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ACTIVATION BARRIERS IN PHOTOSENSITIZED PYRIMIDINE DIMER SPLITTING

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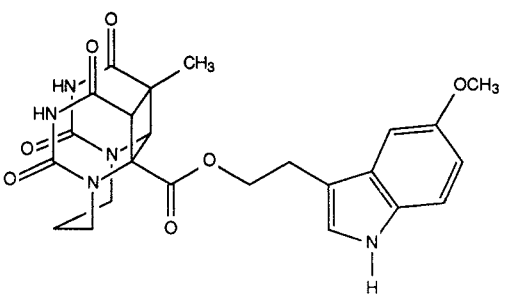
Pyrimidine dimers, which form by a symmetry allowed ($\pi_s^2 + \pi_s^2$) photocycloaddition reaction, are subject to photosensitized cycloreversion by electron donors, such as indoles. In a linked dimer–indole system, photoinitiated electron transfer occurs intramolecularly from indole to dimer to produce a charge-separated species (dimer$^{-\cdot}$–indole$^{+\cdot}$). This species undergoes cycloreversion in competition with back electron transfer. Studies of the temperature dependence and solvent dependence of this competition have allowed the relative values of the activation parameters for the competing processes to be determined. In water (5–65 °C) the free energy of activation of splitting minus that of back electron transfer ($\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{spl} - \Delta G^{\ddagger}_{bet}$) was found to be 1·3 kcal mol^{-1}. The enthalpy of activation difference ($\Delta\Delta H^{\ddagger}$) was found to be 1·1 kcal mol^{-1} and the entropy of activation difference ($\Delta\Delta S^{\ddagger}$) was found to be −0·51 cal mol^{-1} K^{-1}. In EPA (diethyl ether–isopentane–ethanol, 5:5:2; −85 to 25 °C) the value of $\Delta\Delta G^{\ddagger}$ remained the same, but the entropy and enthalpy contributions were different ($\Delta\Delta H^{\ddagger} = 0{\cdot}72$ kcal mol^{-1}; $\Delta\Delta S^{\ddagger} = -1{\cdot}8$ cal mol^{-1} K^{-1}). The results have been interpreted in terms of the effect of the polarity of the solvent on the transition states for the two competing processes. Enthalpy effects retard splitting more in water than in EPA, whereas entropy effects favor back electron transfer more in EPA than in water. Potential implications of these results for the mechanism of enzymatic photocycloreversion of pyrimidine dimers in DNA are considered.

INTRODUCTION

Pyrimidine dimers form in DNA exposed to the ultraviolet component of solar radiation in a symmetry allowed ($\pi_s^2 + \pi_s^2$) photocycloaddition reaction.[1] The dimers are deleterious *in vivo*[2] and are substrates for several classes of repair enzymes. Members of one such class of enzymes, the photolyases, catalyze cycloreversion of the dimer to two pyrimidine nucleotides.[3] The photolyases effect cycloreversion by utilization of near-UV and visible light,[4,5] a remarkable phenomenon that has evoked much interest in the mechanism of the cycloreversion. It is believed that the photolyases achieve dimer cycloreversion by photoinitiated electron transfer from an enzyme-bound sensitizer to the dimer[1b,5b,5c,5g] to produce the dimer radical anion, the species that actually splits.[6]

Numerous ions and molecules have been found to sensitize pyrimidine dimer splitting in solution.[7] To model more closely the natural systems, in which electron transfer from the enzyme-bound sensitizer to the enzyme-bound dimer is essentially intramolecular, we have prepared compounds in which dimers are covalently linked to chromophores capable of photoinitiated electron transfer.[6,8] In **1**, for example, a dimer is linked to 5-methoxyindole, which absorbs light and transfers an electron to the dimer. The resulting dimer radical anion in the charge-separated species (dimer$^{-\cdot}$–indole$^{+\cdot}$) can then undergo cycloreversion, which ultimately yields **2**. Alternatively, the dimer radical anion can transfer an



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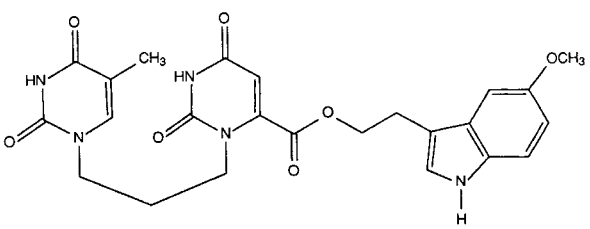

