

Kinetics of the photoinduced dissociative electron transfer reduction of the antimalarial endoperoxide, Artemisinin

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Abstract

The rate constants (k) for reactions between a series of excited singlet state donors and the antimalarial agent, Artemisinin (ART), were measured in acetonitrile using fluorescence quenching techniques. A plot of $\log(k)$ correlates with the excited state oxidation potential of the donor, $E_{D^{\bullet+}/D^*}$, while a similar plot of $\log(k)$ versus the singlet energy of the donor, E_s , which if linear would indicate an energy transfer reaction process, shows a poor correlation. The results suggest that the determined rate constants are for dissociative electron transfer (ET) from the excited state donor to the O–O bond in ART. Using our recently determined standard dissociative reduction potential for ART, E_{diss}^0 , the rate constants are related to the free energy of ET, ΔG_{ET}^0 . Analysis of the kinetic data as a function of ΔG_{ET}^0 correlates well with theories of ET modified for the non-adiabatic nature of the ET to peroxides. A number of thermochemical parameters are estimated from the analysis, in particular the intrinsic barrier (ΔG_0^\ddagger) that is comprised of the solvent reorganization energy (λ) and the bond dissociation enthalpy of the O–O bond. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Heme-Fe(II) mediated electron transfer (ET) to the oxygen–oxygen (O–O) bond of the potent antimalarial endoperoxide, Artemisinin (ART) [1–3] is now generally agreed to be the first step in its antimalarial bioactivity and that of its semi-synthetic derivatives [4–9]. Our work [10,11]¹ and the work of others [12,13] have demonstrated that ET to ART is dissociative, resulting in fragmentation of the O–O bond to yield a distonic radical anion, Eq. (1). The reactivity of the distonic radical anion (or an Fe–oxygen related species derived from it) is believed to produce the cytotoxic intermediates responsible for the destruction of the malarial parasite [1–3,5–7]. Despite the many structure–reactivity studies that attempt to understand the reactivity and mechanism of action of ART and other trioxanes few kinetic studies are reported, in particular those of the initial ET process.

In contrast, many studies have investigated the reaction kinetics of excited state donors with peroxides [14–19]. Most of these studies concluded, based on correlations with either the singlet or triplet energies of the donors, that the reaction process was a bimolecular energy transfer from the excited state donors to the peroxide. ET was generally neglected because the calculated energetics for photoinduced energy transfer (PET), predicted little or no driving force. Determination of the driving force for PET is calculated from an expression that relies on knowing the excited state oxidation potential of the donor substrate and the reduction potential of the peroxide.

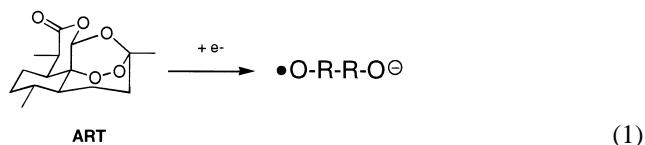
We now know that the reduction potentials for peroxides reported in the past, based on the directly measured reduction peak potentials (E_p) from simple electrochemical experiments, are not an accurate measure of the standard reduction potentials [10,11,20–24]. The rate limiting heterogeneous ET from the electrode to the substrate was not taken into account. For acyclic peroxides, we estimated errors of up to 1 eV (23 kcal mol⁻¹) when the directly observed reduction peak potentials are used without the correction [20,24]. Our recent studies [10,11,20,21], along with those of others [22–24] have concluded, using careful electrochemical analysis, that the standard reduction potentials of O–O bonds in peroxides and endoperoxides are, indeed, significantly less negative than previously reported [15].

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¹ The original value was reported to be -0.89 V versus SCE, but included an arithmetic mistake in the correction for the double layer. Our accepted value is -0.82 ± 0.10 V versus SCE.

