Mechanism of Fast Intramolecular Electron-Transfer Reactions

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Abstract: Solvent motion controls the rate of fast intramolecular electron transfer. This conclusion is based on the finding that τ_1' [$=(\epsilon_{op}/\epsilon_s)\tau_1$] for solvents correlates well (slope = 1) with the relaxation time, τ_{fl}, for intramolecular electron transfers within the initial S_1 states of TNSDMA [6-((4-methylphenyl)amino)-2-naphthalenesulfonyl dimethylamide] and DMAB [4-(dimethylamino)benzonitrile]. Two approaches toward understanding the result are used. A simplified molecular model [microscopic steps: (a) electron transfer, (b) solvent motion (including that which may have preceded step a: only one solvent molecule is shown in motion), and (c) hydrogen motion] illustrates the molecular rearrangements involved in the electron-transfer process. A simplified dipole interaction model [microscopic steps: (a) substrate dipole change in the Franck–Condon state, (b) solvent dipole motion, and (c) electron transfer] shows the changes in electrostatic interactions in the course of the electron-transfer process. Solvent dipolar motion in the absence of the reaction field should be characterized by τ_1', corresponding to the constant charge case outlined by Friedman (Friedman, H. L. *J. Chem. Soc., Faraday Trans. 2* **1983**, *79*, 1465–1467). The movement of the solvent molecule is favored by an energy term proportional to $(1/\epsilon_{op})(\Delta\Delta G/\epsilon_{op})$ and retarded by interaction of the moving solvent molecule with the reaction field of the stationary solvent molecules $(1/\epsilon_s)(\Delta\Delta G/\epsilon_s)$. The kinetic constants are not easily related to these energy terms. The molecular model shows the close relationship between two kinetically similar systems (6,2-ANS and DMAB) and appears to fit additional less-well-studied systems. Explanations for the photophysical behavior of the *N*-methyl-6,2-ANS case and the very fast quenching of the S_1 excited state of a complex rhodamine derivative can be derived from the model. "Slower" electron-transfer processes (e.g., $S_{1,ct} \rightarrow S_{0,np}$ in TNSDMA) exhibit relaxation times that are greater than τ_1 by a factor which varies somewhat with the strength of the solvent–$S_{1,ct}$ interactions (6.8 for ethanol to 3.5 for 1-decanol). The model suggests that this reflects the strength of the organization induced by the ion pair in the solvent and possibly some internal reorganization (bond length and/or angle changes). The model also leads to some insights about the details of the long distance electron transfers reported by Miller, Calcaterra, and Closs (Miller, J. R.; Calcaterra, L. T.; Closs, G. L. *J. Am. Chem. Soc.* **1984**, *106*, 3047–3049).

The conclusion of a long series of investigations is that solvent motion is the controlling factor in the formation and decay of the charge-transfer states of (arylamino)naphthalenesulfonate and (dimethylamino)benzonitrile derivatives.[2-18] We made the remarkable finding that the relaxation of the initially formed $S_{1,np}$ state to the $S_{1,ct}$ state was correlated by the solvent dielectric relaxation parameter, τ_1' [$=(\epsilon_{op}/\epsilon_s)\tau_1$], with a slope of 1.[14,15] (np = nonplanar, ct = charge transfer). This type of relaxation is expected for a polar, polarizable fluid[19] (often denoted as τ_L, the longitudinal relaxation time) and was suggested by Mozumder[19c] and Onsager[19d] to apply to some cases. The same idea was also put forward by theoreticians in a number of studies on solvent effects,[20-24] but the underlying reasons for the correlation we found were not clear. Friedman has analyzed the difference between τ_1 and τ_1' in terms of the basic theory and has pointed out that τ_1' should govern the relaxation of a solvent dipole under the influence of a constant charge.[25] The overall problems of electron-transfer reactions have now been reviewed by Newton and Sutin.[26]

It is important for a chemist to have some understandable physical model for a process. We now propose two related approaches toward understanding the kinetic results. The first approach involves the construction of a simplified molecular model for the transformation of the S_0 state of a key substrate (see below) into a charge-transfer state, $S_{1,ct}$. The second approach involves the designing of a dipole interaction model related to the molecular model. The molecular model includes the sequence (a) electron transfer (or charge rearrangement), (b) solvent motion [including that which may have preceded the electron transfer in step a), and (c) hydrogen motion and illustrates the molecular rearrangements involved in the electron-transfer process. Only *one* solvent molecule is shown in motion. The simplified dipole interaction model [microscopic steps: (a) substrate dipole change through excitation to the Franck–Condon state, (b) solvent dipole motion, and (c) electron transfer] shows the changes in electrostatic interactions in the course of the electron-transfer process. A reaction field dipole sums the dipoles of the other solvent molecules.