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electron to the covalently linked indole radical cation. In dimer–indoles such as **1**, however, back electron transfer limits the quantum yield of intramolecularly photosensitized splitting ($\Phi = 0{\cdot}1$).[8]

In a previous study,[8b] we found that the dimer radical anion in the charge-separated species faced thermal barriers to splitting that were insurmountable at 77 K. To examine the competition between back electron transfer and dimer radical anion splitting, we have measured splitting efficiency of **1** in EPA and in water over a wide range of temperatures. The results have allowed the activation enthalpies and entropies for back electron transfer and splitting in two solvents to be compared. From the activation parameters, a semi-quantitative energy diagram depicting the alternative fates of dimer radical anions in the charge-separated species has been constructed. These studies revealed features of the transition states for splitting and back electron transfer and have potential implications for the enzyme-catalyzed cycloreversion reaction.

EXPERIMENTAL

General. The synthesis of the linked dimer–indole used in this study (**1**) has been reported.[8d] EPA consisted of diethyl ether–isopentane–ethanol (5 : 5 : 2, v/v).

Quantum yield measurements. Splitting quantum yields were measured as follows. For **1** dissolved in water, photolysis was carried out with an Oriel deep UV source consisting of a Model 68811 power supply, 500-W Hg–Xe short arc lamp and fused silica, four-element condenser. The beam was focused onto the entrance slit of a Jarrel-Ash 0·25-m monochromator equipped with a ruled grating (2360 grooves mm^{-1}) blazed at 300 nm. The light beam leaving the monochromator was focused on a quartz cuvet containing a stirred solution of **1**. In the photolysis carried out at 25 °C, the beam was split with a quartz plate to allow simultaneous irradiation of **1** and a ferrioxalate actinometer solution. The solutions were irradiated at 304 nm (1·6 nm bandwidth). The extent of dimer splitting was determined from the increase in absorbance of the solution at 276 nm.[8a] To obtain quantum yields of dimer splitting at 5, 45 and 65 °C, the absorbance at 276 nm was monitored at intervals of 30 s of irradiation and the data were plotted as $\ln(A - A_\infty)/(A_0 - A_\infty)$ versus time. Comparison of the slopes to the slope from a photolysis that was carried out at 25 °C allowed quantum yields at the three other temperatures to be evaluated.

For **1** dissolved in EPA, the light source was a 500-W high-pressure Xe arc lamp with a Princeton Applied Research Model 301 power supply. The light beam was focused onto the entrance slit of a Jobin-Yvon Model M-25 holographic grating monochromator. Photolyses at 300 nm (15 nm bandwidth) were carried out for 45 min at 25, −10, −70 and −85 °C. Samples of **1** dissolved in EPA ($A_{300} = 0{\cdot}228$) were placed in a quartz tube (3 mm i.d.), which in turn was placed in a quartz Dewar vessel containing a bath equilibrated at the desired temperature. The baths used were ethylene glycol–CO_2 (−10 °C), isopropanol–CO_2 (−70 °C) and diethyl ether–CO_2 (−85 °C). The shape of the Dewar vessel prevented solid CO_2 from obstructing the light beam. The irradiation was periodically interrupted to allow agitation of the bath to maintain a uniform temperature. Temperatures were measured with a Weksler thermometer (range −100 to 50 °C) that was checked against a calibrated thermocouple. The thermometer was inserted into the space to be occupied by the quartz tube when the irradiation was performed.

A solution of **1** in EPA at 25 °C was also irradiated at 304 nm with the Hg–Xe deep UV source, which allowed the quantum yield of splitting to be determined by comparison to the value obtained for **1** in water at the same temperature. The quantum yields for the irradiation of **1** in EPA at various temperatures with the Xe source were then calculated from the value determined for **1** in EPA at 25 °C with the Hg–Xe source.

Fluorescence emission measurements. Fluorescence emission measurements were carried out on **1** and 5-methoxytryptophol with instruments described previously[8a] and yielded intensities F and F_0, respectively. For **1** dissolved in EPA, the excitation wavelength was 300 nm. For **1** dissolved in water, the fluorescence intensity was monitored with excitation at 304 nm.