We recently showed, using heterogeneous electrochemical methods that ART undergoes a *concerted* dissociative ET reduction of the O–O bond, where ET and bond fragmentation occurs in a single step, Eq. (1). In the same study, we determined the first accurate value of the standard dissociative reduction potential (E_{diss}^0) of ART: -0.82 V versus SCE in *N,N*-dimethylformamide (DMF) [11]. This value, 0.8 eV more positive than where the irreversible reduction is observed electrochemically, is the thermodynamic value required to calculate the feasibility of ET from a particular biological donor. Using theories of ET we showed how understanding the ET process can provide other thermochemical information about the substrate.



For the first time, the bimolecular homogeneous ET kinetics for the reaction from a series of singlet excited state donors to ART in acetonitrile solution are reported. Using the accurate standard reduction potential of ART, this study examines how the kinetics of ET varies as a function of the overall driving force for electron transfer, ΔG_{ET}^0 . In addition, our analysis of the kinetic data provides insights into the factors that control PET to ART and may provide a better understanding of ET in the biological environment.

2. Experimental

All of the fluorescent donors used in this study are commercially available from Aldrich. When available, scintillation or gold label grades with purity >99% were used. The other solids were either sublimed and/or recrystallized prior to use. *N,N*-dimethylaniline and *N,N*-diethylaniline were fractional distilled under reduced pressure prior to use. Spectroscopic grade (BDH) acetonitrile was used as received. ART was available from Aldrich and used as received.

2.1. Fluorescence quenching

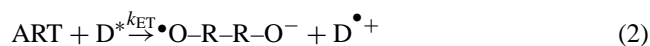
Fluorescence emission and excitation spectra were measured at room temperature using a Fluorolog-311 spectrofluorimeter interfaced to a personal computer with Version 2.2 DataMax software for Windows. The spectrometer uses a 450 W xenon lamp and single-grating monochromators for both emission and excitation. UV–Vis absorption spectra were measured using a Varian Cary 100 double-beamed UV–Vis recording spectrometer. Absorption measurements were performed prior to and at the end of each Stern–Volmer experiment to ensure that ART was not absorbing light at the excitation wavelength at any of the concentrations used.

A stock solution of each fluorescent donor was prepared by sonicating 10–20 mg samples in 100 ml solutions of

acetonitrile for 15 min. Subsequent donor concentrations ranging from 1.0×10^{-4} to 1.0×10^{-6} M were prepared and used for the experiments. The optical density of each solution was typically kept below 0.3 at the 0,0 band. Samples were contained in a 0.7 mm² Suprasil quartz cell and sealed with a Teflon septum. Before the initial addition of ART and thereafter, the solution was purged with nitrogen gas for 10–15 min to remove oxygen. Precautions were taken to prevent volume changes due to evaporation of solvent. Various concentrations of ART were prepared by weighing them directly into the solution of donor. Rate constants were determined from the average of at least two separate experiments that consisted of a minimum of five data points.

3. Results and discussion

The kinetics of ET from a series of fluorescent excited state donors to ART was determined using Stern–Volmer quenching experiments; the overall reaction is described in Eq. (2). The donors were chosen such that the excited state oxidation potentials, $E_{\text{D}^{\bullet+}/\text{D}^*}$, calculated from Eq. (3), varied over a wide range of energies (see Table 1). The principles of Stern–Volmer quenching are well-established [25]. To explain briefly, the quantum yield of fluorescence of a donor in the absence of any quencher (Φ_0) relative to the quantum yield in the presence of varying concentrations of the quencher (Φ) (in our case, ART) is related to the rate constant for reaction as depicted in Eq. (4), where k is the rate constant and τ the singlet fluorescence lifetime of the excited state donor. In practice, it is the fluorescence intensity and not the quantum yield that is measured:



$$E_{\text{D}^{\bullet+}/\text{D}^*}^0 \text{ (kcal mol}^{-1}\text{)} = 23.06(E_{\text{D}^{\bullet+}/\text{D}}^0 - E_s) \quad (3)$$

where both E_s , singlet energy, and $E_{\text{D}^{\bullet+}/\text{D}}^0$ are in eV.

