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and spectral and chromatographic comparison from the previously obtained material.

Diene Diol 22a. A 100-mg (0.43 mmol) sample of diene lactone **14** and 100 mg (2.63 mmol) of lithium aluminum hydride in 10 mL of ether were stirred overnight at room temperature. Water (200 μL) and 10% sodium hydroxide (160 μL) were added. After approximately 30 min, the mixture was filtered through a pad of sodium sulfate and the ether was evaporated, leaving 100 mg (98%) of diene diol **22a**, which was sublimed (75 °C, 0.01 mm) for characterization: mp 100–103 °C; $[\alpha]^{24}{}_D$ −279° (c 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.77 (dd, J = 5, 9 Hz, 1 H), 5.68 (m, 1 H), 5.13 (d, J = 9 Hz, 1 H), 4.3–3.3 (complex m, 5 H), 1.90 (s, 3 H), 0.92 (s, 3 H), 0.90 (d, J = 5 Hz, 3 H); IR (Nujol) 3200, 3020, 1655, 1105, 1085, 1065, 1045, 1025, 975, 900, 875 cm^{-1}; mass spectrum m/e 236 (M^+).

Anal. Calcd for $C_{15}H_{24}O_2 \cdot {}^1/_4H_2O$: C, 74.80; H, 10.25. Found: C, 74.89; H, 10.05.

(−)-Dictyolene (2). To 50 mg (0.21 mmol) of diene diol **22a** in 1.45 mL of dry pyridine cooled to −40 °C under argon was added 200 mg (1.0 mmol) of recrystallized p-toluenesulfonyl chloride. After the mixture was stirred for 2 h at −30 to −40 °C, 110 μL (0.87 mmol) of chlorotrimethylsilane was added. Ice chips were then added after an additional 15 min at −30 to −40 °C and the reaction mixture was allowed to warm to room temperature. The reaction product was isolated with ether in the usual manner to afford crude tosylate trimethylsilyl ether **22b** as an oil: IR (film) 3030, 1650, 1600, 1365, 1250, 1190, 1175, 1095, 1055, 840 cm^{-1}.

To a mixture of 3-methyl-2-butenylmagnesium chloride (ca. 3 mmol) and 1-pentynylcopper[32] (50 mg, 0.38 mmol) in 2 mL of ether at −30 to −40 °C under argon was added the above tosylate **22b** in 0.5 mL of ether. The mixture was stirred for 2.5 h at −20 °C and then poured into saturated aqueous ammonium chloride–ether and stirred for 15 min. The crude trimethylsilyl ether was isolated with ether and then subjected to hydrolysis using 15 mL of a AcOH–THF–H_2O solution (3:2:1). After 45 min at room temperature, the solvents were evaporated at 25 °C under reduced pressure and the resulting oil was purified by dry column silica gel chromatography using 1% ethyl acetate–hexane to give 23 mg (38%) of dictyolene (**2**): $[\alpha]^{23}{}_D$ −154° (c 0.8, $CHCl_3$); ^1H NMR[12] (250 MHz, $CDCl_3$) δ 5.70 (dd, J = 5.5, 9 Hz, 1 H), 5.65 (m, 1 H), 5.26 (d, J = 9 Hz, 1 H), 5.12 (t, J = 7 Hz, 1 H), 4.06 (br dd, J = 2.5, 5 Hz, 1 H), 2.04 (d, J = 5 Hz, 1 H), 1.87 (s, 3 H), 1.70 (s, 3 H), 1.61 (s, 3 H), 1.03 (s, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); IR[12] (film) 3030, 1655, 1640, 1450, 1375, 1025, 985 cm^{-1}; UV[12] (C_2H_5OH) 206 nm (ϵ 4400), 266 (4000); mass spectrum m/e 288 (M^+, 18%).

Comparison of the above spectra with those kindly provided by Professor Erickson of naturally derived dictyolene, in particular the 250- and 270-MHz NMR spectra, unambiguously confirmed the identity of the synthetically derived material.

Acknowledgments. The author thanks his colleagues, Professor Crabbé, Dr. Luche, and Dr. Edgar for their interest in this work. In addition, the author is grateful to Professor Marshall for a preprint of his paper, to Professors Sims, Minale, and Fattorusso for authentic samples of pachydictyol A, and to Professor Erickson for the spectra of dictyolene. This work was supported by the CNRS (ERA No. 478).

Long-Distance Intramolecular Electron Transfer in a Macrocyclic Crown Ether, a Thermoneutral, Nonadiabatic Process

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Abstract: The anion radical of 19,22,23,26-tetracyano-2,3:11,12-dibenzo-1,4,7,10,13,16-hexaoxaoctadeca-2,11-diene (I) was generated in solution by both electrolytic and chemical reduction. Electrochemistry and ESR and optical spectroscopies were employed to characterize the structure, spin distribution, ion pairing, and intramolecular electron transfer kinetics of $I^{-}\cdot$. Under most conditions the evidence is consistent with unpaired electron spin localized on one of the two equivalent aromatic rings (a_N = 1.86 G, a_H = 1.45 G, g = 1.0027). However, when $I^{-}\cdot$ was present as an ion pair with Na^+ or K^+ in dimethoxyethane, intramolecular electron transfer became detectable on the time scale of ESR. The Arrhenius parameters for this process (E_a = 1.4 kcal/mol, A = 4.6 × 10^7 s^{-1}) are exceptionally small. The results are interpreted in terms of electrostatic contributions to the energetics and a nonadiabatic mechanism, whereby very weak electronic coupling between reactant and product wave functions depresses the time-average probability of electron transfer in the activated complex. (Spectroscopic results are also presented for anion radicals of the related molecules II and III and for the diradical dianion I^{2-}.)

Introduction

Electron transfer between species of comparable electron affinity does not require intimate interaction of the reaction partners. Weak mixing between the reactant and product wave functions is sufficient to permit transfer to occur on virtually every excursion of the nuclei through the activated complex configuration. In order for this to be the case, interaction between donor and acceptor orbitals need only be a very small perturbation, orders of magnitude less than typical bond energies. This requirement can be easily met by the vast majority of examples which have been studied, and this is why the adiabatic description of electron transfer has met with substantial success.[2,3]

It is of interest to know how electron-transfer reactions behave in the limit of extremely feeble electronic coupling. For example, is there a threshold below which the mechanism changes qualitatively? Are nonadiabatic mechanisms operative in solution? Considerable effort has been devoted to theoretical characterization of this situation. However, with the possible exception of highly exothermic reactions, experimental evidence remains ambiguous.[2a]

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(2) (a) H. Taube, "Bioinorganic Chemistry", *Adv. Chem. Ser.*, **No. 162** (1977); (b) N. Sutin in "Inorganic Biochemistry", Vol. II, G. Eichorn, Ed., Elsevier, Amsterdam, 1973.