RESULTS

Splitting quantum yields and fluorescence intensity

Dimer splitting by **1** during steady-state irradiation at 304 nm followed first-order kinetics, as evidenced by the linearity of the semi-logarithmic plot shown in Figure 1. This ensured that under these conditions only intramolecular photosensitization was occurring. In a typical experiment (25 °C, water) the absorbance at 276 nm increased from $A_0 = 0{\cdot}118$ to $A_\infty = 0{\cdot}391$. The values of Φ_{spl} in water and in EPA at various temperatures are given in Table 1. The measured fluorescence intensity ratios for **1** and 5-methoxytryptophol are also given in Table 1.

Evaluation of activation parameters

Irradiation of **1** in water and in EPA at different temperatures allowed activation parameters to be assessed as follows. It is assumed that the dimer radical anion has two reactions open to it, back electron

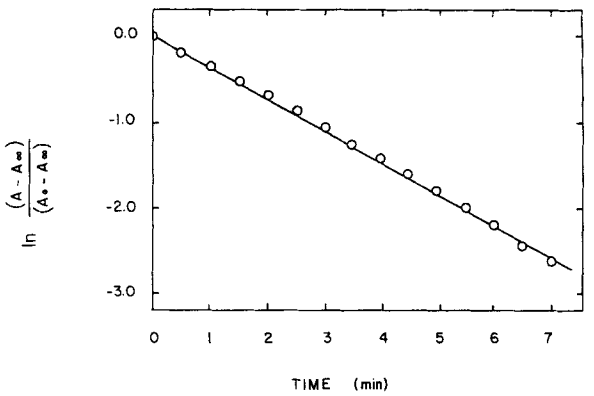

Figure 1. Kinetics of the cycloreversion of **1** to **2**

Table 1. Splitting quantum yields (Φ_{spl}) for **1** and fluorescence intensity ratios (F/F_0) for **1** (F) relative to 5-methoxytryptophol (F_0) as a function of solvent and temperature

	F/F_0		Φ_{spl}	
T (°C)	Water	EPA	Water	EPA
65	0·02		0·13	
45	0·04		0·11	
25	0·03	0·12	0·10	0·094
5	0·03		0·090	
−10		0·17		0·078
−70		0·53		0·031
−85		0·54		0·025

transfer and splitting. The partitioning of dimer radical anion between these paths depends on their activation barriers. Based on transition-state theory,[9] the rate constants for splitting (k_{spl}) and back electron transfer (k_{bet}) are related to their respective free energies of activation by

$$k_{spl}/k_{bet} = \exp[-(\Delta G^{\ddagger}_{spl} - \Delta G^{\ddagger}_{bet})/RT] \quad (1)$$

The rate constants are related to the observed quantum yield of dimer splitting and the quantum efficiency of formation of the precursor charge-separated species ϕ_{css} by

$$\Phi_{spl} = \frac{k_{spl}}{k_{bet} + k_{spl}} \cdot \phi_{css} \quad (2)$$

which can be rearranged to

$$\frac{k_{spl}}{k_{bet}} = \frac{\Phi_{spl}}{\phi_{css} - \Phi_{spl}} \quad (3)$$

If it is assumed that attachment of dimer to indole simply provides a new decay path (electron transfer[8e]) for the indole in its excited singlet state, then the quantum yield of formation of the charge-separated species (ϕ_{css}) is related to the observed fluorescence of **1** (F) relative to that of a corresponding indole without attached dimer (F_0) by*

$$\phi_{css} = 1 - (F/F_0) \quad (4)$$

Combination of equations (3) and (4) with equation (1) and conversion to logarithmic form gives

$$\ln\left[\frac{\Phi_{spl}}{1 - (F/F_0) - \Phi_{spl}}\right] = -(\Delta G^{\ddagger}_{spl} - \Delta G^{\ddagger}_{bet})/RT \quad (5)$$