The molecular model shows the similarity of two kinetically similar systems (6,2-ANS and DMAB) and appears to fit ad-

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(2) Kosower, E. M.; Dodiuk, H.; Tanizawa, K.; Ottolenghi, M.; Orbach, N. *J. Am. Chem. Soc.* **1975**, *97*, 2167–2178.
(3) Dodiuk, H.; Kosower, E. M. *J. Phys. Chem.* **1977**, *81*, 50–54.
(4) Kosower, E. M.; Dodiuk, H. *J. Am. Chem. Soc.* **1978**, *100*, 4173–4179.
(5) Kosower, E. M.; Dodiuk, H.; Kanety, H. *J. Am. Chem. Soc.* **1978**, 100, 4179–4189.
(6) Kosower, E. M.; Dodiuk, H. *J. Phys. Chem. 82*, **1978**, 2012–2015.
(7) Dodiuk, H.; Kanety, H.; Kosower, E. M. *J. Phys. Chem.* **1979**, *83*, 515–521.
(8) Dodiuk, H.; Kosower, E. M. *J. Phys. Chem.* **1979**, *83*, 2053–2054.
(9) Dodiuk, H.; Kanety, H.; Kosower, E. M. *J. Luminesc.* **1979**, *18/19*, 495–499.
(10) Huppert, D.; Kanety, H.; Kosower, E. M. *Chem. Phys. Lett.* **1981**, *84*, 48–53.
(11) Kosower, E. M. *Acc. Chem. Res.* **1982**, *15*, 259–266.
(12) Kosower, E. M.; Kanety, H. *J. Mol. Struct.* **1982**, *84*, 259–267.
(13) Kanety, H.; Kosower, E. M. *J. Phys. Chem.* **1982**, *86*, 3776–3780.
(14) Huppert, D.; Kanety, H.; Kosower, E. M. *Discuss. Faraday Soc.* **1982**, *74*, 161–175.
(15) Kosower, E. M.; Huppert, D. *Chem. Phys. Lett.* **1983**, *96*, 433–435.
(16) Kosower, E. M.; Kanety, H.; Dodiuk, H.; Striker, G.; Jovin, T.; Boni, H.; Huppert, D. *J. Phys. Chem.* **1983**, *87*, 2479–2484.
(17) Kosower, E. M.; Kanety, H. *J. Am. Chem. Soc.* **1983**, *105*, 6236–6243.
(18) Huppert, D.; Rand, S. D.; Rentzepis, P. M.; Barbara, P. F.; Struve, W. S.; Grabowski, Z. R. *J. Chem. Phys.* **1985**, *75*, 5714.
(19) (a) Fröhlich, H. "Theory of Dielectrics"; Oxford University Press: New York, 1949. (b) Calef, D. F.; Wolynes, P. G. *J. Phys. Chem.* **1983**, *87*, 3387–3400. (c) Mozumder, S. *J. Chem. Phys.* **1969**, *50*, 3153, 3162. (d) Onsager, L. *Can. J. Chem.* **1977**, *55*, 1819.
(20) Hubbard, J.; Onsager, L. *J. Chem. Phys.* **1977**, *67*, 4850.
(21) Hubbard, J. *J. Chem. Phys.* **1978**, *68*, 1649.
(22) van der Zwan, G.; Hynes, J. T. *J. Chem. Phys.* **1982**, *76*, 2993.
(23) Calef, D.; Wolynes, P. *J. Chem. Phys.* **1983**, *78*, 470–482, 4145–4153.
(24) Berne, B. J. *J. Chem. Phys.* **1975**, *62*, 1154–1160.
(25) Friedman, H. L. *J. Chem. Soc., Faraday Trans. 2* **1983**, *79*, 1465–1467.
(26) Newton, M. D.; Sutin, N. *Annu. Rev. Phys. Chem.* **1984**, *35*, 437–480.

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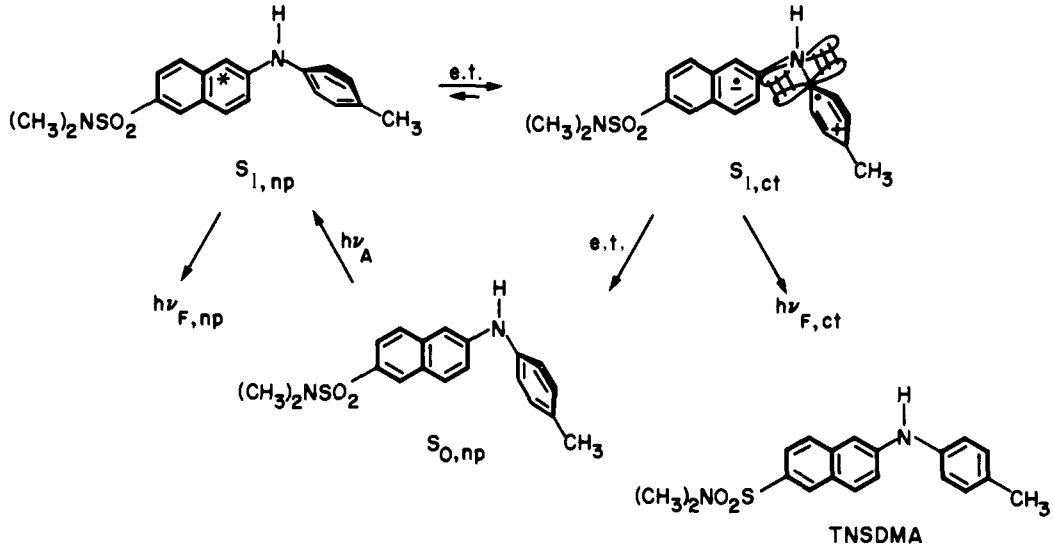
Scheme I