(3) W. L. Reynolds and R. W. Lumry, "Mechanisms of Electron Transfer", Ronald Press, New York, 1966, Chapter 5.

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Scheme I

$$M^{+}\text{-}R_1\sim R_2 \rightarrow R_1\sim R_2\text{-}M^{+}$$

$$^{-}R_1\sim M^{+}\sim R_2 \rightarrow R_1\sim M^{+}\sim R_2^{-}$$

The chief difficulty lies in trying to distinguish various alternative sources of rate retardation. Clearly, experimental systems for which the activation barrier is small offer a particular advantage.

Activation barriers for electron transfer may be traced to the Franck–Condon principle which dictates that electronic energy should be conserved during the transition from reactant to product electronic state. Consequently, prior to the transition, reactants and their solvation sphere must undergo reorganization, within thermally accessible regions of the potential-energy surface, to structures which represent a compromise between equilibrium geometries of reactants and products. The more extensive this reorganization, the greater will be the barrier. Electronic coupling between the donor and acceptor (unless sufficiently strong to compete with bonding and solvation energies[4]) has little or no influence on the activation energy. In fact, so long as the requirements for adiabaticity are met, it should not affect the reaction rate at all. Based on these observations, the best experimental approach must combine unusually weak electronic coupling with minimal structural reorganization.

Aromatic hydrocarbons and their anion radicals can exchange electrons with very little readjustment of molecular structure. Typically, activation energies lie between 5 and 10 kcal/mol. Moreover, this barrier is almost entirely due to reorganization of the solvent and counterions.[5] (It is interesting that the influence of ion pairing has long been recognized by experimentalists, but has been neglected in even the most sophisticated theoretical discussions.) The situation is complicated by the fact that solvation and ion pairing are strongly interrelated.

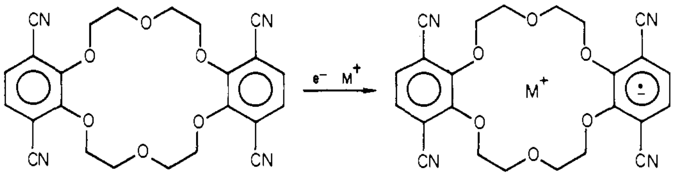
Experiments described here concern electron transfer between distant aromatic rings. The key feature of our approach has been to minimize contributions of the Franck–Condon barrier due to changes in solvation and ion pairing. The problem has been attacked within the constraints of solution chemistry according to the following strategy.

Experimental Strategy

Intramolecular electron transfer between equivalent pairs of functional groups, R_1 and R_2, of an anion radical (Scheme Ia) has been thoroughly investigated for a variety of different examples.[6-11] In several cases,[7-9] unsymmetrical ion pairing has been shown to play a decisive role in the kinetics. (Transfer of the cation from one end of the molecule to the other is rate limiting.) Solvents of low dielectric constant tend to give the tightest ion pairs and consequently the lowest rate of transfer. By using highly dielectric solvents it is possible to dissociate counterions and suppress their influence. However, it is exactly these solvents which interact most strongly themselves with the "free" anion. Consequently, neither situation is an acceptable approximation to the ideal isolated molecule.

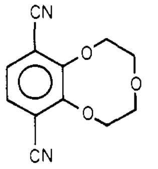
The strategy adopted here was to specifically incorporate the counterion into the molecular structure at a position midway between donor and acceptor groups, i.e., to create a zwitterionic mixed valence system (Scheme Ib).[12] The most important advantage is to minimize displacements of the cation along the reaction coordinate. A further, perhaps less obvious, advantage is that electrostatic interactions with solvent should be less for the zwitterionic system than for a "free" anion. Electron transfer in (Ib) constitutes inversion of a dipole which interacts with solvent by dipole–dipole forces. These fall off much more rapidly with distance than do the charge–dipole forces operating with the free anion. For (Ib), interactions beyond the first solvation sphere may well be negligible.

In the present study, the reactive functional groups are *p*-dicyanobenzene rings positioned at opposite ends of a macrocyclic crown ether. According to plan, the neutral precursor, I, was reduced under various conditions in hopes of obtaining $I^{-}\cdot/M^{+}$ (M = Na or K). Electrochemistry and electron spin resonance (ESR) and optical spectroscopies were used to characterize the reduction product. In order to draw meaningful conclusions, it has also been necessary to characterize the free anion, $I^{-}\cdot$, the dianion, I^{2-}, and also analogous reduction products from the cyclic ethers II and III.

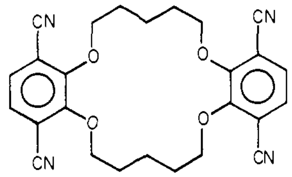


I

$I^{-}\cdot/M^{+}$



II



III

The following issues are addressed:

(i) What are the rate constants and activation parameters for intramolecular electron transfer between the aromatic rings of $I^{-}\cdot$ and $III^{-}\cdot$?

(ii) What is the nature of ion pairing between these radical anions and alkali metal cations, and how does it influence the electron transfer rate?

(iii) What is the magnitude of electronic coupling between the two aromatic rings, and is it a limiting factor in the kinetics?

Experimental Section

The instrumentation used was as follows: for IR, a Perkin-Elmer Model 283; for ^{1}H NMR, a Bruker HX-270; for UV–visible–near-IR, either a Cary Model 14 or a Beckman Acta MIV; for ESR, a Varian E-9 system; for mass spectra, an AEI MS-9. Electrochemical measurements were performed with a Princeton Applied Research Model 173 potentiostat, Model 175 programmer, and Model 179 coulometer. Chemical reductions employing solvated electrons generated at a Na or K mirror were performed according to techniques previously described.[13] It was found useful to isolate the compartment containing the metal mirror behind a coarse sintered-glass disk, in order to prevent small particles of metal from overreducing the solutions. Electrochemical reductions and coulometry employed a 10-mL-capacity, three-electrode cell. This consisted of a Pt-grid working electrode (80 mesh), a Pt wire auxiliary isolated behind a porous Vycor disk, and a Ag/AgCl(s) reference electrode. The cell was designed to be dried, degassed, and used under vacuum (to 10^{-3} Torr). (Detailed drawings and instructions are available upon request.)

1,2-Dimethoxyethane (DME) was twice distilled from NaH, then degassed and stored over Na/K alloy. *N,N*-Dimethylformamide (DMF) was distilled from 4A molecular sieves. Tetrabutylammonium per-

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[4] Reactions between strongly interacting donors and acceptors are more appropriately considered as "inner-sphere" reactions for which more detailed kinetic models are required.

[5] P. J. Zandstra and S. I. Weissman, *J. Am. Chem. Soc.*, **84**, 4408 (1962); N. Hirota, R. Caraway, and W. Schook, *ibid.*, **90**, 3611 (1968).

[6] J. E. Harriman and A. H. Maki, *J. Chem. Phys.*, **39**, 778 (1963).

