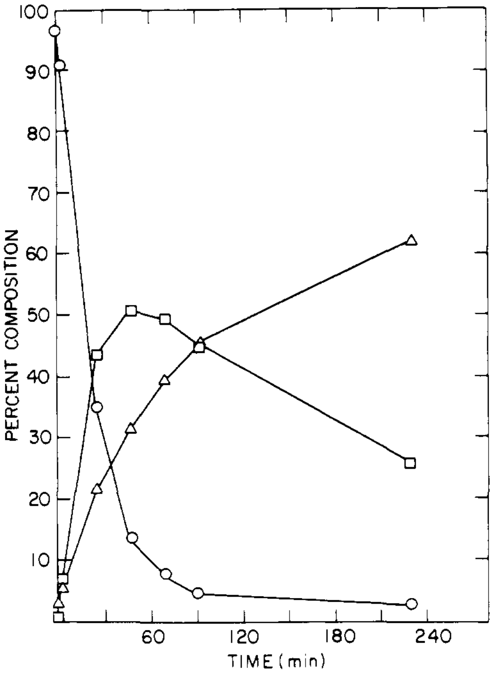
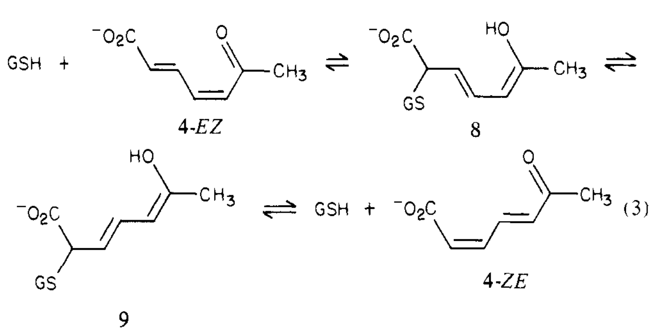


Figure 1. Typical kinetics of the maleylacetone cis-trans isomerase catalyzed isomerization of 6-oxo-2,4-heptadienoic acids at pH 7.4 in the presence of coenzyme, glutathione. Note the early, predominant formation of 4-*ZE* from 4-*EZ*. Circles, 4-*EZ*; squares, 4-*ZE*; triangles, 4-*EE*.

Surprisingly, the isomerase also processes **4**-*EZ*. Moreover, the product generated is remarkable because *the enzyme converts* **4**-*EZ directly to* **4**-*ZE*; *it catalyzes a double cis-trans isomerization.* The first product formed in the enzyme-catalyzed isomerization of **4**-*EZ* is **4**-*ZE*; **4**-*EE* forms on a slower time scale (Figure 1). Similarly, **4**-*EZ* is formed from **4**-*ZE* when GSH and the isomerase are present.

The K_M for **4**-*EZ* is 1.9×10^{-3} M. The enzyme processes **4**-*EZ* ~1.6 times faster than maleylacetone. When **4**-*EZ* is the initial enzyme substrate, **4**-*EE* and **4**-*ZE* form in a branching ratio of 1:3. **4**-*EE* and **4**-*EZ* form, however, in a branching ratio of approximately 2.7:1 when **4**-*ZE* is the initial substrate. A calculated equilibrium constant,[10] [**4**-*ZE*]/[**4**-*EZ*] $\simeq$ 21, compares reasonably with a measured value of 16 ± 7 for the enzyme equilibration.

Since the enzyme-catalyzed double isomerization requires GSH and substrate maleylacetone inhibits enzymatic processing of either **4**-*ZE* or **4**-*EZ*, the same active site is probably used by all three substrates. The mechanism for this extraordinary transformation remains to be elucidated, but we note here that it could be accommodated by a mechanism parallel to that for isomerization of maleylacetone (eq 2). As with maleylacetone, enzyme-bound GSH could add to C2 of enzyme-bound **4**-*EZ* or **4**-*ZE* to form a dienol intermediate (eq 3). If the carboxyl, the GS backbone, and the enolic oxygen are utilized for binding to the enzyme then the termini of the intermediate would be relatively immobile. Internal concerted rotation about the C2–C3 and the C4–C5 single bonds could still occur, however, provided that the enzyme topology does not interfere.[12,13] Rotation in this way would cause the two



dienol intermediates, **8** and **9**, to equilibrate and subsequent ketonization with expulsion of GSH would provide **4**-*EZ* and **4**-*ZE*, respectively. Formation of **4**-*EE* from either analogue could occur from the same dienol intermediate by suggesting that the enolic oxygen binding is weak. If the intermediate were held only at the GS/carboxyl terminus, the relaxation to the **4**-*EE* geometry would appear to have a strong driving force. Consistent with this is the observation that **4**-*EE* is the sole product of nucleophilic catalysis of isomerization of **4**-*EZ* or of **4**-*ZE* by thiocyanate ion at the same pH.