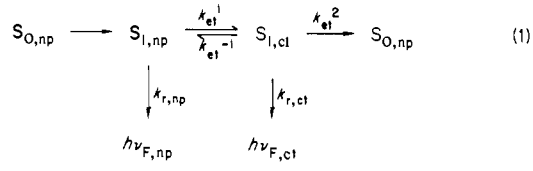


ditional less well-studied systems. Explanations for the behavior of the *N*-methyl-6,2-ANS case (the higher substituent sensitivity of the charge-transfer emission for NCH_3 as opposed to NH derivatives) and the very fast quenching of a complex rhodamine derivative can be derived from the model. The model allows us to clarify the meaning of the "slow" solvent motion-controlled $S_{1,ct} \rightarrow S_{0,np}$ process, as well as the "slow" (or fast) intramolecular electron transfers involving an aryl radical anion and an aryl group attached to a rigid steroid framework,[27]

Scheme I and eq 1 summarize the conclusions of much research[2-18] on ANS derivatives. The conversions of 6-((4-methylphenyl)amino)-2-naphthalenesulfonyl dimethylamide [TNSDMA] are illustrated by formulas for the three states.

Molecular Model

In order to visualize the most important features of the solvent influence on the electron-transfer process, we have formulated a molecular model for the conversion of the ground state of TNSDMA ($S_{0,np}$) into a charge-transfer state ($S_{1,ct}$) (Figure 1).

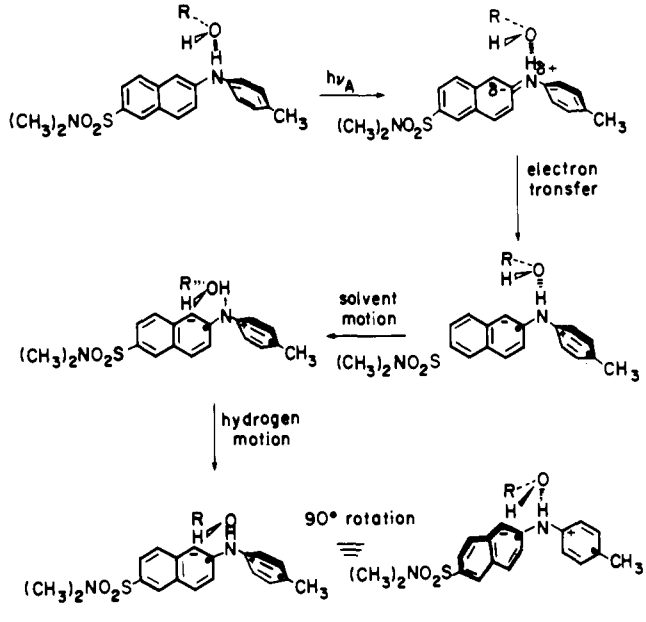


The model is simplified through (a) use of one solvent molecule rather than the two (or three or four) which constitute the local solvation group and (b) the showing of only one set of specific resonance structures. The individual steps are not, in fact, physically separable but are selected so as to create an understandable physical model for the overall process. In particular, that part of the solvent relaxation which occurs prior to the transition state for electron transfer is not shown. Excitation of the $S_{0,np}$ state leads to a locally excited state, $S_{1,np}$, followed by the steps (1) electron transfer, (2) solvent motion, and (3) hydrogen motion. Molecular formulas show the result of each step. The last formula is also presented in a 90° rotated form so as to indicate the geometry of the solvent molecule–substrate combination more clearly.