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[8] P. Fürderer, F. Gerson, J. Heinzer, S. Mazur, H. Ohya-Nishiguchi, and A. H. Schroeder, *J. Am. Chem. Soc.*, **101**, 2275 (1979).

[9] K. Shimada, Y. Shimozato, and M. Szwarc, *J. Am. Chem. Soc.*, **97**, 5831, 5834 (1975).

[10] K. Shimada and M. Szwarc, *J. Am. Chem. Soc.*, **97**, 3313, 3321 (1975).

[11] K. Shimada and M. Szwarc, *Chem. Phys. Lett.*, **28**, 540 (1974).

[12] Probably the first, and certainly a very unusual, kind of zwitterionic mixed valence compound was recently reported: D. O. Cowan, P. Shu, F. L. Hedberg, M. Rossi, and T. J. Kistenmacher, *J. Am. Chem. Soc.*, **101**, 1306 (1979). However, this example apparently suffers from rather large structural differences among the subunits, ferrocene and ferrocenium. Consequently, the activation barrier to electron transfer is substantial.

[13] F. Gerson, G. Moshuk, and M. Schwyzer, *Helv. Chim. Acta*, **54**, 361 (1971).

Table I. Electroanalytical Data[a]

compd	$E°$, V vs. Ag/AgCl	ΔE_p, mV	n^b
I	-1.58^c	75	1.98
II	-1.63	60	1.07
III	-1.62^c	75	2.02

[a] All experiments using 0.10 M TBAP in DMF, cyclic voltammetry at 50 mV/s with *iR* compensation. [b] Electrons/molecule, determined coulometrically at controlled potential of −1.80 V vs. Ag/AgCl. [c] In these cases the apparent $E°$ actually represents an average for two independent redox couples; see text.

chlorate (TBAP) (from commercial tetrabutylammonium hydroxide) was recrystallized from ethyl acetate and dried in vacuo. All other commercial materials were used without further purification.

3,6-Dicyanocatechol was prepared according to the method of Loudon and Steel.[14] Although yields were variable (generally less than 20%), those of subsequent steps were not very sensitive to the purity of this compound, so careful purification was not required.

Reaction of 3,6-Dicyanocatechol with 2-Tosylethyl Ether (Diethylene Glycol Bis(*p*-toluenesulfonate)). To a cooled solution of 3,6-dicyanocatechol (1.0 g, 6.25 mmol) in DMF (3 mL) was added NaH (0.3 g, 1 equiv of a 50% oil dispersion). The mixture was allowed to warm to room temperature and to it was added 2-tosylethyl ether (1.3 g, 3.65 mmol) in 2 mL of DMF. The mixture was stirred at 70 °C until all of the tosylate had reacted (about 24 h). The solution was recooled to 0 °C, and the sequence was repeated using 0.3 g of NaH dispersion and 1.3 g of tosylate. Finally, the mixture was acidified with dilute HCl, and all solvent was removed under reduced pressure. The residue was treated with 20 mL of H_2O and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, concentrated, and fractionated by column chromatography. Elution with petroleum ether–benzene (1:1) yielded a compound, mp 193 °C, identified as 10,13-dicyano-2,3-benzo-1,4,7-trioxacyclononene (II, 0.35 g, 24%): IR (KBr) 3080 (w), 2960 (m), 2940 (m), 2240 (s), 1590 (w), 1555 (w), 1480 (s), 1290 (s), 1260 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (s, 2 H), 4.60 (m, 4 H), 3.96 (m, 4 H); mass spectra included a parent ion at *m/e* 230.069 (calcd for $C_{12}H_{10}N_2O_3$, 230.069). Further elution with $CHCl_3$ provided a second compound, mp 220 °C (recrystallized from benzene–$CHCl_3$), identified as 19,22,23,26-tetracyano-2,3:11,12-dibenzo-1,4,7,10,13,16-hexaoxaoctadeca-2,11-diene (I, 70 mg, 5%): IR (KBr) 3080 (w), 3020 (m), 2960 (m), 2900 (m), 2240 (s), 1440 (s), 1255 (s), 1130 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (s, 4 H), 4.50 (m, 8 H), 3.96 (m, 8 H); mass spectra included a parent ion at *m/e* 460.143 (calcd for $C_{24}H_{20}N_4O_6$, 460.138).

Reaction of 3,6-Dicyanocatechol with 1,5-Pentanediol Ditosylate.[15] The reaction conditions and scale were the same as those given above. Two products were separated by preparative thin layer chromatography (silica gel eluted with $CHCl_3$). The first of these, mp 135 °C (recrystallized from benzene–petroleum ether), was identified as 10,13-dicyano-2,3-benzo-1,4-dioxacyclononene (9% yield): IR (KBr) 2940 (s), 2240 (s), 1465 (s), 1440 (s), 1255 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (s, 2 H), 4.48 (m, 4 H), 2.07 (m, 6 H); mass spectra included a parent ion at *m/e* 228 (calcd for $C_{13}H_{12}N_2O_2$, 228.090). The second product, mp 187–188 °C (recrystallized from benzene–petroleum ether), was identified as 19,22,23,26-tetracyano-2,3:11,12-dibenzo-1,4,10,13-tetraoxaoctadeca-2,11-diene (III): IR (KBr) 2950 (s), 2240 (s), 1445 (s), 1250 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (s, 4 H), 4.27 (m, 8 H), 2.12 (m, 12 H); mass spectra included a parent ion at *m/e* 456.178 (calcd for $C_{26}H_{24}N_4O_4$, 456.180).

Results

For each of the neutral precursors, reductions were carried out both chemically and electrolytically. The relevant electroanalytical data are summarized in Table I. Spectroscopic properties of the various reduction products are presented below. In order to avoid complications from rapid intermolecular spin exchange and intermolecular electron transfer, ESR spectra were determined at concentrations $\leq 5 \times 10^{-4}$ M. The results for II are discussed first, since the rather straightforward spectroscopic parameters of $II^{-}\cdot$ provide a basis for understanding the more interesting bifunctional cases.

10,13-Dicyano-2,3-benzo-1,4,7-trioxacyclononene (II). The electrochemical behavior of II was particularly simple. As indicated in Table I, a single, reversible, one-electron redox couple was observed at $E° = -1.63$ V. Except for slight variations in $E°$ (uncorrected for junction potential changes), the same results were observed in DME and DMF with either TBAP or sodium tetraphenylborate (NaTPB) as supporting electrolyte. Solutions of $II^{-}\cdot$ generated either electrolytically or by alkali metal reduction in DME were sufficiently stable to permit subsequent analyses within a period of 2–3 h at room temperature.