The present results provide support for proposals which suggest that the enzyme binds maleylacetone in the region of the 6-oxo function as well as by its carboxyl group.[1]

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Supplementary Material Available: A table of vinyl ^{1}H NMR chemical shifts and coupling constants for **4**-*EZ*, **4**-*ZE*, **5**-*ZZ*, and **5**-*EE* (1 page). Ordering information is given on any current masthead page.

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[10] If 4-*EZ* equilibrates with 4-*ZE* through several intermediates it can be shown[11] that the equilibrium constant, [4-*ZE*]/[4-*EZ*], equals $(V_{\max,4\text{-}EZ}/V_{\max,4\text{-}ZE})(K_{M,4\text{-}ZE}/K_{M,4\text{-}EZ})C$, where C is a correction factor, (3/4)/(1/3.7), to take account of the branching ratio for each substrate.

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[13] Similar molecular dynamics have been postulated in a model for the photoconversion of 11-*cis*-retinal in rhodopsin to its all-trans isomer by a concerted rotation ("bicycle pedal motion") in which the cis double bond migrates toward the Schiff base terminus (Warshel, A. *Nature* (*London*) **1976**, *260*, 679).

Intramolecular Long-Distance Electron Transfer in Radical Anions. The Effects of Free Energy and Solvent on the Reaction Rates[1]

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As an extension of the work on long-distance *inter*molecular electron transfer (ET) in rigid matrices carried out by one of us[2-5] for some time, we have embarked on a study of *intra*molecular long-distance ET in fluid solution. In a recent communication we have reported not only that such reactions can occur over considerable distance (~10 Å) but also that, given the appropriate driving force (exothermicity), the observable rates can be very fast indeed.[6] In this communication we wish to demonstrate the dependence of the ET rates on the exothermicity of the reaction and report a remarkable solvent dependence of the observed rates. The rates show a strong deviation from the classical Brønsted

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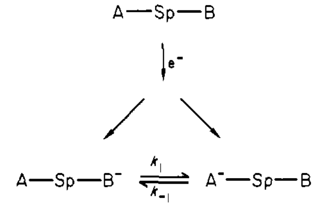
Table I. Rate Constants[a] for Intra- and Intermolecular Electron Transfer in Anions of Bifunctional Steroids A–Sp–B⁻ (B = 4-biphenylyl) at $T = 296$ K

		MTHF		isooctane	
acceptor group (A)	$-\Delta G°$, eV	k_{intra}, s^{-1}	$10^{-9}k_{\text{inter}}$,[a] $M^{-1}\ s^{-1}$	k_{intra}, s^{-1}	$10^{-9}k_{\text{inter}}$,[a] $M^{-1}\ s^{-1}$
4-biphenylyl	0	5.6×10^5 [b]		1×10^9 [b]	
2-naphthyl[e]	0.05[c]	$(1.5 \pm 0.5) \times 10^6$	5.7	$(1.5 \pm 0.5) \times 10^9$	6.7
9-phenanthryl	0.16[c]	$(1.25 \pm 0.2) \times 10^7$	7.0	$>2 \times 10^9$	13.9
1-pyrenyl	0.52[d]	$(1.5 \pm 0.5) \times 10^9$	12.0	$>2 \times 10^9$	13.5
hexahydronaphthoquinon-2-yl	1.23[d]	$>2 \times 10^9$	11.1	$(1.0 \pm 0.5) \times 10^9$	12.9
2-naphthoquinonyl	1.93[d]	$(3.8 \pm 1) \times 10^8$	9.9 ± 1	$>2 \times 10^9$	17.1
2-benzoquinonyl	2.10[d]	$(2.5 \pm 0.3) \times 10^8$	6.2	$(3.6 \pm 0.8) \times 10^6$	10.9
5-chlorobenzoquinon-5-yl	2.29[d]	$(1.7 \pm 0.2) \times 10^8$	4.4	$(3.5 \pm 0.5) \times 10^6$	9.5
5,6-dichlorobenzoquinon-2-yl	2.40[d]	$(7 \pm 3) \times 10^7$	3.0 ± 1	$(1.4 \pm 0.25) \times 10^8$	9.8