$$\frac{\Phi_0}{\Phi} = 1 + k\tau[\text{ART}] \quad (4)$$

The fluorescence spectra of a variety of donors were measured in acetonitrile in the absence and presence of increasing concentrations of ART. Fig. 1 illustrates the quenching plots of two excited state donors by ART: chrysenes and *N,N,N',N'*-tetramethylbenzidine, respectively. This figure demonstrates the effect on the emission intensity on adding ART incrementally to a solution of donor. In each case examined, the addition of ART resulted in a decrease of the fluorescence intensity and no new emission bands were ever observed. To ensure that the observed decrease in fluorescence intensity was not due to dilution effects or to inner filter effects caused by ART absorbing light, an UV–Vis absorption spectrum of the solution was measured after each kinetic study.

Table 1

Rate constants for ET from excited singlet state donors (D^*) to ART measured in acetonitrile by fluorescence quenching techniques at 25°C

Donor	$E_{D^{\bullet+}/D}$ (V versus SCE)	E_s (eV)	$E_{D^{\bullet+}/D^*}$ (eV) ^b	τ (10^{-9} s)	k (10^8 M ⁻¹ s ⁻¹)	ΔG_{ET}^0 (kcal mol ⁻¹) ^a
<i>N,N,N',N'</i> -tetramethylphenylenediamine	0.16 ^c	3.37	-3.21	7.1 ^d	22	-55.1
<i>N,N,N',N'</i> -tetramethylbenzidine	0.43 ^c	3.60	-3.17	10.0 ^e	130	-54.2
<i>N,N</i> -dimethylaniline	0.79 ^c	3.83	-3.04	2.8 ^d	150	-51.2
<i>N,N</i> -diethylaniline	0.76 ^c	3.80	-3.04	2.8 ^f	120	-51.2
Indole	1.21 ^g	4.24	-3.03	4.6 ^d	51	-51.0
Acenaphthene	1.21 ^h	3.89	-2.68	39.6 ⁱ	22	-42.9
Naphthalene	1.54 ^h	4.01	-2.47	105 ^j	7.4	-38.0
Anthracene	1.09 ^h	3.30	-2.21	5.8 ^k	6.0	-32.1
Pyrene	1.16 ^h	3.34	-2.18	323 ⁱ	1.3	-31.4
Chrysene	1.35 ^h	3.45	-2.10	42.6 ^d	1.9	-29.5
Benzo(<i>ghi</i>)perylene	1.01 ^h	3.10	-2.09	119 ⁱ	2.1	-29.3
Phenanthrene	1.50 ^h	3.59	-2.09	57.5 ^l	2.4	-29.3
Perylene	0.85 ^h	2.85	-2.00	6.0 ^k	1.3	-27.2
Fluoranthene	1.45 ^h	3.16	-1.71	46.4 ⁱ	0.49	-20.5
Coronene	1.23 ^h	2.87	-1.64	299 ⁱ	0.096	-18.9

^a Calculated using Eq. (5) and $E_{diss}^0 = -0.82$ V versus SCE.^b Calculated using Eq. (3).^c P. Iwa, U.E. Steiner, E. Vogelmann, H.E.A. Kramer, J. Phys. Chem. 86 (1982) 1277.^d I.B. Berlman, Handbook of Fluorescence Spectra of Aromatic Molecules, 2nd Edition, Academic Press, New York, 1971.^e S. Hashimoto, J.K. Thomas, J. Phys. Chem. 88 (1984) 4044.^f A.E.W. Knight, B.K. Selinger, Chem. Phys. Lett. 10 (1971) 43.^g A.I. Novaira, C.D. Borsarelli, J.J. Cosa, C.M. Previtali, J. Photochem. Photobiol. A 115 (1998) 43.^h E.S. Pysh, N.C. Yang, J. Am. Chem. Soc. 85 (1963) 2124.ⁱ Measured.^j S.L. Murov, I. Carmichael, G.L. Hug, Handbook of Photochemistry, 2nd Edition, Marcel Dekker, New York, 1993.^k W.R. Ware, J. Phys. Chem. 66 (1962) 455.^l W.L. Wallace, R.P. Van Duyne, F.D. Lewis, J. Am. Chem. Soc. 98 (1976) 5319.