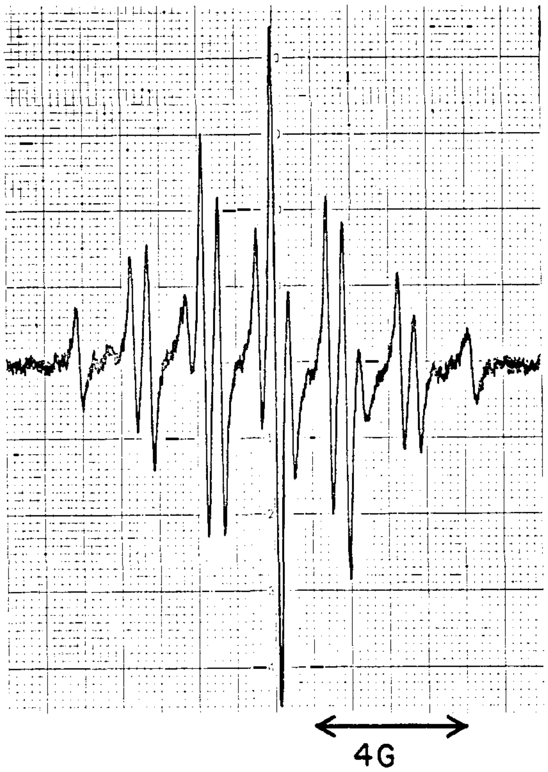

Figure 1. ESR spectrum of $II^{-}\cdot$ generated electrolytically in DMF with 0.10 M TBAP, at 18 °C.

The ESR spectrum of $II^{-}\cdot$ (Figure 1) was similarly insensitive to the conditions of its generation. This spectrum may be seen by inspection to derive from an unpaired electron spin (isotropic *g* factor 2.0027 ± 0.0001) coupled to one pair of equivalent, $I = 1$, nuclei (isotropic hyperfine 1.86 ± 0.01 G depending upon the solution), and a second equivalent pair of $I = {}^1/_2$ nuclei (hyperfine constant 1.45 ± 0.04 G). These values are very close to those reported for the anion radical of 1,4-dicyanobenzene[16] ($a_N = 1.81$, $a_H = 1.59$ G). Thus for $II^{-}\cdot$ these couplings may be confidently assigned to the ^{14}N nuclei and aromatic protons, respectively. Under conditions of optimum resolution, additional structure could sometimes be resolved. This was tentatively assigned to two not quite equivalent pairs of protons ($a_H \sim 0.1$ G), most probably those of the methylene groups α to the phenolic oxygen atoms. The spectra were insensitive to temperature changes from room temperature to −60 °C, apart from minor changes in line width.

ESR gave no indication of interactions between $II^{-}\cdot$ and either Na^+ or K^+. However, optical spectroscopy provided compelling evidence that they are strongly associated. Solutions of $II^{-}\cdot$ in DME containing either Na^+ or K^+ were yellow. The optical spectrum is shown in Figure 2b. (Evolution of this spectrum in the course of reduction was characterized by an isosbestic point at 326 nm and a parallel increase in the intensity of the ESR signal.) Figure 2c is a spectrum of $II^{-}\cdot$ generated in exactly the same way, except that included in the solution was a slight stoichiometric excess of dicyclohexyl-18-crown-6 (DC-18-C-6). The latter has a significantly greater affinity for alkali metal ions than any of the aromatic ethers used in this study.[24] Despite the profound changes in the optical spectrum, ESR spectra in the presence of DC-18-C-6 were the same as in its absence.

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(14) J. D. Loudon and D. K. Steel, *J. Chem. Soc.*, 1165 (1954).

(15) W. D. Emmons and A. F. Ferris, *J. Am. Chem. Soc.*, **75**, 2257 (1953).

(16) P. H. Rieger, I. Bernal, W. H. Reinmuth, and G. K. Frankel, *J. Am. Chem. Soc.*, **85**, 683 (1963).

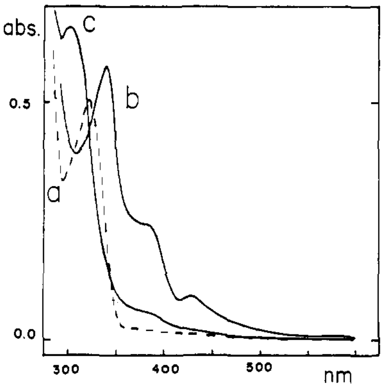

Figure 2. Optical spectra of II in DME (a), $II^{-}\cdot/K^+$ in DME (b), and $II^{-}\cdot$ in DME with dicyclohexyl-18-crown-6 (c), at 18 °C. (The concentration for (b) differs slightly from that of the other two.)[36]

Evidently, association between $II^{-}\cdot$ and alkali-metal cations produces a dramatic bathochromic shift in the principal electronic absorption band, from 300 to 340 nm. By sequestering the cation in the aliphatic crown ether, one presumably observes the spectrum of free $II^{-}\cdot$. Of course, the actual structure of $II^{-}\cdot/K^+$ remains ambiguous. In principle, the cation may be coordinated at any of the three electron-rich sites of the anion: the ether oxygens, aromatic π system, or the nitriles. We shall return to this issue at a later stage.

19,22,23,26-Tetracyano-2,3:11,12-dibenzo-1,4,7,10,13,16-hexaoxaoctadeca-2,11-diene (I). The presence of a second reducible functionality in I introduces an important complication. Two redox couples need now be considered:

$$I \underset{E_1°}{\overset{e^-}{\rightleftharpoons}} I^{-}\cdot \underset{E_2°}{\overset{e^-}{\rightleftharpoons}} I^{2-}$$

Cyclic voltammograms consisted of only a single wave (ΔE_p = 75 ± 5 mV) centered at −1.58 V. No further electroactivity was detected to −2.9 V. Coulometry confirmed that two electrons per molecule were involved (controlled-potential electrolysis at −1.80 V). Thus $E_1°$ and $E_2°$ are sufficiently close that the voltammetric waves merge. Situations of this sort have been rather fully analyzed in recent years.[17,18] The following generalization is relevant. Consider a bifunctional molecule in which the reduction potentials of the two electroactive groups are identical and, furthermore, the electron affinity of each is independent of the oxidation state of the other. As a result of simple statistical contributions to the entropy, the thermodynamic redox potentials for the first and second electron transfers to such a molecule will differ, nonetheless, by an amount (RT/F) ln 4. (For example, neglecting spin, there are still two equivalent ways to add an electron to I or remove one from I^{2-} but only one way to either add or subtract an electron for $I^{-}\cdot$.)[19] Whereas voltammetric waves for the situation $E_1° = E_2°$ are characterized by ΔE_p = 29 mV at 25 °C, the statistical entropy factor results in a wave form identical with that of a one-electron reversible couple (ΔE_p = 59 mV),[18] even though two electrons are actually involved. For the case of I, the separation of peak potentials exceeds this value by 16 mV. We therefore conclude:

$$E_1° - E_2° \simeq (RT/F) \ln 4 + 16 \text{ mV} = 52 \text{ mV} \quad (1)$$

Thus $E_1° = -1.554$ and $E_2° = -1.606$ V vs. Ag/AgCl.