[a] Uncertainties ±15% (1 standard deviation) unless noted otherwise. [b] The rate of the exchange reactions in B⁻–Sp–B were *not* measured but were estimated by extrapolating from measured data. [c] From equilibria measured by pulse radiolysis. [d] Estimated from redox potentials in DMF (ref 18–21). [e] The forward rate constant is reported. The rate of approach to equilibrium is $k_{\text{fwd}} + k_{\text{rev}}$.

relationship and are a striking confirmation of ET theories[7-12] descending from the Marcus theory, which predicted such behavior almost 30 years ago[7] but seemed to be contradicted by almost all experiments in solution.[13,14]

We have synthesized a homologous series of eight compounds of the general structure A–Sp–B[15] where B is 4-biphenylyl, Sp is a rigid saturated hydrocarbon spacer, the steroidal 5α-androstane skeleton, and A is one of a series of eight different molecular groups with π-electron networks listed in Table I. In all cases the distances between A and B are identical (~10 Å edge to edge). The experiment involves subjecting a liquid solution of these molecules in either 2-methyltetrahydrofuran (MTHF) or isooctane at room temperature to a 30-ps pulse of solvated electrons generated by the Argonne 20-MeV Linac. The electrons are captured by either A or B with almost statistical probability. Photometric absorption measures the rates of how this initial ion distribution attains equilibrium. The sequence of events is summarized in the following scheme:



It should be noted that the ET reactions are free ion reactions, as it is well-known that in ion pairs created by pulse radiolysis the average ion pair distances are quite large.[16,17] The intermolecular contributions to the observed rates were assessed by measuring ET rates in solutions of the monofunctional model compounds of structure A–Sp and B–Sp.[15] With these data it was possible to extract intramolecular ET rates in the bifunctional molecules. The rate constants are listed in the table and are plotted against the free energy change ($\Delta G°$) in Figure 1. Here the $\Delta G°$ values are taken from electrochemical literature data[18-21] with the exceptions of the first two points (β-naphthyl and 9-phenantryl) where actual equilibria were measurable in our pulse radiolysis experiments.

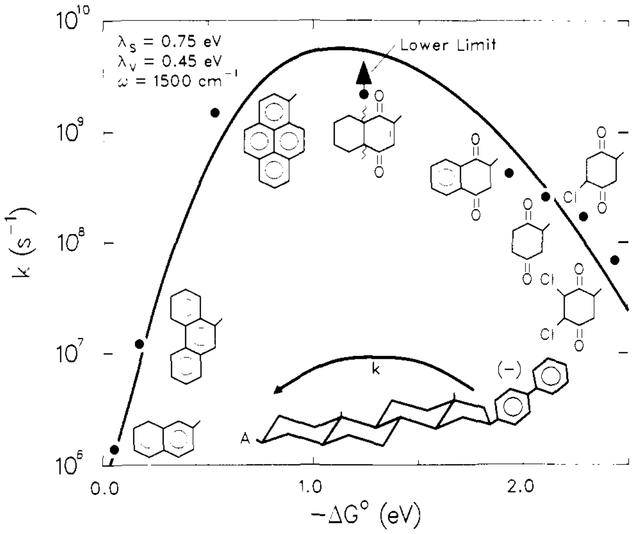


Figure 1. Intramolecular electron-transfer rate constants as a function of free energy change in MTHF solution at 296 K. Electrons transferred from biphenyl ions to the eight different acceptor groups, A (shown labeling the points), in eight bifunctional molecules having the general structure shown in the center of the figure.

Focusing first on the data obtained in MTHF, it is apparent that the rates span a range of more than 3 orders of magnitude with the maximum occurring at approximately 1.2 eV. According to theory[7-12] this maximum should occur when $-\Delta G°$ matches the total reorganization energy λ, accompanying the charge redistribution. The major contributions to λ are the solvent reorganization energy, λ_s, and the change in internal vibrational modes, λ_v. The solid curve in Figure 1 was calculated[22] for $\lambda_s \sim 0.75$ eV and $\lambda_v = 0.45$, very similar to values found in MTHF glass.[4] Since the maximum of this curve has not yet been determined experimentally, there is some uncertainty (estimated at 20%) associated with the λ-values. The maximum rate corresponds to a transfer in which the Franck–Condon factors are maximized. The fall off at large exothermicity is caused by an increasing mismatch of the overlap of the vibrational wave functions.