Dipole Interaction Model

To clarify the electrostatic interactions involved in the electron-transfer process, we have constructed a dipole interaction model in which the important dipolar interactions are illustrated. Simplifications in this model include (a) the use of an approximate molecular dipole for the one solvent molecule, (b) summation of the dipoles of all other solvent molecules as a reaction field dipole, and (c) the showing of only the critical dipole changes for the substrate molecule. The four states shown in Figure 2 correspond to (1) the ground state, (2) the Franck–Condon state (before solvent motion) with an indication of the state energy after vibrational relaxation within the substrate molecule, (3) the transition state for the conversion of the initial excited state to the relaxed charge-transfer state, and (4) the charge-transfer state. The transition state for the conversion of the $S_{1,ct}$ to the $S_{0,np}$ state is also indicated.

We also include in Figure 2 a free energy diagram, showing the $S_{0,np}$, the $S_{1,np}$, and the $S_{1,ct}$ states. The dielectric constant applicable to the interaction of the solvent molecules and the



Molecular Scheme for 6,2-ANS

Figure 1. Molecular model for the conversion of the ground state of TNSDMA [6-((4-methylphenyl)amino)-2-naphthalenesulfonyl dimethylamide] to the charge transfer state, $S_{1,ct}$, via excitation to the $S_{1,np}$ state. One solvent molecule is associated with the substrate molecule. Electron transfer changes the nature of the electrostatic interactions between the solvent and the substrate. The solvent molecule rotates from a position in the plane of the naphthalene ring to one in the plane of the phenyl ring. That part of the solvent motion which occurs prior to electron transfer (that indicated in the dipole interaction model) is not shown for the sake of simplicity. The hydrogen attached to the nitrogen rotates with the solvent molecule.

(27) Miller, J. R.; Calcaterra; Closs, G. L. *J. Am. Chem. Soc.* **1984**, *106*, 3047–3049.

Table I. Comparison of Solvent Dielectric Relaxation Times (τ_1 and τ_1') and Fluorescence Decay Times ($\tau_{d,np}$ and $\tau_{d,ct}$) for 6-((4′-Methylphenyl)amino)-2-naphthalenesulfonyl Dimethylamide (TNSDMA)

solvent	n^{20}_D	ϵ	τ_1,[a] ps	τ_1',[b] ps	$\tau_{d,np}$,[c] ps	$\tau_{d,ct}$, ps	$\tau_{d,ct}/\tau_1$
methanol	1.3285	32.6	58[d]	3.7		400	6.9
ethanol	1.3611	24.3	175[d]	9.8	<20	1200	6.8
1-propanol	1.3853	20.1	408	39	53	1940	4.8
1-butanol	1.3972	17.1	624	71	81	2680	4.3
1-pentanol	1.4064	13.9	850	121	95	3940	4.6
1-hexanol	1.4226	13.2	1106	170	106	4750	4.3
1-octanol	1.4295	10.2	1597	320	300	5300	3.3
1-decanol	1.4372	8.1	1828	464	400	6410	3.5

[a] Dielectric relaxation times at 23 °C, ascribed to breaking of hydrogen bond and reorientation of the molecule. (Garg, S. K.; Smyth, C. P., *J. Phys. Chem.* **1965**, *69*, 1294. Böttcher, C. J. F.; Bordewijk, P.; "Theory of Electric Polarization"; Elsevier: Amsterdam, 1978; Vol. 2, p 561ff]. [b] $\tau_1' = (\epsilon_{op}/\epsilon_s)\tau_1$. [c] At 23 °C. [d] Values interpolated from those reported by Bertolini, Cassettari, and Salvetti (Bertolini, D.; Cassettari, M.; Salvetti, G. *J. Chem. Phys.* **1983**, *78*, 365–372). Somewhat different relaxation times (methanol, 68 ps, and ethanol, 129 ps) are derived from the results of Saxton et al. (Saxton, J. A.; Bond, R. A.; Coats, G. T.; Dickinson, R. M. *J. Chem. Phys.* **1962**, *37*, 2132.