The fluorescence intensity ratio of the initial spectrum without ART relative to the intensity with various concentrations of quencher were plotted versus the concentration of ART according to Eq. (4). In all cases, the Stern–Volmer plots were linear ($R^2 > 0.960$) and consisted of a minimum of five data points. Values of k were determined from the slopes of these plots ($k\tau$) using known or measured values for the excited state lifetimes of the donors. Representative plots for a number of donors are shown in Fig. 2 and the data are summarized in Table 1.

Figs. 3 and 4 illustrate the correlation of the measured $\log(k)$ values with the singlet energy, E_s , of each donor and the free energy of ET, ΔG_{ET}^0 , respectively. The linear correlation with E_s is poor ($R^2 = 0.525$), suggesting that the quenching mechanism is not by energy transfer. In contrast, the plot of $\log(k)$ with ΔG_{ET}^0 , shows the expected quadratic correlation for an ET process, and thus supports the ET dissociative reductive cleavage mechanism. Because of the nature of the dissociative ET processes, back electron transfer, or the reverse of Eq. (2) to give peroxide, is not important. The $\log(k)$ data appears to asymptotically reach the diffusion controlled limit of 2×10^{10} M⁻¹ s⁻¹ for the most exothermic reactions. Overall, the measured rate constants vary by a factor of 1600 over the 36 kcal mol⁻¹ free energy range.

The $\log(k)$ values can be correlated to the free energy change for the ET reaction, ΔG_{ET}^0 , calculated according to

Eq. (5) (where C is the Coulombic term, considered negligible in acetonitrile) using our reported value for the E_{diss}^0 (ART). Although the value of the standard reduction potential for ART was measured in DMF the E_{diss}^0 of peroxides are similar in acetonitrile [20,21]. We wish to reiterate that if the irreversible reduction peak potential (E_p) was used instead of the thermodynamic E_{diss}^0 (ART), then the ΔG_{ET}^0 would be shifted to more positive energies (less driving force) by ca. 18 kcal mol⁻¹.

$$\Delta G_{ET}^0 = 23.06(E_{D^{\bullet+}/D^*}^0 - E_{diss}^0(\text{ART})) + C \quad (5)$$

The $\log(k)$ versus ΔG_{ET}^0 data in Table 1 can be fit to a form of the Marcus expression derived for dissociative ET by Savéant [26–30], which relates the activation free energy, ΔG^\ddagger , to the reaction free energy, ΔG_{ET}^0 , Eq. (6) and to the Eyring expression, Eq. (8). Savéant's expression is similar to the well-known Marcus equation with the exception that the intrinsic barrier (ΔG_0^\ddagger) contains contributions from the bond dissociation enthalpy (BDE) of the relevant bond (in this case the O–O bond) in addition to the solvent reorganization energy (λ), Eq. (7) [27]. The fit, shown as a solid line through the data in Fig. 4, generates values for ΔG_0^\ddagger as well as provides a reasonable estimate of the pre-exponential term (κZ). From the fit of the $\log(k)$ versus ΔG_{ET}^0 plot, values of $\log(\kappa Z) = 9.8$ and $\Delta G_0^\ddagger = 12.1$ kcal mol⁻¹ are determined. The fit indicates the data are nearing the inverted

