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Induced intramolecularity in the reference reaction can be responsible for the low effective molarity of intramolecular general acid–base catalysis†

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ABSTRACT: Whereas intramolecular catalysis by nucleophilic groups can be associated with values of effective molarities ranging from 10^5 to 10^8 M in the absence of strain, values below 10 M are usually observed for general acid–base catalysis. Based on the grounds that the efficiency of intramolecular reactions is related to the entropic disadvantage of bimolecular reactions, this low efficiency is usually explained by a loose transition state for proton transfer that is diffusion limited in the thermodynamically favorable direction. However, the transient formation of a hydrogen bond at an electronegative center provides another possibility that can account for the low efficiency of general acid–base catalysis when the reaction is not diffusion limited. Any proton transfer at a site that forms hydrogen bonds to the solvent and that is concerted with a slower process is likely to take place along a hydrogen bond with the catalyst and thus to have an intramolecular character. As a result, low benefits can be earned from further intramolecularity. This analysis has important consequences for intramolecular and enzymatic proton transfers to and from carbon atoms. Owing to the absence or the weak strength of hydrogen bonds capable of inducing intramolecularity in the non-catalyzed mechanism, high effective molarities could be recovered. As a result, the existence of strong hydrogen bonds with carbon acids would no longer be needed to account for the high effective molarities that have been observed in some cases for intramolecular proton transfer to or from carbon. Moreover, the introduction of new concepts such as short, strong hydrogen bonds (low-barrier hydrogen bonds) to account for the high efficiency of enzymatic proton abstraction from carbon would not be necessary.

KEYWORDS: enzymatic catalysis; general acid–base catalysis; hydrogen bonds; induced intramolecularity; neighboring group participation; proton transfer

INTRODUCTION

The efficiency of intramolecular reactions is generally measured by the effective molarity (EM) of the intramolecular reagent (the ratio of the unimolecular rate constant for the intramolecular reaction to that of a similar bimolecular process).[1] In contrast to nucleophilic reactions for which EM values above 10^5 M are customarily found, EMs ranging from 1 to 10 M are generally observed for intramolecular general acid–base catalysis.[1] This low efficiency is usually explained by the diffusion-limited character of proton transfer between electronegative atoms (O, N, S) in the thermodynamically favorable direction.[2] The almost absence of a free energy barrier for proton transfer along a hydrogen bond through the Eigen mechanism was first proposed to account for these fast rates.[3] However, the substantial intrinsic barrier of ca 5 kcal mol^{-1}(1 kcal = 4.184 kJ), deduced from experimental data,[4] was subsequently explained by an indirect transfer due to the slow removal of the last water molecule during the diffusion step.[5]

The driving force for general acid–base catalysis arises from large changes in pK_a that are usually associated with chemical reactions,[6] as for example when an unstable intermediate must be trapped by a diffusion-limited proton transfer for the reaction to proceed. However, if the intermediate becomes still less stable and thus reverts to the reactants faster than the diffusion of the catalyst, this process is no longer efficient and any observed catalysis must take place through pre-association or concerted mechanisms.[6] In this case, the general acid or base must already be present in the ground state. The lowest energy path is then likely to involve a direct

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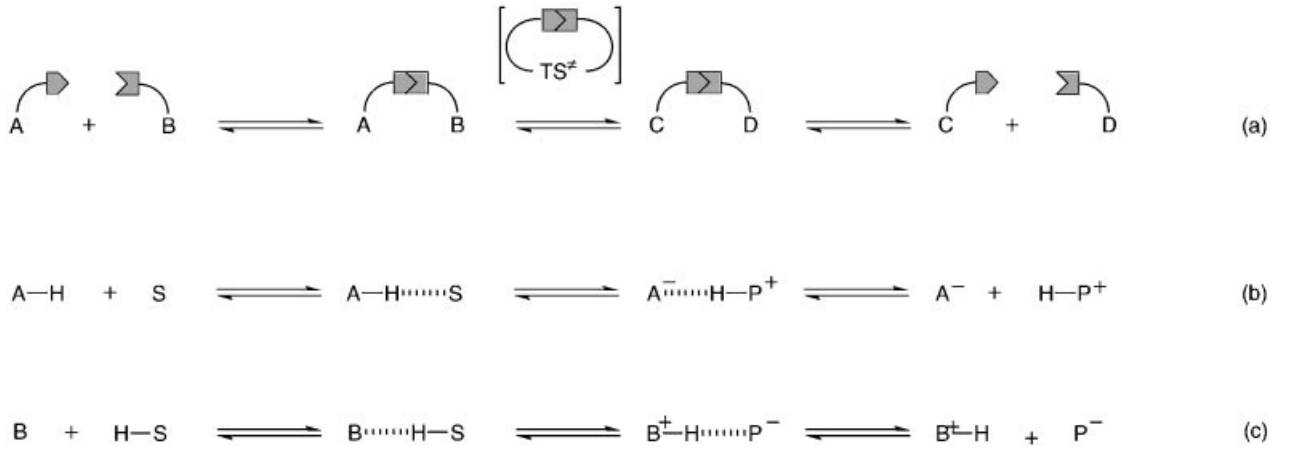


