Vol. 50, No. 3, 1973 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS

ENTROPY CONTRIBUTIONS TO RATE ACCELERATIONS OF INTRAMOLECULAR REACTIONS IN WATER VS NON-STRUCTURED SOLVENTS

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Received December 11, 1972

Summary: The calculations of Page and Jencks showing that translational entropy factors may play a significant role in enzymatic rate accelerations are extended to the solvent water. The picture changes significantly due to the large entropy terms associated with solvation of hydrocarbons. While translational entropy should still contribute significantly to enzymatic rate accelerations, it is argued that this effect will appear in $\Delta H^{\ddagger}$ rather than $\Delta S^{\ddagger}$.

Recently Page and Jencks[1] have argued that translational and rotational entropy provides an important driving force for enzymatic rate accelerations. Their analysis was based on a calculated value for the entropy of a reaction occurring in an organic solvent in which two molecules react to give one molecule of product and no charge is produced in the transition state. We have extended their treatment to the solvent water and find that the loss of translational entropy due to the combination of two reactants is cancelled by the destruction of one structured solvent cage as the two reactants form a single product. While this complicates the analysis, it seems likely that the translational entropy factor cited by Jencks may still make an important contribution to enzymatic rate accelerations.

The treatment of Page and Jencks[1] is as follows. They chose the dimerization of cyclopentadiene as a model reaction and we shall follow suit. In the gas phase reaction of A + B to give C (see Fig. 1), there is a large loss of translational and rotational entropy. Note that C can be either product or a transition state. Using standard thermodynamic techniques, it can be shown that an entropy loss of ca. -40 to -50 eu is expected for the dimerization of molecules having molecular weights of ca. 50. The problem is to calculate the entropy loss for this reaction in solution. Cyclopentadiene dimerization is a good model reaction since it has been thoroughly studied and does not involve a highly polar transition state. This calculation was done using the entropy cycle shown below and estimating the entropy of transfer of cyclopentadiene and dicyclopentadiene from the gas phase to solution. Obviously the critical step is the estimation of the

Fig. 1 Calculation of the Entropy of Activation for A Diels-Alder Reaction in Solution (from ref. 1).

$$\begin{tikzcd}
\text{Gas} & A \arrow[d, "-9\text{ eu}"'] & + & B \arrow[d, "-9\text{ eu}"'] \arrow[rr, "-30 - -40\text{ eu}^{2,3}"] & & C \arrow[d, "-15\text{ eu}"] \\
\text{Solution} & A_s & + & B_s \arrow[rr, "\begin{array}{c}-27 - -37\text{ eu}\\ \text{calculated}\end{array}"'] & & C_s
\end{tikzcd}$$

entropy of transfer of cyclopentadiene and dicyclopentadiene from the gas phase to the solution. This was done by estimating the entropy of vaporization using Trouton's Rule, then correcting for the concentration difference between the neat liquid compounds and the gas phase. This procedure should be reliable and indeed the predicted values for this reaction (-31 eu) agrees well with that observed in sovents like benzene, carbon disulfide, and carbon tetrachloride.[2] This treatment uses the reactant molecule itself as the solvent but it should be appliccable to other non-polar non-structured solvents. Page and Jencks[1] went on to argue that, in general, there would be a large entropy loss for reactions in solution and that this loss would not occur in an enzyme catalyzed reaction since the reactants lost translational and rotational entropy when complexed with the enzyme. Thus this unfavorable entropy of activation term would disappear leading to a large rate acceleration.

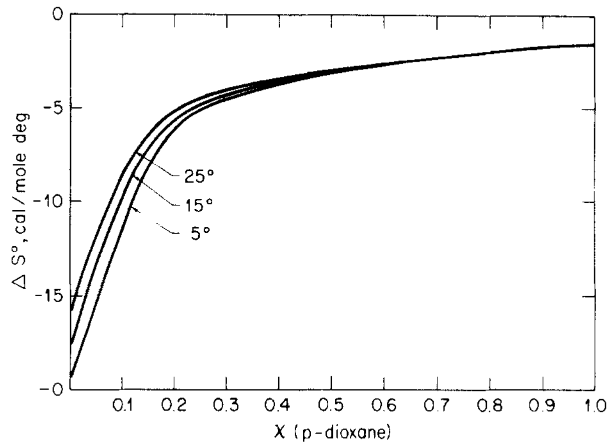

Figure 2. $\overline{S}^{o}$ of solution of Argon as a Function of Mole Fraction of p-Dioxane at Different Temperatures (from ref. 7).

Since enzymatic reactions occur in water and their rates should be compared with the uncatalyzed reaction in water, we have extended the treatment of Page and Jencks using water as the solvent and find the picture changes markedly. The entropy of solution of a non-polar molecule is quite different in water and non-polar solvents. This has long been recognized and discussed at some length.[4-6] A good example of this effect is the entropy of solution of Ar in dioxane water mixtures.[7] The excellent data of Ben-Naim are shown in Fig. 2. In water quite large negative values are observed, chiefly due to the formation of regions of increased water structure around the inert gas molecule.[8] In addition to the effect of inducing water structure, gas phase translational motion becomes a vibration in a solvent cage when the gas is dissolved in a highly structured medium. Thus there are two factors to consider, the entropy increase due to formation of the solvent cage and the entropy decrease due to the loss of vibrational freedom on passing from the vapor state to a solvent. It is quite clear that non-polar solvents are quite poor models for aqueous systems.

