning paradigm of chemical reactivity, having comprehensively replaced its earlier rival, the collision theory [3,4]. In its qualitative manifestation ACT is employed almost routinely, as a simple and direct basis for understanding the finer details of chemical transformation. ACT is the basis of the most widely used theory of enzymic reactivity [10], which proposes that enzymes stabilize the rate-determining AC. The formal ACT also continues to be pursued vigorously by modern theoretical methods [11-13]. All the same, some of the tenets of ACT have been debated [7], although not seriously enough for it to be supplanted.

This paper re-examines the key concepts that form the basis of ACT and proposes fundamental changes. Intriguingly, it appears that classical ACT is founded on a debatable assumption, which can only be remedied, however, by reconsidering certain key concepts of thermodynamics. (Again, this underscores the close correspondence between chemical kinetics and thermodynamics, discussed above.)

Discussion

Inconsistencies within ACT

The central assumption of ACT is that the AC is in thermodynamic equilibrium with the reactants (Scheme 1 and Fig. 1). Without this key concept the basic equations that evolve into ACT cannot be set down. The key assumption has been questioned, but only insofar as it is unsubstantiated [7]; otherwise, it is generally accepted as a reasonable basis for a theory that is indeed extremely useful in practice.



Scheme 1. Conventional activated complex theory (ACT, *cf.* Fig. 1)

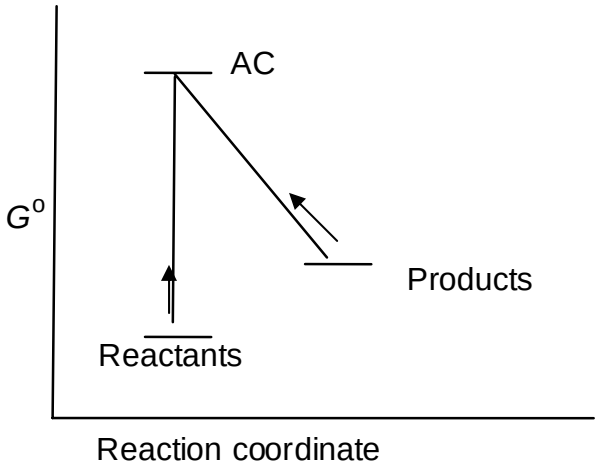


Figure 1. A representation of conventional activated complex theory (ACT, *cf.* Scheme 1). The arrows indicate that the profiles may be traversed in both forward and reverse directions, thus conforming to the PMR.

This key assumption, however, may need to be re-considered, for the following reasons. In any consecutive sequence of chemical changes, a particular step can attain thermodynamic equilibrium only if it is very much faster than any subsequent step. This is an accepted argument that is generally applied to chemical reactions that occur *via* several steps with the formation of intermediate species. Thus, in a two-step process occurring *via* the initial formation of an intermediate (I), the first step would be a pre-equilibrium when – and only when – the subsequent formation of final products from I is very much slower than the initial formation of I. The same reasoning should equally apply to the formation and decomposition of an AC.

Thus, ACT (Scheme 1) is also based on a two-step sequence of bonding changes in the reactant molecule that involves the formation and subsequent collapse of the AC. The collapse of the AC to products is proposed to occur at a rate (k_BT/h) that is faster than the frequency of vibration of the breaking bond. This follows from the assumption that this vibration is to be treated as a translation at the AC. Interestingly, however, this not only implies that every such vibration results in the collapse of the AC, but also that it leads either to reactants or to products. In turn, this implies that the rates of collapse of the AC to reactants or products are about equal.

Quantitatively, the term $k_BT/h \sim 10^{12}\ s^{-1}$, whereas the rate of bimolecular diffusion is $\sim 10^{10}\ M^{-1}s^{-1}$ [14]: this implies (at normal temperatures and a concentration of 1 *M*), that even if all the collisions of the reactants were to lead to the AC, the formation of the AC would still be far slower than its collapse to the products. (In fact, only a small fraction of the collisions results in the formation of the AC.)