This information allows us to compute the equilibrium constant for disproportionation:

$$2I^{-}\cdot \rightleftharpoons I + I^{2-}$$

$$K_d = \frac{(I)(I^{2-})}{(I^{-}\cdot)^2} = \exp(F(E_2° - E_1°)/RT) = 0.14 \pm 0.1 \quad (2)$$

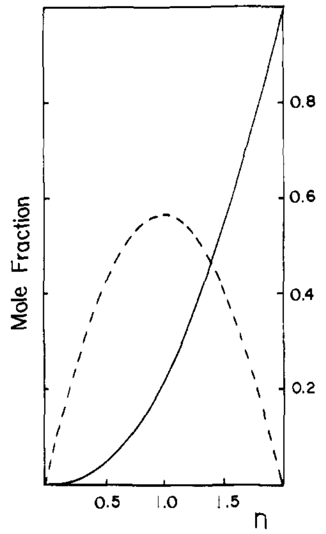

Figure 3. Equilibrium concentrations of $I^{-}\cdot$ (dashed line) and I^{2-} (solid line), calculated as a function of the total stoichiometric extent of reduction, for K_d = 0.14.

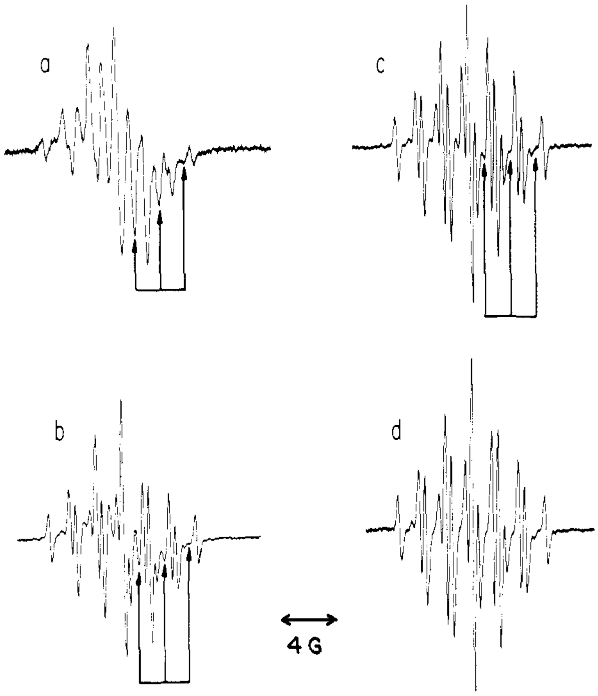

Figure 4. ESR spectra recorded at successive stages in the reduction of I by K in DME, at 18 °C.

Thus disproportionation will strongly influence the concentrations of these species and preclude the preparation of $I^{-}\cdot$ entirely free of I^{2-}. Considerable control can, however, be exercised via the extent of reduction. Figure 3 illustrates variations in the mole fractions of $I^{-}\cdot$ and I^{2-} calculated for K_d = 0.14 as a function of n, the stoichiometric number of electrons added. For values of n between 0.4 and 1.0 it is apparent that substantial concentrations of $I^{-}\cdot$ can be obtained in considerable excess over I^{2-}. This discrimination proved to be of great importance since I^{2-} was found to be a paramagnetic diradical (vide infra).

Measurements of ESR and optical spectra were made following incremental increases in the extent of reduction. This was most conveniently accomplished using the chemical reduction technique. Figure 4 shows ESR spectra obtained at four sequential stages in the reduction of I in DME using a K mirror. Reduction was carried out by successive additions of nonquantitative aliquots of solvated electrons (and K^+ ions). In this instance, nine aliquots were required to complete the reaction (Figure 4d). Further additions produced no further changes in the spectrum other than

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(17) F. Ammar and J. M. Savéant, *J. Electroanal. Chem.*, **47**, 215 (1973).

(18) J. B. Flanagan, S. Margel, A. J. Bard, and F. C. Anson, *J. Am. Chem. Soc.*, **100**, 4248 (1978).

(19) The situation is precisely analogous to protonation equilibria of dibasic acids.

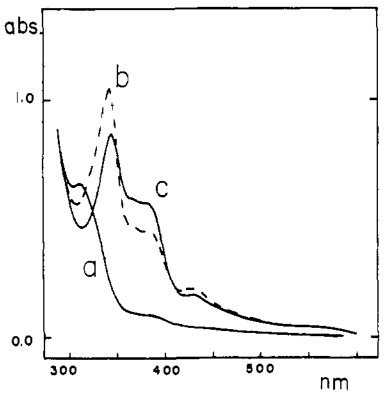

Figure 5. Optical spectra of I in DME (a), following reduction with K to a stage represented by the ESR spectrum in Figure 4a (b), and finally after complete reduction (c). Reduction in the presence of dicyclohexyl-18-crown-6 (not shown) provided spectra identical with Figure 2c.[36]

a gradual decrease in intensity, apparently due to formation of nonparamagnetic secondary products. At each stage represented in Figure 4, the solution was stable for a period of at least 1 h. (Identical results were obtained using Na. Experiments employing Cs produced only insoluble precipitates.) Optical spectra corresponding to stages of reduction represented in Figures 4a and 4d are reproduced in Figure 5.

To summarize, the first aliquots produce an ESR spectrum (Figure 4a) very different from that of $\mathrm{II}^-\cdot$, but exhibiting a g value which is the same within experimental error (2.0027 ± 0.0001). On further increase of n, this is gradually replaced by a new spectrum, virtually identical with that of $\mathrm{II}^-\cdot$. The transition is complete at the stage shown in Figure 4d. At intervening stages, lines corresponding to the two extremes are superimposed, their relative intensities changing monotonically with n. (This can be seen by following the "decay" of the family of three lines indicated by arrows.) It is significant that neither the overall spectral width nor the field positions of any individual lines change detectably throughout the experiment.

The following experiment established that these changes are not simply due to decomposition of some radical initially produced; rather, that the two different spectra in fact correspond to different oxidation states of I which can be interconverted via conproportionation. A solution of I in DME was reduced as above to a stage corresponding to Figure 4d. Then, by means of a glass break-seal, the sample was mixed with an equal quantity of unreacted I. (The entire system had been previously vacuum dried and degassed.) The resulting ESR spectrum exactly matched Figure 4a.

It was also possible to establish that the spectrum in Figure 4d corresponds to I^{2-} (i.e., $n = 2$). A solution of I in DME with 0.2 M TBAP was electrolytically reduced at −1.8 V until the current had dropped to background level and the integrated current represented $n = 1.97$. The solution was poured directly into a quartz flat cell mounted on the electrolysis vessel. The ESR spectrum was identical with Figure 4d.