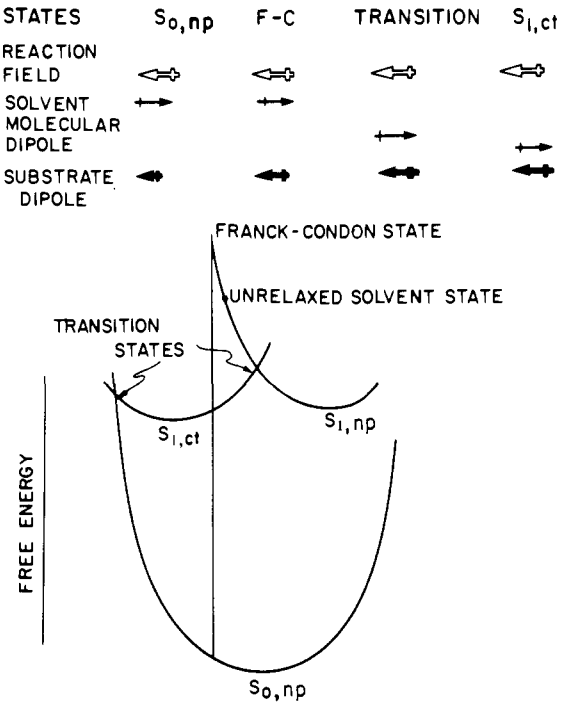


Figure 2. Dipole interaction model for the conversion of the ground state of TNSDMA to the charge-transfer state, $S_{1,ct}$, via excitation to the $S_{1,np}$ state. The location of the Franck–Condon (F–C) state is indicated along with the position of a state in which the substrate molecule is vibrationally relaxed but the solvent molecules are not yet relaxed ("unrelaxed solvent state"). One solvent molecular dipole is shown. The overall process involves a change in the position of the solvent molecular dipole and an increase in the size of the substrate dipole. The crossing from the $S_{1,np}$ state to the $S_{1,ct}$ state is denoted as a transition state. The transition state for the conversion of the $S_{1,ct}$ state to the ground state, $S_{0,np}$ state, is also marked.

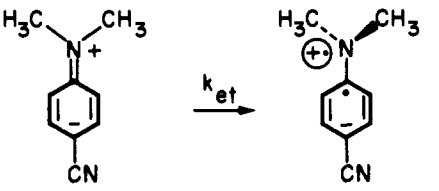
substrate molecules which are immediate neighbors is best approximated by ϵ_{op}. (Interaction via other solvent molecules would contribute only a small amount to the interaction energy.)

The energy of the transition state will be raised by the interaction of the solvent molecular dipole with the reaction field dipole by an amount equal to $\Delta\Delta G/\epsilon_s$.

The electron-transfer (charge displacement) process for the dipole interaction model would be characterized by the relaxation time $\tau_1' = (\epsilon_{op}/\epsilon_s)\tau_1$. The model shown in Figure 2 suggests that the motion of the solvent molecular dipole is driven by the change in the substrate dipole. The dipole interaction model represents a view of the dynamics of the molecular model. (The events illustrated in the two models are not exactly parallel for the sake of simplicity but could be made more so by including in the molecular model that part of the solvent relaxation which occurs prior to the $S_{1,np} \rightarrow S_{1,ct}$ electron transfer.) Bixon and Jortner[28]

(28) Bixon, M.; Jortner, J. *Discuss. Faraday Soc.* **1983**, *74*, 17–29.

Scheme II



have pointed out that fast charge transfer after solvent relaxation would exhibit τ_1' behavior. This model is somewhat different from that which has been proposed by Marcus (Marcus, R. A., private communication) for the TNSDMA case, with a fast electron transfer (tunneling) followed by a τ_1'-controlled relaxation of the solvent. Marcus has suggested that time-resolved emission spectra of TNSDMA could reveal whether or not states with intermediate-type solvation exist between the initial and final states, and experiments (like those cited below for DMAB (4-(dimethylamino)benzonitrile)) will be undertaken to examine this aspect of the problem. The remarkable parallelism between the experimental relaxation times for the first electron-transfer step for TNSDMA and τ_1' in a series of linear alkanols is shown in Table I. (The slope for the correlation is close to 1.)[15] The rise time for the formation of the charge-transfer state is longer than the decay time of the $S_{1,np}$ state, as is reasonable in terms of the free energy diagram (Figure 2).

(Dimethylamino)benzonitrile (DMAB)

The model for intramolecular electron transfer is not highly dependent on the nature of the molecule. As we have already reported,[15] intramolecular electron transfer in (dimethylamino)benzonitrile (Scheme II) has essentially the same relaxation times as those for TNSDMA in the same solvents.

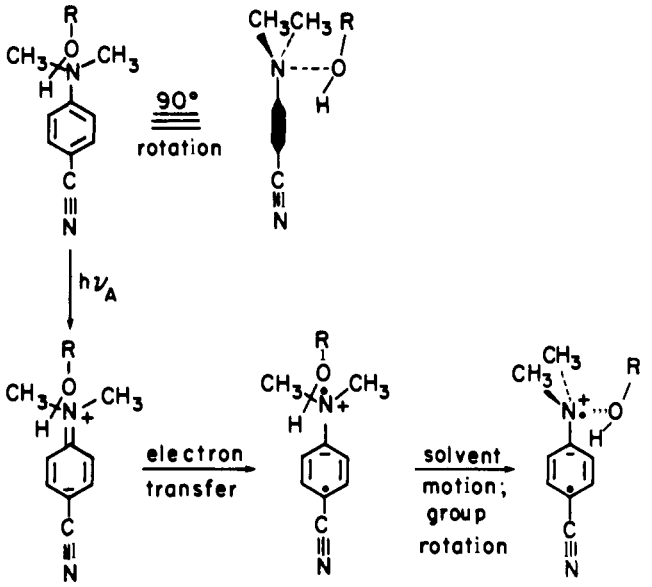
The similarity between TNSDMA and DMAB is made clear with the molecular scheme for DMAB shown in Figure 3. The shift (rotation) of the proximate solvent molecule near the amine nitrogens is very similar in the two cases. This is true even though the molecules are different and the DMAB system involves charge rearrangement within a highly dipolar excited state rather than electron transfer (charge rearrangement) within a weakly dipolar state. The first excited state of DMAB is converted smoothly into the second excited state, time-resolved emission spectra exhibiting an isosbestic point with no sign of an intermediate state.[29,30]