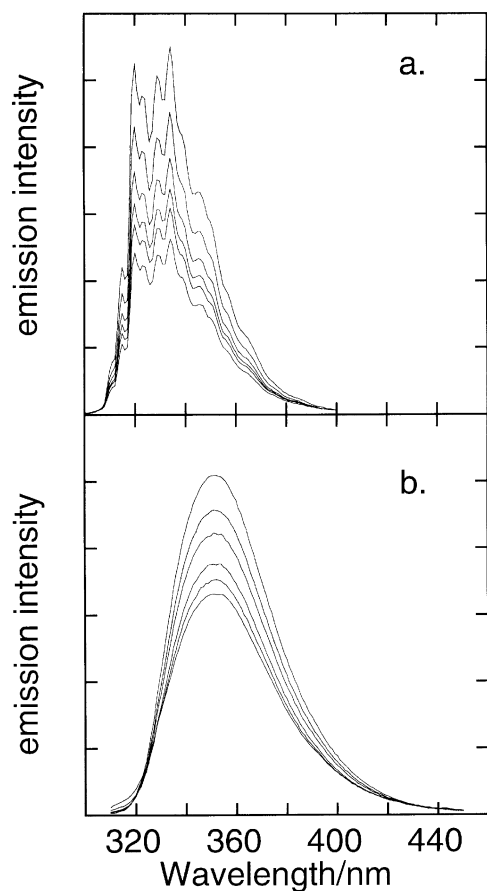


Fig. 1. Fluorescence spectra of: (a) chrysene and (b) N,N,N',N' -tetramethylbenzidine in MeCN measured at 25°C illustrating the decrease in the emission intensity with increasing concentration of ART.

region. We do not imply that we would observe data in the inverted with sensitizers with larger driving forces, since it is seldom observed in PET. A fit to the Rehm–Weller expression shows the usual plateau at the diffusion limit. This

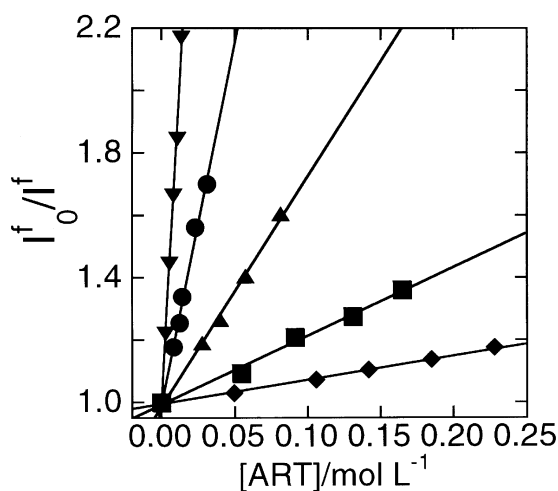


Fig. 2. Representative Stern–Volmer plots for ART quenching the fluorescence of: (▼) naphthalene; (●) indole; (▲) chrysene; (■) fluoranthene; (◆) perylene.

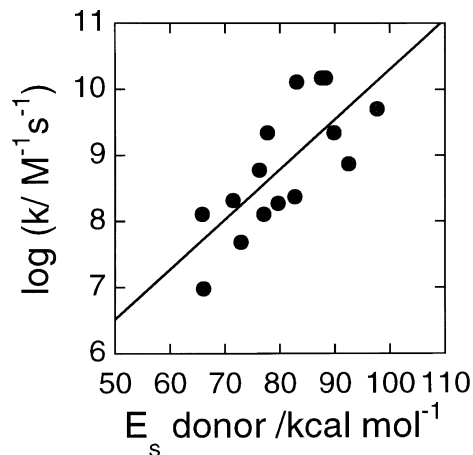


Fig. 3. Plot illustrating the variation of $\log(k)$ with a variety of excited state donors quenched by ART as a function of the donor's singlet energy, E_s .

fit yields similar, but slightly higher value of the intrinsic barrier.