The near identity of ESR spectra for I^{2-} and $\mathrm{II}^-\cdot$ requires that coupling between the two electron spins of I^{2-} (the exchange integral J) must be smaller than the weakest hyperfine splitting resolvable.[20] As in the case of $\mathrm{II}^-\cdot$, additional structure could be detected, consistent with four roughly equivalent methylene protons ($a_{\mathrm{H}} \simeq 0.11$ G). Thus J must not exceed about 10^{-5} cm^{-1}, qualifying I^{2-} as a ground-state diradical.

The evidence presented so far circumstantially suggests that Figure 4a is the ESR spectrum of $\mathrm{I}^-\cdot/\mathrm{K}^+$, a conclusion which was strongly supported by more detailed analysis. This spectrum proved to be temperature dependent. Figure 6 illustrates variations observed between 36 and −78 °C. These spectra were successfully simulated (Figure 6d–f) by calculations[21] which included dynamic exchange of the electron spin between a pair of equivalent sites, each with hyperfine couplings and degeneracies very similar to those of $\mathrm{II}^-\cdot$. Values of the coupling constants and exchange rates which provided the best fit to the experimental spectra are summarized in Table II along with the kinetic activation parameters. The same spectra were obtained when concentrations of unreduced I were varied from about 5×10^{-5} to 10^{-3} M, indicating that the dynamic exchange process is intramolecular (see Note Added in Proof).

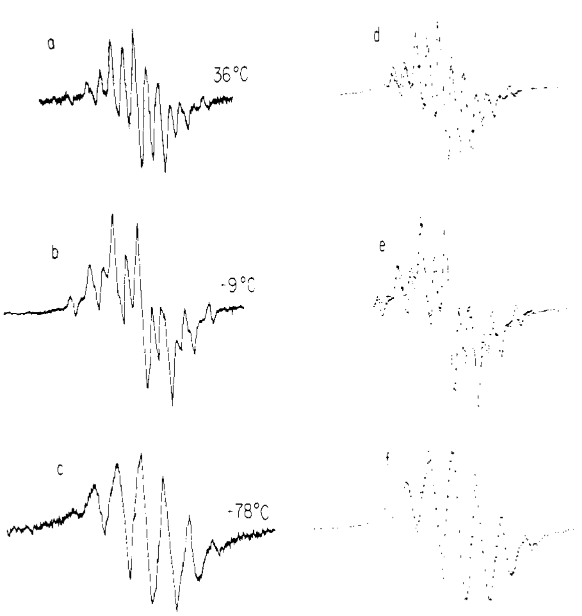

Figure 6. Temperature dependence of ESR spectra (a–c) of $\mathrm{I}^-\cdot/\mathrm{K}^+$ in DME (3×10^{-4} M); (d–f) are computer simulations generated from parameters given in Table II.

Table II. Magnetic and Kinetic Parameters[a] Corresponding to Temperature-Dependent ESR Spectra of $\mathrm{I}^-\cdot/\mathrm{K}^+$ in DME

t, °C	a_{N}, G	a_{H}, G	$k \times 10^{-6}$, s^{-1}
36	1.760	1.506	4.90
18	1.861	1.490	3.92
−9	1.895	1.449	3.14
−30	1.919	1.411	2.49
−50	1.921	1.402	2.03
−78	1.911	1.472	0.88[b]

E_{a}, kcal/mol	A, s^{-1}	ΔH_{298}, kcal/mol	$\Delta S^{\ddagger} + R \ln \kappa$, cal/(K·mol)
1.4 ± 0.2	$4.6 \pm 0.1 \times 10^{7}$	0.8 ± 0.2	−25 ± 1

[a] Parameters determined by least-squares "best fit" by simulated spectra; see ref 21. [b] This point alone deviates markedly from the Arrhenius plot. It was therefore not included in the determination of activation parameters.

Detection of dynamic intramolecular spin exchange in $\mathrm{I}^-\cdot$ was found to require both an associated alkali metal ion (Na^+ or K^+) and a solvent of low dielectric constant. Thus, reduction of I with K or Na in DME in the presence of DC-18-C-6 provided only ESR spectra corresponding to localized spin density (similar to Figure 4d), regardless of the extent of reduction. Such spectra were also observed following electrolytic reduction of I in DME with TBAP or in DMF with NaTPB. (In the latter experiments, n was maintained below 0.7.) It is unfortunate that ESR does not provide any distinction between I^{2-} and a "localized" $\mathrm{I}^-\cdot$ (a consequence of the very small value of J for the former). However, the electrochemical behavior was virtually identical under all conditions, so it is unlikely that these results were due to variations in K_{d}. We therefore feel justified in concluding that ESR spectra obtained at low conversions correspond to $\mathrm{I}^-\cdot$ (or its ion pair) under all conditions.

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(20) See J. E. Wertz and J. R. Bolton, "Electron Spin Resonance", McGraw-Hill, New York, 1972, pp 250–255.

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19,22,23,26-Tetracyano-2,3:11,12-dibenzo-1,4,10,13-tetraoxaoctadeca-2,11-diene (III). The crown-4 derivative, III, was of interest in attempting to elucidate the role of the coordination cavity in ion pairing and in the intramolecular electron transfer mechanism. Under all reduction conditions, only the ESR spectrum characteristic of localized spin density was observed (values of n as low as 0.3). Optical spectra obtained in DME with alkali metal reduction exhibited the same characteristic long-wavelength bands (345, 388, and 450 nm) indicating that, here again, ion pairing is involved and that the structure of the ion pairs is not vastly different from those formed by $\mathrm{I}^{-}\cdot$ or $\mathrm{II}^{-}\cdot$.

Discussion

Of the various conditions studied, intramolecular electron transfer was actually observed for $\mathrm{I}^{-}\cdot$ only when associated with Na^+ or K^+ in DME. Of course the ability of ESR to reveal a dynamic process is limited to rates between about 10^5 and 10^8 s^{-1}. Presumably the same reaction occurs under the other conditions, but at a rate less than 10^5 s^{-1}. (Investigations at temperatures above 36 °C were not possible owing to rapid decomposition of the samples.)

The results are in rather good accord with expectations based on the qualitative electrostatic arguments presented earlier. According to this view, contributions from ion pairing to the activation barrier for electron transfer should be negated when the cation is located midway between the donor and acceptor. Furthermore, this association was expected to weaken electrostatic "trapping" by the solvent. The very low activation energy measured for $\mathrm{I}^{-}\cdot/\mathrm{K}^+$ in DME, as well as the substantial retardation caused by sequestering the cation with DC-18-C-6, is perfectly consistent with both of these notions. That is, the activation barrier is apparently significantly higher for dissociated $\mathrm{I}^{-}\cdot$, regardless of the solvent. If one assumes the preexponential factor to be independent of ion pairing, then E_a for dissociated $\mathrm{I}^{-}\cdot$ must be greater than 2.7 kcal/mol. (As we shall see, DME is capable of providing an electrostatic barrier of at least this magnitude.) In DMF, interaction must be significantly stronger still. It is, therefore, reasonable that electron transfer was too slow to be detected by ESR, even with K^+ ions present.