Scheme 1. Comparison of (a) a schematic picture of induced intramolecularity in stoichiometric reactions with concerted processes of (b) general acid or (c) general base catalysis. Scheme (a) can be applied to processes (b) and (c) considering the fact that both the binding site and the center at which general acid–base catalysis occurs are at the same place in (b) and (c)

proton transfer along a preformed hydrogen bond between the catalyst and the reaction center.

It must be remarked that the formation of this complex is associated with the loss of translational and rotational entropy. As a result, little benefit can be earned from further intramolecularity, in agreement with the fact that entropy is not likely to be significantly altered by proton location unless the hydrogen bond is broken. Although it has been overlooked, this intramolecular character (Scheme 1) has important consequences for understanding general acid–base catalysis in enzymatic transformations and intramolecular reactions. The following discussion of its consequences is based on the interpretation of rate accelerations in intramolecular reactions as corresponding to the entropic disadvantage of bimolecular reactions.[7] Much debate has been devoted to the explanation of these high rates.[8,9] However, it must be emphasized that the main conclusions of this work depend on intramolecularity (or induced intramolecularity) in the reacting systems but are actually independent of the explanation given to account for its efficiency.

DISCUSSION

Catalysis associated with the transfer of a proton at an electronegative center

A representative example of concerted general acid catalysis at an electronegative center, which is normally hydrogen-bonded, is analyzed in Scheme 2. Overall rate constants for the unimolecular (k_{intra}) or bimolecular (k_{inter}) processes can be deduced from first-order rate constants k^1 or k^2, respectively [Eqns (1) and (2)]. This calculation takes into account the relative stability of hydrogen bonds with the intramolecular (K^1) or intermolecular (K^2) acid catalyst as compared with the hydrogen bond with water.

$$k_{intra} = k^1/(1 + [H_2O]/K^1) \quad (1)$$

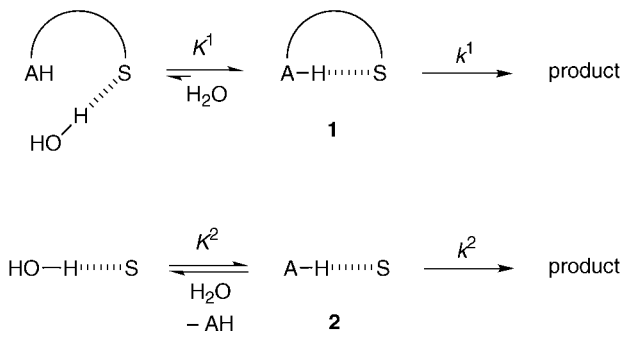
$$k_{inter} = k^2/([AH] + [H_2O]/K^2) \quad (2)$$

According to the above hypothesis, the reaction rates can be considered as identical starting from either hydrogen-bonded adduct **1** or **2** ($k^1 = k^2$), independently of additional intramolecularity in **1**. EM can be determined as the ratio of rate constants as defined in Eqn. (3) and developed in Eqn. (4):

$$EM = k_{intra}/k_{inter} \quad (3)$$

$$EM = ([AH] + [H_2O]/K^2)/(1 + [H_2O]/K^1) \quad (4)$$

Numerical values can be obtained considering standard conditions ([AH] = 1 M) and the molarity of water ([H_2O] = 55 M). A value between 1 and 55 can be estimated for the equilibrium constant K^2 by the following observations (values in agreement with these



Scheme 2. An illustrative example of intramolecular general acid catalysis compared with its bimolecular counterpart

estimations have been reported.[10]) First, acids stronger than water only can give rise to observable catalysis (exceeding the effect of water), and as a result the hydrogen bond would then be more stable than that with water ($K^2 \geq 1$). Second, stable intermolecular hydrogen bonds are not observed in this solvent because of the competition with water ($K^2 \leq 55$). Using these conservative hypotheses in the case of a stable intramolecular hydrogen bond ($K^1 \gg 55$ M) results in an estimate of 2–56 M for the effective molarity [Eqn. (3)] of an intramolecular general acid, in good agreement with the observed 1–10 M range. Less stable intramolecular hydrogen bonds ($K^1 \leq 55$ M) would lead to lower EM values. The involvement of induced intramolecularity in the bimolecular reaction is therefore consistent with observed EM values for general acid–base catalysis. This involvement is independent of likely contributions from overlapping of molecular orbitals to the proton transfer process and implies no supposition about the nature of hydrogen bonds and the potential associated with them.