In a recent publication, we showed that ET to the O–O bond of acyclic peroxides has a high degree of non-adiabaticity that we attributed to poor electronic coupling between the peroxide and electron potential energy surfaces [20,21]. For these acyclic peroxides, the transmission coefficient, κ , was determined to be equal to 0.01. In an adiabatic ET $\kappa = 1$. Thus, in the present case the usual adiabatic $\log(Z) = 11.5$ becomes $\log(\kappa Z) = 9.5$; this value is in agreement with the pre-exponential term determined in the present study. It should be noted that the fit of the data using the usual adiabatic value of $\log(Z) = 11.5$ is poor and results in ΔG_0^\ddagger values that are 4 kcal mol⁻¹ larger and thus leads to unreasonable estimates of the λ or the BDE

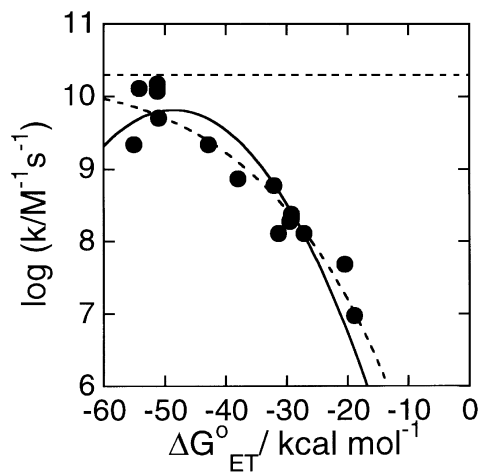


Fig. 4. Plot illustrating the variation of $\log(k)$ with a variety of excited state donors quenched by ART as a function of the free energy for ET, ΔG_{ET}^0 . The solid line through the data is a fit to the Marcus expression using Eqs. (6) and (8). The broken line is the fit to the Rehm–Weller expression [D. Rehm, A. Weller, *Isr. J. Chem.* 8 (1970) 259].

(see below).

$$\Delta G^\ddagger = \Delta G_0^\ddagger \left(1 + \frac{\Delta G_{\text{ET}}^0}{4\Delta G_0^\ddagger} \right)^2 \quad (6)$$

$$\Delta G_0^\ddagger = \frac{1}{4}(\text{BDE} + \lambda) \quad (7)$$

$$k = \kappa Z \exp\left(-\frac{\Delta G^\ddagger}{RT}\right) \quad (8)$$

The value estimated for ΔG_0^\ddagger in the present case is higher than the value of 8.4 kcal mol⁻¹ determined from our heterogeneous electrochemical study of ART [11]. In this earlier study we used an average λ value of 10.9 kcal mol⁻¹, from data for a number of acyclic peroxides, to estimate the O–O BDE in ART to be 24 kcal mol⁻¹. The value of the λ can also be estimated from an expression derived by Savéant, Eq. (9), for the electron exchange reactions between aromatic anion radicals and alkyl halides, where r_D and r_{ABeff} are the radius of the donor and the effective radius of the acceptor molecules, respectively. Thus, values for the radius of the donor, r_D , and the radius of the acceptor, r_{AB} , are required for a reasonable estimate of λ . An average r_D of 3.80 Å was chosen for the donors [31]. The radius of ART was determined to be 4.42 Å from the reported density [32] and using the $r_{\text{AB}} = [(3M/4\pi N_A \rho)^{1/3}]$ [29]. This molecular radius was then transformed into the effective radius to better represent the size and portion of the molecule where the electron is accepted. The effective radius was determined using $r_{\text{ABeff}} = [r_B(2r_{\text{AB}} - r_B)/r_{\text{AB}}]$, where AB in this case is the radius of ART and B is the effective radius of the *tert*-butyl alkoxide anion, a model of the anion generated in the ET to ART [20]. The effective radius for the *tert*-butyl alkoxide anion determined similarly, is 1.88 Å with AB the radius of *tert*-butyl alkoxide and B the radius of an oxygen atom [20]. This approach leads to an effective radius of ART equal to 2.96 Å. These lead to a value of $\lambda = 15.1$ kcal mol⁻¹ using Eq. (9).