Marcus theory[22] provides a means to estimate electrostatic contributions of solvation to the free energy of activation for electron transfer between ions and neutrals. For the case of dissociated $\mathrm{I}^{-}\cdot$, this energy is given by

$$\tfrac{1}{4}(1/r - 1/R)(1/\epsilon_{\mathrm{op}} - 1/\epsilon)e^2 \qquad (3)$$

where r is the effective radius of the donor HOMO (taken to be an antibonding π orbital localized on one of the two aromatic rings), and R is the distance between the centers of the two rings. ϵ_{op} and ϵ are respectively the optical and static dielectric constants of the solvent. These two parameters vary only rather little with temperature, and in the same direction. Consequently, this electrostatic free energy, to a good approximation, is reflected only in the enthalpy of activation. For values of $r = 6$ Å and $R = 10$ Å (the latter based on published[23] crystal structures for complexes of 1,10-dibenzo-18-crown-6), the calculated energies are 4.5 kcal/mol for DME and 8.7 kcal/mol for DMF. The fact that $\Delta H^{\ddagger}$ for $\mathrm{I}^{-}\cdot/\mathrm{K}^+$ in DME is only 0.8 kcal/mol reflects the remarkable extent to which cationic association has liberated the anion from the solvent dipole field.

Structural Details. Two aspects of the structure of $\mathrm{I}^{-}\cdot/\mathrm{K}^+$ are of particular importance for understanding the mechanism of electron transfer: the distance between the aromatic rings and the location of the cation. Our results bear only indirectly on these details, but certain conclusions can be justified.

Crystallographic studies by Bright and Truter[23] for the parent system, dibenzo-18-crown-6, and its Na^+ and Rb^+ complexes, provide a basis for understanding the conformational properties of $\mathrm{I}^{-}\cdot/\mathrm{K}^+$. The configuration of the macrocycle is remarkably similar for free and complexed crowns. The angle between planes containing the aromatic rings varies somewhat, but in all cases the 1,2-dioxyethane bridges were found to adopt a staggered *gauche*-butane conformation and the distance between the center of the two π systems lies between 9 and 11 Å.

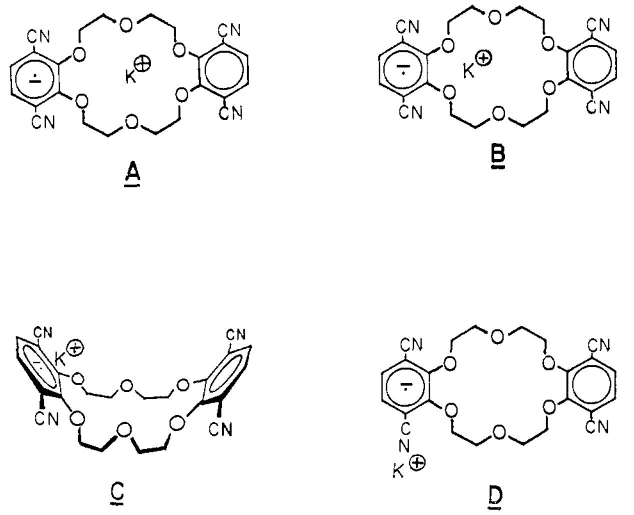

Figure 7. Alternative structures for $\mathrm{I}^{-}\cdot/\mathrm{K}^+$.

It is tempting to imagine that electron transfer in $\mathrm{I}^{-}\cdot/\mathrm{K}^+$ might occur via a less stable, folded conformation in which the aromatic rings are more proximal. Inspection of molecular models indicates that a distance as small as 4 Å can be achieved, but only at the expense of severe van der Waals interactions between the phenolic oxygens (O–O distances of about 2.4 Å with lone-pair orbitals juxtaposed). Moreover, interconversion between this folded conformer and the more extended geometry favored by dibenzo-18-crown-6 requires eclipsing each of the 1,2-dioxyethane bridges. Our kinetic results require that any such intervening conformational changes must be accomplished with less than 0.8 kcal/mol, yet a barrier of at least 5 kcal/mol must be anticipated for internal rotations of this sort. Alternatively, a folded conformer could benefit from one-electron donor–acceptor (DA) bonding between the aromatic rings. If this interaction were sufficiently strong to stabilize the folded conformer, then of course no rearrangement would have to precede electron transfer. However, here again the evidence is negative.

Two pieces of information are relevant to assessing the magnitude of DA bonding between the two aromatic rings of $\mathrm{I}^{-}\cdot/\mathrm{K}^+$. First, in the limit of slow intramolecular exchange, hyperfine couplings were detected for nuclei of only one ring at a time. If we crudely equate charge density with spin density, then the extent of instantaneous charge delocalization must not exceed about 5% (the ratio of spectral resolution to the largest hyperfine splitting observed). The second point is that optical spectra gave no evidence of an intramolecular charge-transfer transition (or optical intervalence transition). Spectra were recorded from 280 to 2200 nm. The limit of sensitivity corresponded to an extinction coefficient of about 20. Beyond the mere lack of positive evidence, these facts indicate that DA bonding cannot exceed 0.19 kcal/mol. (This conclusion is justified by analysis presented in the following section.) It therefore seems highly unlikely that unusual folded conformers play any role, transient or otherwise, in the electron-transfer process.

As already noted, coordination of alkali-metal ions could involve any or all of three distinct electron-rich sites on the anion. Figure 7 summarizes the various alternatives. Structures B, C, and D feature varying degrees of dissymmetry. The least symmetric, D, can be tentatively discounted on the basis of ESR. N-Coordination should perceptibly distort the spin distribution within a single aromatic ring such that the two $^{14}\mathrm{N}$ nuclei would display different hyperfine couplings. Since this was never observed for any of the anion radicals studied here, either N-coordination is unimportant or else the cation migrates between the two nitrogens of a given ring roughly 100 times faster than it is transferred to the opposite ring.

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The absence of detectable electron transfer for $\mathrm{III}^{-}\cdot/\mathrm{K}^{+}$ indicates that the central ether oxygens of $\mathrm{I}^{-}\cdot/\mathrm{K}^{+}$ must play an important role. Accordingly, the fully symmetric structure A remains the most likely representation of the activated complex for electron transfer. Our data are insufficient to indicate whether or not it also represents the equilibrium geometry for the ion pair.

It would be desirable to have more certain evidence regarding these structural details. Nonetheless, our limited results are consistent with a picture in which very little motion is required to interconvert between the two unsymmetrically charged ground states.