Other Molecules

Clark and his co-workers[29] have found that 4-aminophthalimide has the same excited-state relaxation time in 1-propanol (ca. 50 ps) as TNSDMA and DMAB. Steady-state fluorescence maxima in a series of different solvents vary in a simple way with solvent polarity, suggesting that only one emitting state is involved. Time-resolved emission spectra reveal a continuous shift from the

(29) Yeh, S. W.; Phillips, S. P.; Webb, S. P.; Buhse, L. F.; Clark, J. H., unpublished results.

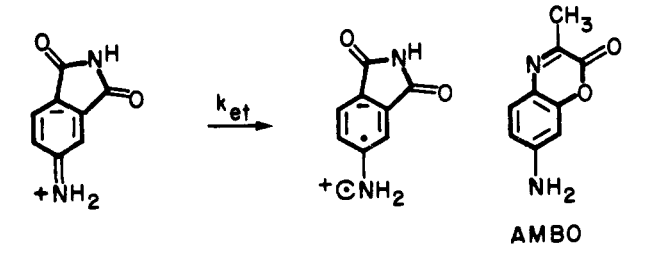
(30) Declemy, A.; Rulliere, C.; Kottis, Ph. *Chem. Phys. Lett.* **1983**, *101*, 401–406.



Molecular Scheme for DMAB

Figure 3. Molecular model for the conversion of the ground state of DMAB [4-(dimethylamino)benzonitrile] into the $S_{1,ct}$ state. One solvent molecule is associated with the substrate. The motion of the solvent molecule in the overall process is very similar to that which is shown in Figure 1 for the solvent molecule associated with TNSDMA.

Scheme III

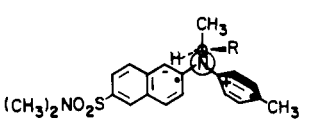


AMBO

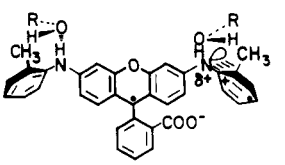
initial emission spectrum to the final spectrum. Thus, an intramolecular electron-transfer process is *not* likely (i.e., the two excited states, S_1 and $S_{1,TICT}$, shown in Scheme III). It appears that the S_0 state has organized the solvent sufficiently so that solvent rearrangement rates of the initial S_1 are controlled by τ_1'. The fast changes in emission spectra observed for 7-amino-3-methyl-1,4-benzoxazin-2-one (AMBO) and ascribed to hydrogen bond formation[28] will probably be found to have initial decay rates similar to τ_1' on more detailed examination (in ethanol, the rise time for the final fluorescent state is <50 ps). Further effort on the AMBO molecule is clearly of interest. As Marcus has pointed out,[31] many more cases should be examined to test the generality and limits of the correlation of excited-state decay with τ_1' (see Note Added in Proof).

An *N*-methyl group in TNSDMA does not move with the solvent molecule as does the *N*-hydrogen (Figure 1). In the charge-transfer state, the nitrogen is not conjugated with the phenyl group as shown by the unusually high sensitivity of the fluorescence maxima to substituent change, with a Hammett ρ value between 25 and 33. Physically, this shows that the substituent is probing a higher positive charge than in the NH case (charge delocalized onto nitrogen, ρ value −10.6). The state was therefore labeled $S_{1,ct(U)}$ (U = unconjugated).[4,5,11] A formula representing the charge-transfer state before solvent relaxation is shown below for *N*-methyl-TNSDMA (the single solvent molecule is above the nitrogen–naphthalene plane). As in the cases of TNSDMA and DMAB, some rotation of the dipole of the single solvent molecule is required to reach the transition state to the $S_{1,ct(U)}$ state. We might expect from our models that the relaxation times will correlate with τ_1', and we hope to measure these rates in the future.