Therefore, it does appear highly unlikely that the AC can be in thermodynamic equilibrium with the reactants: for this to obtain, the collapse of the AC to reactants has to be very much faster than its collapse to products.

$$K^{\ddagger} = [\text{AC}]/[\text{Reactants}]^{n} \qquad (4)$$

$$\Delta G^{\ddagger} = -RT \ln K^{\ddagger} \qquad (5)$$

$$K^{\ddagger} = (k^{\ddagger}_{f})/(k^{\ddagger}_{r}) \qquad (6)$$

$$k^{\ddagger}_{f} = [(k_B T)/h]K^{\ddagger} \qquad (7)$$

$$k^{\ddagger}_{f} = [(k_B T)/h]\exp(-\Delta G^{\ddagger}/RT) \qquad (8)$$

Furthermore, the key premise of ACT is that the AC can be formally treated as a chemical species with a finite (although fleeting) existence. Therefore, its equilibrium with the reactants is treated in the normal way, and represented by an equilibrium constant ($K^{\ddagger}$, *cf.* eqn. 4, n being the reaction order), and a corresponding free energy of formation ($\Delta G^{\ddagger}$, eqn. 5). (This is identical to the free energy of activation for the overall reaction.)

The equilibrium constant ($K^{\ddagger}$), however, cannot be expressed in its kinetic formulation, *i.e.* as the ratio of the specific rates of formation and collapse of the AC ($k^{\ddagger}_{f}$ and $k^{\ddagger}_{r}$ respectively, eqn. 6), as this leads to the following inconsistency. The rate of collapse of the AC to products is set at $k_B T/h$ (*vide supra*); as noted above this should also be the rate of its reversal to reactants. If this be considered the specific rate $k^{\ddagger}_{r}$, $k^{\ddagger}_{f}$ would be $(k_B T/h)K^{\ddagger}$ (eqn. 7). Also, $K^{\ddagger} = \exp(-\Delta G^{\ddagger}/RT)$ by eqn. 5, so $k^{\ddagger}_{f} = (k_B T/h)\exp(-\Delta G^{\dagger}/RT)$ (eqn. 8), which is identical to the specific rate of the overall reaction (*cf.* eqn. 3). On this basis, all of the AC species would pass directly into products.

It is clear from the above discussion that ACT is beset with serious conceptual inconsistencies. In particular, the assumption that the AC is in equilibrium with the reactants (Scheme 1), even though it collapses to reactants and products at nearly equal rates, seems unviable.

Revised formulation of ACT

A possible resolution of these inconsistencies within ACT is based on the following revision of its key assumptions: the AC is formed in a rapid pre-equilibrium step; and the formation of the final products occurs *via* the slow diffusion (together) of AC species (Scheme 2).

In this proposal, the AC represents a maximum on the potential energy profile (*cf.* Fig. 2), despite its rapid, pre-equilibrium formation. This is possible as the AC is a thermally excited species that is formed simultaneously with the attainment of thermal equilibrium by the reactants. This is expected to be very rapid, relative to the subsequent step in which two or more AC species need to diffuse together. Therefore, in contrast to the 'instantaneous' formation of the AC, the rate of bimolecular diffusion of AC species would be ~10^{10} $M^{-1}s^{-1}$ at normal temperatures [14]. (In cases of higher molecularity, the diffusion would be even slower.)

As the AC is thus formed relatively rapidly, its formation may be represented by an equilibrium constant and a corresponding free energy of formation (*cf.* eqns. 4-6). The rate of the overall reaction (ν) would be the product of the concentration of the AC and the rate of diffusion, ν_{diff} (eqn. 9). Combining eqns. 4 and 9 leads to eqn. 10 for the overall rate of reaction. The free energy formulations for the overall rate (eqn. 11) and the rate constant (eqn. 12) derive from eqns. 5 and 10. These are analogs of the well-known relations derived in conventional ACT, noting that ν_{diff} replaces k_BT/h.

$$\nu = [AC]\nu_{diff} \qquad (9)$$

$$\nu = K^{\ddagger}[\text{Reactant}]\nu_{diff} \qquad (10)$$

$$\nu = \exp(-\Delta G^{\ddagger}/RT)[\text{Reactant}]\nu_{diff} \qquad (11)$$

$$k = \nu_{diff}K^{\ddagger} = \nu_{diff}[\exp(-\Delta G^{\ddagger}/RT)] \qquad (12)$$

(X = AC or solvent)

Scheme 2. Reformulated activated complex theory (ACT, *cf.* Fig. 2)