$$\lambda = 2.149 \left(\frac{1}{r_{\text{ABeff}}} + \frac{1}{r_D} - \frac{2}{r_{\text{ABeff}} + r_D} \right) \quad (9)$$

Using Eq. (7) and the values of λ and ΔG_0^\ddagger from above, the BDE for ART is estimated to be 33 kcal mol⁻¹. This value is significantly larger than our original estimate of 24 kcal mol⁻¹ [11]. For comparison, the estimated BDE in the simple endoperoxide, ascaridole, is in the order of 26–28 kcal mol⁻¹ [10,21]. Despite the difference, the determined BDE is still less than that of acyclic peroxides, which have BDEs of 37 kcal mol⁻¹ and are essentially independent of substituent. Endoperoxides and trioxanes are expected to have a lower BDE than acyclic peroxides due to the added strain of the cyclic structures and the eclipsing interaction of the lone pair electrons on the oxygen atoms. Based on our experience with a number of endoperoxides, 28 kcal mol⁻¹ represents an upper limit for the O–O

BDE in ART. When our estimate of the BDE is used instead to determine λ from the ΔG_0^\ddagger , we obtain a value of $\lambda = 20$ kcal mol⁻¹: this is almost twice the value estimated for other endoperoxides and acyclic peroxides [10,21,24].

The above discussion serves to illustrate that the ΔG_0^\ddagger value obtained from PET is larger than that obtained from homogeneous and heterogeneous electrochemical methods. This leads to either a higher BDE value or a higher λ value than previously obtained. Since there is a limited amount of kinetic data and it is near the diffusion limit, there may be some error in defining the curve and the estimating ΔG_0^\ddagger . Using the previous lower value for the intrinsic barrier, no reasonable fit of the data by adjusting $\log(\kappa Z)$, could be achieved. Thus the larger ΔG_0^\ddagger in the present case could either be the result of the BDE or λ . Since the BDE is an intrinsic property, the larger ΔG_0^\ddagger must be the result of extra contributions to λ .

There are several factors that might contribute to the higher λ in this study. The model used to estimate the expected λ (Eq. (9)) may in fact underestimate the value. The model is derived for ET from anion radicals to neutrals and not for PET systems, where charged species are created from two neutral precursors. Upon charge formation there may be an additional contribution to the solvent reorganization energy. Factors such as those that influence dissociative PET are only now being addressed [33,34]. Another key difference in the present case compared to acyclic peroxides and R–X systems, is that on ET to ART, the charge and spin remain in the same molecule, so ET is accompanied by significant structural changes. This would involve some additional *internal* reorganization energy of the strained structure that is not explicitly accounted for in Savéant's model of estimating the *solvent* reorganization energy. In Savéant's model any contribution to the internal reorganization energy is generally considered small compared to the BDE. This may not be true for systems with very low BDEs. The role of additional internal reorganization energy in dissociative ET has been recently discussed for the dissociative oxidation of the oxalate anion [35]. The nature of the factors that contribute to λ , whether from significant contributions from the internal reorganization term in these bicyclic systems or due to the formation of charge in PET, is still a matter for discussion. At the present time there is no clear way to estimate this energy. This aspect of dissociative PET in bicyclic endoperoxides is a topic of current investigation in our laboratory.

4. Conclusion

Rate constants for ET from a series of excited singlet state donors to ART were measured in acetonitrile. Using the recently determined value of E_{diss}^0 for ART, the rate constants were evaluated as a function of the driving force for ET to determine estimates of the ΔG_0^\ddagger and the pre-exponential term. Our results are consistent with our

previous conclusion that ET to O–O bonds in peroxides and endoperoxides contains some degree of non-adiabaticity. Estimates of other thermochemical data relied on Eq. (7) and knowledge of either the BDE or the solvent reorganization energy calculated using conventional methods. The results suggest that the approach used to estimate the solvent reorganization energy may not be the most suitable for PET. This may be the result of reorganization energy that is not generally accounted for in dissociative systems.

Acknowledgements

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