Another interesting example is that of the *N*-di-(*o*-tolyl)rhodamine (NDTR). The aryl groups decrease drastically the fluorescence lifetime of the rhodamine from the nanosecond range to the picosecond range in the lower alkanols. The fluorescence lifetimes in a series of alkanols correlate with a fractional power of the viscosity ($\eta^{2/3}$).[32] We find that the reported τ_{fl} decrease less rapidly (methanol, 9 ps; 1-decanol, 110 ps] than τ_1' but more rapidly than might have been expected for τ_2 (methanol, 12 ps; 1-decanol, 48 ps). In this connection, it is worth noting that Chase and Hunt[33] found a good correlation between the relaxation time for electron solvation and τ_2. The molecular model suggests that the factor for the relaxation times (1-decanol/methanol) should be 0.5 of that for a single solvent molecule complex (predicted τ_{fl} (1-decanol) 220 ps, found 110 ps). A formula for the double solvent molecule complex with the charge-transfer state of NDTR is shown below.



N-CH$_3$-6,2-TNSDMA



NDTR

The second electron transfer in TNSDMA (see Scheme I) (similar behavior is found for the *N*-methyl-TNSDMA and DMAB) is much slower than the first electron transfer. The rate constants parallel the dielectric relaxation rates in linear alkanols. From the dipole interaction model, the second electron-transfer relaxation times, if fast enough, should correlate with τ_1, since the rearrangement of the solvent is the chief component of the activation process. Small factors, $\tau_{d,ct}/\tau_1$, (6.8 for ethanol and 3.5 for 1-decanol) characterize the discrepancy between $\tau_{d,ct}$ and τ_1; these are listed in the last column of Table I. The smaller alkanols can interact more effectively which the charge-transfer state, and the local organization in these states would be more extensive. Molecular dynamics calculations[34] have suggested that the relaxation of water around a Li^+ will be retarded by a factor of 3–4, which should not be smaller in alkanols. We surmise that for a large dipole decrease case, there will be a deviation from τ_1 by an amount which is related to the solvent–solute interaction.

The model can be applied to other molecular systems in which intramolecular charge-transfer occurs. The electron transfer, $D^{\cdot-}$–ST–A → D–ST–$A^{\cdot-}$, proceeds at the highest rate in MTHF for the case in which ΔG is ca. −1.2 V, with D = biphenyl, A = 5a,6,8,8a-tetrahydro-1,4-naphthoquinone, and ST = the steroid skeleton.[27] Solvent reorganization is thought to be the most important component of the transition-state energy. Our treatment suggests that one should consider a model in which one solvent molecule interacts with a radical anion. An estimate for the point charge–dipole interaction energy (dipole moment for tetrahydrofuran, 1.7D) with ϵ_{op} as the dielectric constant comes close to that estimated from the experiment (ca. 14 kcal/mol). Thus the model allows a more specific insight on the electron-transfer process than might be derived from a macroscopic theory.

Conclusion

Simplified models for the role of the solvent in intramolecular electron transfer are shown to be helpful, both qualitatively and semiquantitatively, in interpretation. A parametrized relationship of the kinetics of intramolecular electron transfer and dielectric friction to solvent interactions with ion pairs as characterized by *Z* values[35] has been developed by van der Zwan and Hynes.[36] The mechanism of the relaxation correlated by τ_1' is of interest. It

(31) Marcus, R. A. *Discuss. Faraday Soc.* **1983**, *74*, 199.

(32) Osborne, A. D.; Winkworth, A. C. *Chem. Phys. Lett.* **1982**, *85*, 513–517.
(33) Chase, W. J.; Hunt, J. W. *J. Phys. Chem.* **1975**, *79*, 2835–2845.
(34) Heinzinger, M. *Studies Phys. Theor. Chem.* **1982**, *27*, 61–80.
(35) Kosower, E. M. *J. Am. Chem. Soc.* **1958**, *80*, 3253–3260.
(36) van der Zwan, G.; Hynes, J. T., unpublished results.

might be possible to show by femtosecond techniques that the rapid fluctuations shown for solvent dipolar correlations in time-dependent dielectric friction[36] or in computer simulation studies of dipolar fluids[37,38] appear as fluctuations in fluorescence maxima or intensities.

Note Added in Proof. The conversion of the initially formed excited state ($S_{1,bent}$) of bimanes (1,5-diazabicyclo[3.3.0]octa-3,6-dien-2,8-diones[39,40]) into a successor state ($S_{1,quasi-planar}$) is characterized by τ_1' in linear alkanols. The conversions involve a modest degree of charge rearrangement.[41]

Acknowledgment. E.M.K. is grateful for the facilities afforded him by Prof. A. Streitwieser, Jr., and the Chemistry Department, University of California, Berkeley, during the fall semester, 1983. Helpful discussions with Prof. Berni Alder (Berkeley-Livermore), Prof. H. L. Friedman (Stony Brook), Prof. M. Bixon (Tel-Aviv), and Prof. R. A. Marcus (California Institute Technology) are greatly appreciated. Information from Prof. J. H. Clark (Berkeley) in advance of publication was very helpful.