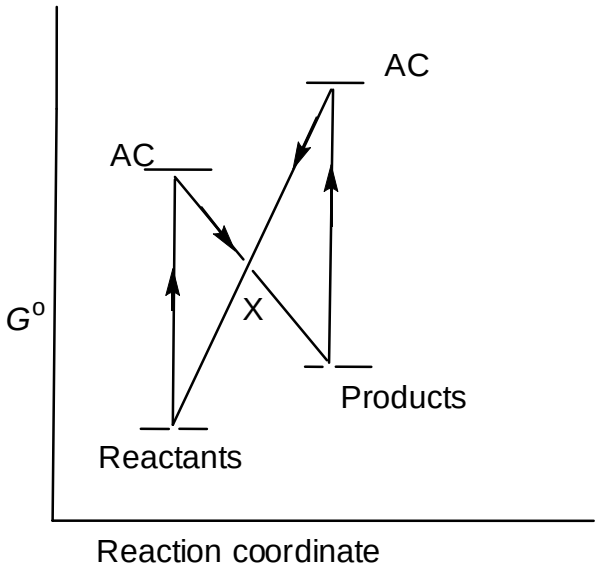


Figure 2. A representation of the reformulated activated complex theory (ACT, *cf.* Scheme 2), with breakdown of microscopic reversibility. 'X' represents the transition state, the point of maximum structural change.

However, whereas k_BT/h has units of s^{-1}, the units of ν_{diff} would be $M^{(1-n)}s^{-1}$ (the reaction order, $n \geq 1$). Note, in particular, that $K^{\ddagger}$ is dimensionless, as it represents the thermal activation of the substrate molecule. For a unimolecular reaction ν_{diff} would be the rate of diffusion of the AC and a molecule of solvent. Although this would be a bimolecular process ($n = 2$), ν_{diff} would also include the molarity of the solvent, and (overall) possess units of s^{-1}. (For example, in the case of an S_N1 reaction, ν_{diff} would represent the solvation-assisted ionization of a thermally activated alkyl halide.)

The noteworthy feature of the current proposal is that it 'de-links' the notions of potential energy and rate: thus the relatively slow diffusion step occurs after the highest energy point (the AC) has been passed. However, the potential energy barrier – representing the free energy of activation – determines the overall rate (as previously, *cf.* eqns. 3 and 12).

Also, the definition of the AC in this proposal is different from the earlier one. In the current definition, the activated complex represents a highly activated form of the reactant, which has not yet undergone any significant structural reorganization towards the final product. Thus, the necessary structural changes occur during the second (and slow) diffusion step. The structural transition point, therefore, does not represent a potential energy maximum anymore.

The potential energy profiles, therefore, would now be represented as in Fig. 2. Interestingly, the AC for the reverse reaction would now be different from that for the forward reaction. This is because it would be formed by thermal activation of the product molecules. This, however, would violate the principle of microscopic reversibility (PMR), which requires that the same AC be traversed in both forward and reverse directions [3-5,15]. (Microscopic reversibility was maintained in the earlier ACT.) This, of course, represents a critical departure from accepted convention, which also has important thermodynamic consequences as discussed below.

Thermodynamic consequences

In particular, a general violation of the PMR would invalidate the relationship (eqn. 13) between the equilibrium constant (K) and the standard Gibbs free energy change (ΔG^o) in a reaction [1,2,5]. This is because the equilibrium constant is defined as the ratio of the rate constants for the forward and reverse reactions (k_f and k_r respectively, eqn. 14). If the PMR is violated, k_f and k_r will not involve the same activated complex, and their ratio (K) will depend on the path of equilibration.

$$\Delta G^o = -RT \ln K \qquad (13)$$

$$K = k_f/k_r \qquad (14)$$

$$\Delta G^o \neq -RT \ln K' \qquad (15)$$

On the other hand, however, the following arguments need also to be considered. Essentially, eqn. 13 is derived for the idealized case of a process performed reversibly, and its validity for a 'natural' process, *i.e.* one performed irreversibly, is unclear. The standard free energy change (ΔG^o) represents the maximum (non-expansion) work that can be obtained in a process, that is, however, carried out reversibly (and under standard conditions).

Thus, the work obtained will always be less than this for a process carried out irreversibly. The equilibrium constant (K') corresponding to such an irreversible process, would be different from K, and would not relate to the standard free energy difference ΔG^o (*cf.* eqn. 15).