Since it is not yet possible to calculate accurately both of these, we attacked this problem by using the experimental entropies of solution in water of several organic model compounds. Unfortunately, the entropies of solution for cyclopentadiene and bicyclopentadiene are not available, but there are a number of model systems which can be used. One such system is to use benzene as a model for cyclopentadiene and naphthalene as a model for dicyclopentadiene. The entropies of solution of benzene and naphthalene (liq) in water at 298 are +1.88 eu + 9.42 eu respectively.[9] These data refer to saturated solutions which are quite dilute. The entropies of vaporization of these molecules are also available.[9,10] These can be combined in the entropy cycle shown in Fig. 3 to calculate the activation entropy for the dimerization of cyclopentadiene

Figure 3. Calculation of $\Delta S^{\neq}$ for the Dimerization of Cyclopentadiene in Water at 25° Using Benzene and Naphthalene Model Compounds.[a]

$$\begin{tikzcd}
\text{Gas} & A \arrow[d, "-29\text{ eu}"'] & + & B \arrow[d, "-29\text{ eu}"'] \arrow[r, "-34\text{ eu}"] & C \arrow[d, "-28^{a}\text{ eu}"] \\
\text{Liq.} & A_{H_2O} & + & B_{H_2O} \arrow[r, "-4\text{ eu calculated}"'] & C_{H_2O}
\end{tikzcd}$$

[a] The entropy of vaporization at the boiling point was used. Since the entropy of vaporization at 25° will be smaller, it will result in a larger (more positive) value for the entropy of activation for the dimerization. That is, the value shown in probably somewhat too low (too negative).

water as the solvent is to reduce the calculated $\Delta S^{\neq}$ from -31 eu to -4 eu. Using the critically evaluated data of Wauchope and Haque[11] which refer to a different standard state in water, namely $X_s = 1$, $T = 298°$, the calculated $\Delta S^{\neq}$ is 0 eu.

Other models can be used with similar results. A calculation is shown in Fig. 4 using n-pentane as a model for cyclopentadiene and n-decane as a model for dicyclopentadiene. The entropy of transfer of n-pentane from the gas phase to water (ΔS°_{trans}) is available[12] and the value for n-decane was obtained by extrapolating the linear plot of ΔS°_{trans} vs carbon number in ref. 12. Since good linearity is observed from methane to n-nonane, this extrapolation should be reliable. In this case the calculated $\Delta S^{\neq}$ is positive.

Figure 4. Calculation of $\Delta S^{\neq}$ for the Dimerization of Cyclopentadiene in Water at 25° Using n-Pentane and n-Dodecane as Models

$$\begin{tikzcd}
\text{Gas} & A \arrow[d, "-58\text{ eu}"'] & + & B \arrow[d, "-58\text{ eu}"'] \arrow[r, "-34\text{ eu}"] & C \arrow[d, "-70\text{ eu}"] \\
\text{Soln } H_2O & A_{H_2O} & + & B_{H_2O} \arrow[r, "+12\text{ eu calculated}"'] & C_{H_2O}
\end{tikzcd}$$

In going from an unstructured organic solvent to water, $\Delta S^{\neq}$ for this model reaction is expected to change from ca -30 eu to ca 0 eu. This change appears to wipe out the rate acceleration claimed by Jencks; however that is not the case. First, since the loss of translational freedom experienced by a molecule transferred from the gas phase to solution should not change greatly as a function of solvent,[13] the observed difference should be due primarily to changes in water structure. Our discussion may be limited to this factor.

The source of the observed effect is the formation of areas of enhanced water structure around non-polar solutes. Creation of these ordered regions has a large negative entropy. In a reaction in which two molecules form one, there is a large gain in entropy due to the destruction of one of the water "cages." This gain is about equal in magnitude and opposite in sign to the entropy lost when the two molecules merge in a non-polar solvent or the gas phase. This effect will not operate with solutes which do not induce formation of the water cage. Data is available for the entropies of hydration of a variety of organic molecules indicating the presence of a functional group does not necessarily destroy the structure making character of the alkyl group.[14-17]

Now it is well established that such unfavorable changes in entropy due to the formation of water structure are counteracted by a favorable ΔH term, arising presumably from increased hydrogen bonding.[18] Thus the entropy contribution due to formation of water structure should be approximately cancelled by a favorable enthalpy term. If this is so, then the rate acceleration cited by Jencks will be real. It will, however, show up in $\Delta H^{\neq}$, the entropy contributions having cancelled.

Acknowledgement. Helpful discussions with Dr. Ron Magid and the perceptive comments of Dr. W. P. Jencks are gratefully acknowledged.

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