Catalysis of proton transfer to or from carbon atoms

Except that the relevance of using EMs for general acid–base catalysis may be questioned, the above conclusion has no experimental consequences when the site of general acid–base catalysis is an electronegative atom. However, general acid–base catalysis can also be the result of slow proton transfers involving carbon atoms. In this case, the situation is completely different because these centers are normally not hydrogen bonded, and the effect of intramolecularity can therefore be predicted to be 'normal.' As a result, EMs much higher than 10^2 M could be observed if the mechanism corresponds to a direct proton transfer at a center that does not form hydrogen bonds with either water or the catalyst. The upper limit of EMs in the absence of strain, which depends on the entropy loss at the transition state of the bimolecular reaction,[7] could only be reached for rate-determining proton transfers to or from carbon atoms bearing no electron-withdrawing substituents able to confer a partially ionic character to the C—H bond. Because the reaction is not diffusion controlled, this limit has no reason to be much lower than the value of 6.5×10^6 M determined for a hydride transfer reaction.[11] However, weak hydrogen bonds are likely to be formed with most carbon acids, leading to intermediate values. As in any other intramolecular reaction, further limitations resulting from ring size and stereoelectronic requirements are likely to be involved. Moreover, these reactions may be classified apart from other intramolecular reactions (e.g. cyclizations) since a bond in the ring is formed while another is broken, the transition state only being cyclic. Interestingly, equivalent processes for nucleophilic substitution at saturated carbon, corresponding to 5-*Endo-Tet* and 6-*Endo-Tet* ring closures, are not favored according to Baldwin's rules.[12]

Exceptions to the rule that any observed EM above 80 M must result from a process other than general acid–base catalysis have been reported by Kirby.[13] Cyclic systems derived from salicylic acid or proton sponges display high EMs for acetal hydrolysis. These rate increases have been accounted for by the formation of a strong hydrogen bond at the transition state. Several examples of EM values exceeding 10^2 M for intramolecular proton transfers involving carbon atoms have been reported.[14,15] A similar explanation would require strong hydrogen bonds to be formed in this case also. However, such a hypothesis is no longer needed, although not ruled out, if EMs much higher than 10^2 M can result from intramolecularity in proton transfers to and from carbon, as proposed here.

A large number of enzyme-catalyzed reactions involve the abstraction of a proton from a carbon atom adjacent to a carbonyl or carboxylic acid group by an active site general base catalyst. These reactions display rate enhancements exceeding those usually observed for Brønsted buffer catalysis in water.[16] This observation led to the proposal that catalysis is brought about by an unusual stabilization of the transition state by a short, strong hydrogen bond (low-barrier hydrogen bond).[17] Arguments against[18] that hypothesis have been advanced but new contributions were published in support of the existence of low-barrier hydrogen bonds in the transition states of enzyme reactions.[19] According to the above remark, high efficiency in enzyme-catalyzed proton transfers from and to carbon can more simply be explained by the absence of hydrogen bonding in the ground state of the reference reaction. In the mechanism of these enzymes the fixation of the substrate by interactions with functional groups distinct from the C—H bond gives rise to an enzyme–substrate complex in which a general base is available to provide such increases without need to invoke special explanations.

CONCLUSION

Induced intramolecularity is a key component of enzyme power.[20] It also contributes to bringing about catalysis in enzyme mimics or models. Its specific feature is that the formation of a complex is associated with a favorable intrinsic binding energy, which compensates for the entropic cost of the fixation of the substrate,[21] which is already present at the transition state and which disappears only when the product is released. An implicit consequence of the proposition made here is that induced intramolecularity contributes to the high rates of proton transfer along hydrogen bonds. Hydrogen bonds may then be depicted as the simplest enzyme mimics because these rates can in part be explained by the use of binding

energy to compensate for the entropic cost that inhibits the bimolecular reaction.

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