(37) Impey, R. W.; Madden, P. W.; McDonald, I. R. *Mol. Phys.* **1982**, *46*, 513-539.
(38) Edwards, D. M. F.; Madden, P. A. *Mol. Phys.* **1984**, *51*, 1163-1179.
(39) Kosower, E. M.; Ben-Shoshan, M.; Faust, D.; Goldberg, I. *J. Org. Chem.* **1982**, *47*, 213-221.
(40) Goldberg, I.; Kosower, E. M. *J. Phys. Chem.* **1982**, *86*, 332-335.
(41) Giniger, R.; Huppert, D.; Kosower, E. M., unpublished results.

Computation of Molecular Volume

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Abstract: Volume is a fundamental physical property of molecules that is important in understanding their structure, function, and interactions. Present methods for computing volumes of macromolecules from crystallographically determined atomic coordinates introduce numerical errors that are, in the case of highly refined protein structures, larger than the experimental errors in the determination of the atomic coordinates. In order to obtain the maximum benefit from this high-quality experimental data, it is necessary to develop a volume-computation method whose numerical error is significantly less than the experimental error. Such a method is presented here. The molecule is modeled as a static collection of hard spheres which completely exclude a spherical probe representing a solvent molecule. van der Waals volumes are computed exactly, and solvent-excluded volumes are computed with an error of about 0.01%. The method's accuracy makes it particularly useful for comparing three-dimensional structures of a macromolecule in slightly differing conformations. Causes of such differences include temperature, oxidation state, presence of ligands, crystal form, and X-ray crystallographic refinement technique. Molecular volume changes during energy minimization, molecular dynamics simulation, and X-ray refinement can be monitored. This approach should also be of general utility in measuring the volumes of packing defects in protein interiors, ligand-binding pockets on protein surfaces, and gaps between molecules at subunit interfaces. Because the volume is defined analytically, it can be differentiated for use in energy functions.

Molecular volume is important, and it is important to measure it accurately. Volume is directly related to other physical chemical properties, such as charge, temperature, and pressure,[1] and its converse, which is density, has proved useful in studying protein tertiary structure. Density variations in different regions of the protein interior[2,3] and packing defects[4] have been identified and related to conformational fluctuations, hydrogen exchange, and the protein folding problem. These studies have also emphasized the importance of a suitable definition of the molecular surface in order to accurately measure molecular volume. It is important to measure molecular volume accurately in order to make full use of the information contained in high-resolution structural determinations of macromolecules.

Before proceeding to describe the volume computation method, it is necessary to define the terminology used in this work. The van der Waals volume is the volume occupied by the atoms when considered to be hard spheres with van der Waals radii. The solvent-excluded volume is the volume of space from which solvent is excluded by the presence of the molecule, when the solvent molecule is also modeled as a hard sphere, called the probe sphere. The interstitital volume consists of packing defects between the atoms that are too small to admit a probe sphere of a given radius. The solvent-excluded volume is the van der Waals volume plus the interstitial volume. The van der Waals volume can be considered to be a special case of the solvent-excluded volume, where the probe radius is zero. The general term, molecular volume, will be used to refer to both van der Waals and solvent-excluded volumes.

The term solvent-accessible surface will be used to refer to the smooth network of convex and reentrant surface traced by the inward-facing part of the probe sphere as it rolls over the molecule.[5,6] This surface is chemically important because it (i) forms the boundary of the solvent-excluded volume, (ii) has convex regions that are coincident with the part of the van der Waals surface that is accessible to a probe sphere, and (iii) is useful for graphically representing and analyzing the interface of macromolecules with each other and with solvent, drugs, and other small molecules. The term was originally used to refer to the surface traced out by the center of a probe sphere,[7] which is much easier to calculate but which lacks the advantages listed above. The general term, molecular surface, will also be used to refer to the solvent-accessible surface.

Two general approaches to geometric computations may be distinguished: numerical and analytical. A numerical algorithm subdivides a geometric object into a large number of small, similar units. For a three-dimensional object, these units may be cubes. The answer given is only approximate, and the amount of computation required for high accuracy is usually greater than that for an analytical method. An analytical method gives the answer

(1) Morild, E. *Adv. Protein Chem.* **1981**, *34*, 93.
(2) Richards, F. M. *J. Mol. Biol.* **1974**, *82*, 1.
(3) Kuntz, I. D.; Crippen, G. M. *Int. J. Peptide Protein Res.* **1979**, *13*, 223.
(4) Richards, F. M. *Carlsberg Res. Commun.* **1979**, *44*, 47.
(5) Richards, F. M. *Annu. Rev. Biophys. Bioeng.* **1977**, *6*, 151.
(6) Connolly, M. L. *Science* **1983**, *221*, 709.
(7) Lee, B.; Richards, F. M. *J. Mol. Biol.* **1971**, *55*, 379.

0002-7863/85/1507-1118$01.50/0