Finally, substitution of $\Delta H^{\ddagger} - T\Delta S^{\ddagger}$ for $\Delta G^{\ddagger}$ and rearrangement gives

$$\ln\left[\frac{\Phi_{spl}}{1 - (F/F_0) - \Phi_{spl}}\right] = -\frac{(\Delta H^{\ddagger}_{spl} - \Delta H^{\ddagger}_{bet})}{RT} + \frac{(\Delta S^{\ddagger}_{spl} - \Delta S^{\ddagger}_{bet})}{R} \quad (6)$$

Hence the activation parameters for the competing pathways can be evaluated from measurements of splitting quantum yield and fluorescence intensity at various temperatures by plotting the left side of equation (6) versus $1/T$. Data obtained from **1** in water and in EPA over the temperature ranges 5–65 °C and −85 to 25 °C, respectively, are plotted in this way in Figure 2. Also shown are the linear least-squares lines

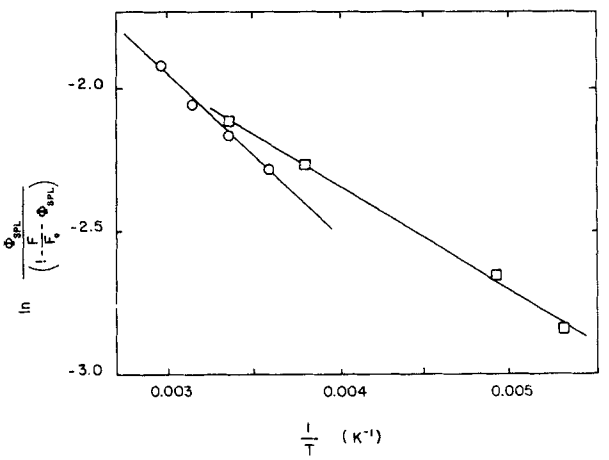

Figure 2. Temperature dependence of cycloreversion of **1** to **2** in water (○) and EPA (□)

*This equation is derived from the following: $F_0 = k_f/(k_f + k_d)$, $F = k_f/(k_f + k_d + k_{et})$ and $\phi_{css} = k_{et}/(k_f + k_d + k_{et})$, where the subscript f signifies fluorescence, d non-radiative decay (other than by electron transfer) and et electron transfer. The derivation also requires the use of $F/F_0 = [(k_f + k_d + k_{et}) - k_{et}]/(k_f + k_d + k_{et})$.

Table 2. Activation parameters for photolysis of **1** in water and EPA

Solvent	$\Delta\Delta G^{\ddagger}$ [a] at 298 K (kcal mol^{-1})	$\Delta\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})
Water	1·3 ± 0·1	1·1 ± 0·1	−0·51 ± 0·25
EPA	1·3 ± 0·1	0·72 ± 0·03	−1·8 ± 0·1

[a] $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{spl} - \Delta G^{\ddagger}_{bet}$. The activation enthalpy and activation entropy differences are defined analogously.

through the data (for water, $r = 0{\cdot}996$; for EPA, $r = 0{\cdot}998$). The activation enthalpy differences ($\Delta\Delta H^{\ddagger}$) were obtained from the slopes, and the activation entropy differences ($\Delta\Delta S^{\ddagger}$) were obtained from the intercepts. From these values the activation free energy differences ($\Delta\Delta G^{\ddagger}$) for **1** in both water and EPA at 25 °C were calculated. The values of these activation parameters are given in Table 2.

DISCUSSION

In the linked dimer–sensitizer system **1**, absorption of light by the indole results in efficient electron transfer to the covalently linked pyrimidine dimer. The pyrimidine dimer radical anion thereby formed undergoes either cycloreversion or back electron transfer. This mechanism is schematically represented by

$$\text{D–I} \xrightarrow{h\nu} \text{D–I}^* \rightarrow$$

1

$$\text{D}^{\cdot-}\text{–I}^{+\cdot} \begin{cases} \xrightarrow{k_{bet}} \text{D–I} \\ \xrightarrow{k_{spl}} \text{Py–Py}^{\cdot-}\text{–I}^{+\cdot} \rightarrow \text{Py–Py–I} \end{cases}$$

2

The fact that the quantum yield of splitting is low (e.g. $\Phi = 0{\cdot}10$ in water at room temperature) implies that back electron transfer is the faster process. From the activation enthalpy and entropy data (Table 2 and Fig. 2), the free energy of activation for splitting in water or EPA at 25 °C was found to be 1·3 kcal mol^{-1} higher than the free energy of activation for back electron transfer. A semi-quantitative energy diagram