It is also noteworthy that a reversible process is a hypothetical construct, although it may be envisaged for a mechanical process. Intriguingly, however, the definition of 'reversibility', a key concept in thermodynamics, is apparently unclear in the general context of chemical

reactions. (The PMR may be viewed as an essential link between the molecular theory of matter and conventional thermodynamics based in the concept of reversible change.)

The consequences of the breakdown of the PMR are shown in Fig. 2. Note in particular that any pathway conforming to the PMR leads to the equilibrium constant (K) predicted by eqn. 13, whereas the alternative (K') must necessarily involve a breakdown of the PMR (assuming the inviolability of ΔG^{o}). Thus, a violation of the PMR implies the breakdown of the reversibility criterion. It would appear, therefore, that a chemical reaction performed irreversibly requires the breakdown of the PMR.

Furthermore, although the PMR is generally considered inviolable, its experimental verification may be fundamentally impossible. The verification of eqn. 13 requires that the equilibrium constant be measured under the same conditions as the standard free energy change. Thus, a key consequence of the PMR – that the equilibrium constant is independent of the path of equilibration – is impossible to verify, as changing the conditions of equilibration will also change the free energy difference.

Significance of violation of the PMR

The PMR is not only the essential link between the kinetic and thermodynamic definitions of equilibrium, but, as now appears, also the key to distinguishing between reversible and irreversible processes. Thus, the mutual compatibility of eqns. 13 and 14 is a consequence of the PMR (and one that was maintained by the original ACT).

However, the possible breakdown of eqn. 13 for an irreversible process also implies the breakdown of the PMR for all natural processes. This may be viewed as the kinetic consequence of irreversibility. Also, the breakdown of the PMR does not imply a violation of accepted thermodynamic laws: energy is neither created nor destroyed, and no perpetual motion is implied.

Interestingly, there is some circumstantial evidence to indicate that the PMR may not be generally followed. This is the observation that the activated complexes of most organic reactions are apparently similar to the reactants rather than to the products [16]. If this is considered as a general trend, it should apply equally to both reactants and products in an equilibrium, thus apparently validating the profiles in Fig. 2.

Activated complex and transition state

The profiles in Fig. 2 indicate that the forward and reverse reaction paths cross at point (X); this, however, is lower in energy than either of the AC's (in contrast to the original ACT). Furthermore, 'X' would represent a common structural transition point, and thus may be termed the transition state (TS). In the original transition state theory (TST), the terms AC and TS were generally used synonymously [3-5]. In the present context, however, a distinction between them helps in de-linking the changes in energy and structure. In the earlier TST the stage of maximum structural change (in terms of bond-making and –breaking) coincided with the energy maximum. In the present formulation, the energy maximum (the AC) occurs at a different (earlier) stage from the point of maximum structural change (TS, point X).

Catalysis

Catalysts accelerate reactions by lowering the free energy of activation (*via* an alternative pathway). In the particular case of enzyme catalysis, however, it is generally believed that catalysis arises from the stabilization of activated complexes [10]. Intriguingly, the breakdown of the PMR proposed above implies that a catalyst can provide alternative pathways for either the forward or reverse reactions (or, of course, both). Analogously, an enzyme may stabilize either (or both) of the two AC's. Clearly, this means that catalysts can alter the equilibrium constant of a reaction – a fundamental departure from the existing convention. This also indicates the possibility that enzymes can exert metabolic control in a manner that has not been considered so far (by altering the equilibrium constant).

Conclusions

The currently accepted activated complex theory (transition state theory) needs to be reassessed, as its central assumption that the activated complex (AC) is formed in thermodynamic equilibrium with the reactants is debatable. The theory can, however, be reformulated so that the AC is formed as a thermally activated form of the reactant molecules in a relatively rapid pre-equilibrium step; the collapse of the AC to final products then follows in a relatively slow, diffusion-controlled step. This, however, involves a breakdown of the principle of microscopic reversibility (PMR) and the well-known relationship between equilibrium constant and standard free energy change ($\Delta G^{o} = RT\ln K$). However, this may possibly be justifiable as a necessary consequence of irreversibility. Therefore, a fundamental reappraisal of key kinetic and thermodynamic concepts is indicated.

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