If the maximum of the curve is indeed defined by λ of which the major component is the solvent reorganization energy, use of a less polar solvent than MTHF should lead to a displacement of the curve to give a maximum at less negative ΔG. This is strikingly confirmed by the results obtained in isooctane. Although the data are not as complete because some of the reactions were too fast to measure with our present equipment, there is no doubt

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that the maximum rate occurs at a much smaller $-\Delta G$ than in MTHF and that the rate falloff at large exothermicity is much more pronounced. In less polar isooctane mildly exothermic reactions are speeded up by factors as large as 10^3 while strongly exothermic ones are slowed down by factors as large as $10^{1.8}$. The possible formation of excited states adds a complicating factor to this relationship and probably accounts for the exceptionally high rates observed for naphthoquinonyl and dichlorobenzoquinonyl in isooctane.[23]

We believe that our observation of diminishing rates with very negative ΔG is the first unambiguous demonstration of the existence of the so-called inverted region in solution ET reactions. The failure of previous efforts can probably be attributed to the fact that most of the ET reactions studied were intermolecular, where diffusion sets a limit to the observable rate, thus cutting off the top of the curve shown in the figure. In support of this conclusion is the observation that the bimolecular rate constants measured with models of type A–Sp and B–Sp vary only by a factor of 4.

The ΔG and solvent dependence of the ET reactions reported here are very different from predictions made by classical physical–organic reasoning and serve to confirm conclusions drawn by one of us from intermolecular ET reactions in rigid glasses.[3-5] In addition, the work emphasizes the fact that ET across an insulating barrier as wide as 10 Å can occur astonishingly fast (~100 ps) if conditions are maximized.

Besides dependence of ET rates on exthermicity and solvent polarity, other important questions concern temperature, distance, and geometry dependences. Such experiments are in progress at the present time.

Acknowledgment. We thank Scott Schell who participated as an Argonne National Laboratory Undergraduate Research Participant in the synthesis of some of the compounds. G. L. C. is grateful for the Argonne National Laboratory Summer Residency (1983). We acknowledge the superior professional competence of the Argonne Linac operators providing us with a superb electron beam, the use of programs from C. D. Jonah, and Bob Clarke's technical help.

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S_N2 Reaction Profiles in the Gas Phase and Aqueous Solution

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Striking demonstraton of the importance of medium effects is provided by bimolecular nucleophilic substitution reactions involving anions and polar molecules. The rates in the gas phase and solution vary over 20 orders of magnitude. Explanations have focused on preferential stabilization of the reactants relative to the charge-dispersed transition state by polar, especially protic, solvents.[1-3] However, the detailed form of the reaction surfaces in solution is unknown. The traditional assumption of a unimodal profile needs critical examination, particularly since the gas-phase reaction is characterized by a double-well surface, with unsymmetrical ion–dipole complexes as minima and a symmetrical transition state.[3,4] Conceivably, analogues of the gas-phase minima and new solvent-separated ones may be present in solution. In this communication, we report the first computation of an energy profile for an S_N2 reaction ($Cl^- + CH_3Cl'$) in aqueous solution. The present statistical mechanics simulations go significantly beyond previous quantum mechanical investigations of S_N2 reactions in the gas phase[5,6] or in the presence of a few water molecules.[7] The latter calculations have bearing on studies of gas-phase clusters[8] but do not include the important effect of bulk solvent reorganization, which contributes significantly to the barrier in solution. The present simulations explicity include a large number of water molecules as well as thermal averaging.

The calculation involved three steps: (i) determination of the gas-phase reaction surface, (ii) development of potential functions to describe the solute–solvent interactions, and (iii) Monte Carlo simulations of the reaction in solution. Ab initio 6-31G* calculations were used to construct the gas-phase energy profile.[9] For fixed values of r_{CCl}, the remaining geometric parameters were optimized in C_{3v} symmetry. The reaction coordinate was defined as $r_c = r_{CCl'} - r_{CCl}$, which is symmetric about the transition state, ($r_c = 0$). The calculated geometric parameters and total energies were fit to analytical functions of r_c. The resultant energy profile (Figure 1, dashed curve) contains two minima flanking the symmetric transition state. The calculated energy of the ion–dipole complex, **1**, relative to the reactants (-10.3 kcal/mol) as well as the energy of the transition state, **2**, relative to **1** (13.9 kcal/mol) are in accord with the experimental complexation enthalpy (8.6 kcal/mol)[10] and intrinsic barrier (~10.2, 11.6 ± 1.8 kcal/mol).[3b,11]

Intermolecular interactions were described with potential functions in the 12–6–1 form and were assumed to be pairwise additive. The parameters for the water molecules correspond to the TIP4P model.[12] A novel and clearly necessary point is that the charges and Lennard–Jones terms for the atoms in the solute cluster vary along the reaction coordinate. These parameters and their dependence on r_c were determined from 6-31G* calculations on a large number of geometries of $CH_3Cl_2^- + H_2O$ spanning the reaction coordinate. The details are provided as supplementary material.

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