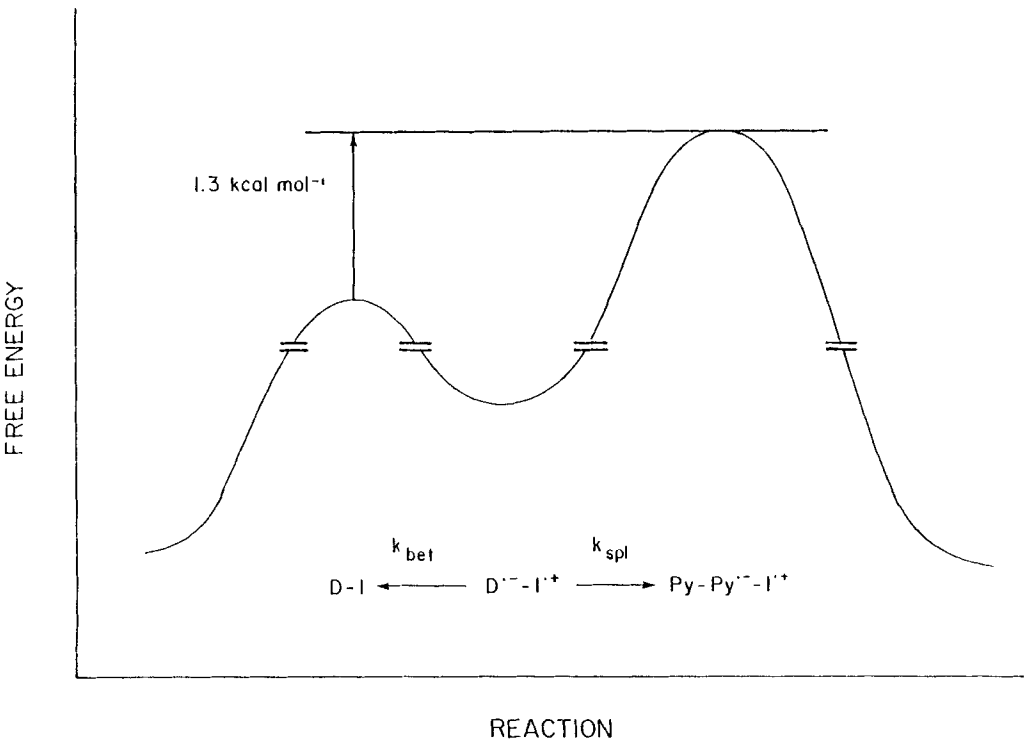

Figure 3. Semi-quantitative energy diagram for the two paths available to the charge-separated species ($D^{\cdot-}$–$I^{+\cdot}$), back electron transfer (k_{bet}) and splitting (k_{spl})

depicting these mechanistic alternatives is shown in Fig. 3. The charge-separated species ($D^{-\cdot}$–$I^{+\cdot}$), generated by photoinitiated electron transfer from indole to dimer, is located centrally on the abscissa. This species faces two energy barriers, one for back electron transfer, which regenerates D–I, and one for splitting, which produces a pyrimidine and a pyrimidine radical anion (Py–$Py^{-\cdot}$–$I^{+\cdot}$).

Although the free energy differences for splitting and back electron transfer are the same (within experimental error) in the two solvents at 25 °C, the enthalpy and entropy contributions to the free-energy barriers are not the same for the two solvents. In water, almost all of the free energy of activation difference arises from the enthalpy component (1·1 out of 1·3 kcal mol^{-1}). The enthalpic and entropic contributions to $\Delta\Delta G^{\ddagger}$ in EPA, however, are more nearly equal ($\Delta\Delta H^{\ddagger}$ accounts for 0·72 out of 1·3 kcal mol^{-1}).

Since splitting produces a pyrimidine radical anion in which charge is more delocalized than in the dimer radical anion, loss of solvation occurs at the transition state for splitting.[10] This manifests itself in the enthalpy component of the free energy barrier. The magnitude of $\Delta\Delta H^{\ddagger}$ is smaller in EPA than water, presumably because of the lower polarity of the solvent mixture EPA (even if the most polar component, ethanol, preferentially solvates the charge-separated species).[10] We have previously found that electron delocalization in the dimer radical anion itself is significant,[6] and this must mitigate the overall increase in charge delocalization that results from splitting.

During splitting, both bond breaking and desolvation may occur on the same time scale. Back electron transfer, on the other hand, does not consist simply of charge annihilation and consequent desolvation at the transition state. Indeed, if this were the case, back electron transfer would experience a greater loss of solvation than splitting does, and $\Delta\Delta H^{\ddagger}$ would probably be negative.

Electron-transfer theories formulate an essential reorganization of solvent and reactants that must occur *prior* to electron transfer.[11] Such reorganization arranges solvent and reactant nuclei in such a way that the energy of the system at the instant of actual electron transfer is the same whether the electron is on the donor or on the acceptor. The reorganization of solvent contributes to the free-energy barrier, and it has enthalpic and entropic components. In the case of **1** in water, the enthalpic component of the solvent reorganization energy is apparently 1·1 kcal mol^{-1} less than the enthalpy change due to partial loss of solvation during splitting.

Entropic effects on splitting and back electron transfer nearly cancel each other in water ($-T\Delta\Delta S^{\ddagger} = 0{\cdot}2$ kcal mol^{-1} at 298 K), but are slightly larger in EPA ($-T\Delta\Delta S^{\ddagger} = 0{\cdot}5$ kcal mol^{-1} at 298 K). This may be a consequence of a higher ordering required of the less polar solvent mixture (EPA) prior to the actual electron transfer step.*

These results have potential implications for the enzyme-catalyzed cycloreversion of dimers in DNA by the photolyases, a highly efficient process ($\Phi = 1$)[5a,b,12] that is temperature dependent.[4b,g] We[8a,c] and others[5b,c] have suggested that the photolyases prevent back electron transfer and/or reduce the energy barrier faced by splitting.[8b] Although specific catalytic steps (i.e. transfer of the charge away from the primary donor) might effectively accomplish these results, the degree of polarity of the active site may also influence splitting efficiency.

The chromophore pocket of at least one photolyase is thought to be hydrophobic.[5a] Based on the results obtained for **1** in EPA, less polar environments are expected to favor splitting relative to back electron transfer via a reduced enthalpy contribution to the splitting barrier, but to retard splitting due to promotion of back electron transfer, as a consequence of entropy effects.† Whether hydrophobic active sites are tailored to reduce the enthalpy contribution to the barrier faced by splitting and/or to counteract the unfavorable entropy effects associated with splitting relative to back electron transfer must await further investigation of the natural systems.

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* These inferences must be drawn with caution, however, because electron transfer may be non-adiabatic.[13] For an adiabatic process the transmission coefficient [which is $\varkappa$ in the transition-state formulation of $k = (\varkappa k_{\text{Boltzmann}}\ T/h)\exp(-\Delta G^{\ddagger}/RT)$] is typically taken to be unity, but for a non-adiabatic process $\varkappa$ can be small. As a consequence, the evaluation of $\Delta\Delta S^{\ddagger}$ from the intercept of the plot shown in Figure 2 will be inaccurate because $\varkappa_{spl}$ is different from $\varkappa_{bet}$. In that case $\varkappa_{spl}$ and $\varkappa_{bet}$ will not cancel when the ratio shown in equation (1) is taken.

† An implicit assumption being made here is that the progression of polarity from water to EPA is accompanied by a trade-off between enthalpy and entropy effects, i.e. as one decreases the other increases, with $\Delta\Delta G^{\ddagger}$ remaining approximately constant. Extrapolation to what might be a very non-polar active site is hazardous and is discussed here only as a plausible implication of the results found for **1**. In a natural system the opposing enthalpy and entropy effects might not, of course, be of comparable magnitude, as was found for **1** in EPA ($\Delta\Delta H^{\ddagger} = 0{\cdot}72$ kcal mol^{-1}; $-T\Delta\Delta S^{\ddagger} = 0{\cdot}54$ kcal mol^{-1} at 298 K). Further, the relative magnitude of the opposing effects for a given active site with a specific polarity might be such as to cause a preponderance of splitting over back electron transfer. In other words, $\Delta\Delta G^{\ddagger}$ might be considerably less than the value found for water and EPA.

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