The Case for a Nonadiabatic Mechanism. While there is nothing unusual about the rates of electron transfer observed for $\mathrm{I}^{-}\cdot/\mathrm{K}^{+}$, the activation parameters are quite exceptional. Arrhenius parameters reported for similar bifunctional radical anions[8,9] fall within the range $E_a = 5$–10 kcal/mol, $A = 5 \times 10^{11}$ to 5×10^{14} s^{-1}. Having already discussed the factors which depress the activation energy, we now turn our attention to the extraordinarily low frequency factor ($A = 4.6 \times 10^{7}\ \mathrm{s}^{-1}$). In the framework of transition-state theory, this corresponds to $\Delta S^{\ddagger} + R \ln \kappa = -25$ cal/(K·mol). Typically, for reactions which involve motion within a single potential-energy surface, one assumes that the transmission coefficient, κ, is close to unity. In the present instance such an assumption is not justified. It would imply an unusually large negative entropy of activation. Considering the limited degrees of freedom available to the molecule and its counterion, it is difficult to imagine how such a large entropy change could be brought about with so little expenditure of enthalpy. On the other hand, a nonadiabatic mechanism, in which electron redistribution at the transition state is rendered inefficient, due to extremely weak coupling between initial and final states, would be expected to give rise to a transmission coefficient much less than unity.

Distinction between adiabatic and nonadiabatic mechanisms has been discussed within the framework of various kinetic models.[2,3,28] Although it is not the sole determining factor, of prime importance is the magnitude of electronic coupling, H_{if}:

$$H_{\mathrm{if}} = \langle \Psi_{\mathrm{i}} | \mathcal{H}_{\mathrm{e}} | \Psi_{\mathrm{f}} \rangle \tag{4}$$

where $\mathcal{H}_{\mathrm{e}}$ is the electronic Hamiltonian constructed according to the adiabatic approximation, and Ψ_{i} and Ψ_{f} are wave functions for the system with the odd electron localized respectively on each of the two aromatic rings. According to various estimates,[2b,3] $|H_{\mathrm{if}}|$ must not exceed 0.1–0.5 kcal/mol in order that κ be significantly affected.

The magnitude of H_{if} has additional significance for the spectroscopic properties of the molecule. If we assume that it is relatively insensitive to the changes of nuclear configuration which attend the electron transfer, then the same parameter governs the extent of charge delocalization, q, in the ground state, and the energy of the intramolecular charge-transfer transition, $h\nu_{\mathrm{ct}}$. According to the perturbational formulation of charge-transfer theory,[25] we have (neglecting overlap)

$$q = H_{\mathrm{if}}^{2}/\Delta^{2} \tag{5}$$

$$h\nu_{\mathrm{ct}} = \Delta + (2H_{\mathrm{if}}^{2}/\Delta^{2}) \tag{6}$$

where Δ is the energy difference between the zeroth-order states, Ψ_{i} and Ψ_{f}, for the particular (unsymmetrical) nuclear configuration (molecular plus solvation) which constitutes the ground-state energy minimum. For our system this is essentially the difference between the vertical ionization potential of $\mathrm{II}^{-}\cdot$ and the vertical electron affinity of II.

As noted earlier, the ESR evidence limits q to a value no greater than about 0.05, and there was no detectable charge-transfer absorption at energies greater than 4500 cm^{-1}. If we assume, as argued by Hush,[26] that $h\nu_{\mathrm{ct}} \simeq 4\Delta H^{\ddagger} = 1120\ \mathrm{cm}^{-1}$, then it follows that $1018 < \Delta < 1120\ \mathrm{cm}^{-1}$, and $|H_{\mathrm{if}}| < 250\ \mathrm{cm}^{-1}$. (Unfortunately, the relevant spectroscopic region was obscured by strong vibrational bands.) The maximum DA bonding energy corresponding to these conditions would be $H_{\mathrm{if}}^{2}/\Delta = q\Delta < 56\ \mathrm{cm}^{-1}$ (0.19 kcal/mol). Alternatively, the charge-transfer transition might not have been detected, owing simply to inadequate oscillator strength ($\epsilon_{\max} < 20$). If so, then according to another approximation of Hush's[26] we obtain $q < 10^{-4}$ and $H_{\mathrm{if}} < 20\ \mathrm{cm}^{-1}$. (This was calculated assuming a broad band (1000 cm^{-1}) centered at 5000 cm^{-1}.)

A more dependable measure of these parameters would be highly desirable; however, the above exercise demonstrates that the coupling must be small, certainly less than 1 kcal/mol, and possibly much less. It is noteworthy that such weak interaction need not be provided by direct through-space communication of the aromatic π orbitals. Indirect coupling, mixing of high-energy configurations involving ionized states of solvent, cations, or bridging groups, may also be involved.[27]

Quantum-mechanical models for electron-transfer kinetics are more general than transition-state theory and can provide some insight regarding $\mathrm{I}^{-}\cdot/\mathrm{K}^{+}$. Following Kestner, Logan, and Jortner[29] and Ulstrup,[30] the unimolecular rate constant may be expressed as follows:

$$k = \frac{2\pi H_{\mathrm{if}}^{2}}{\hbar} \frac{\sum\limits_{v}\sum\limits_{w}[\langle \chi_{\mathrm{i}v} | \chi_{\mathrm{f}w} \rangle]^{2} \delta(\epsilon_{\mathrm{i}v} - \epsilon_{\mathrm{f}w}) \exp(-\epsilon_{\mathrm{i}v}/KT)}{\sum\limits_{v} \exp(-\epsilon_{\mathrm{i}v}/KT)} \tag{7}$$

where $\chi_{\mathrm{i}v}$ and $\chi_{\mathrm{f}w}$ are the total vibrational wave functions respectively for the vth quantum level of the initial state and the wth level of the final state. $\epsilon_{\mathrm{i}v}$ and $\epsilon_{\mathrm{f}w}$ are corresponding energies. The δ function is included in accord with the Franck–Condon principle; it has units of reciprocal energy.

This relation has been shown[29] to produce the normal Arrhenius temperature dependence within suitably restricted temperature ranges as determined by the frequency distribution of the various modes. That is, for many experimental systems such as ours, the distinction can be drawn between high-frequency molecular modes, coordinates $Q_1, Q_2, ..., Q_m$, for which the available thermal energy is inadequate to populate any but the ground states, and low-frequency modes, coordinates $Q_{m+1}, Q_{m+2}, ..., Q_{3n-6}$, which are thermally excited. Only the latter modes contribute to the temperature dependence of k, the empirical activation energy. The corresponding frequency factor takes the form

$$A = (2\pi H_{\mathrm{if}}^{2}/\hbar)\sum_{w}[\langle \chi'_{\mathrm{i}0}(Q_1, ..., Q_m) | \chi'_{\mathrm{f}w}(Q_1, ..., Q_m) \rangle]^{2} \delta(\epsilon'_{\mathrm{i}0} - \epsilon'_{\mathrm{f}w}) \tag{8}$$

where $\chi'_{\mathrm{i}0}$ and $\chi'_{\mathrm{f}w}$ are those cofactors of the total vibrational wave functions which govern the high-frequency modes and $\epsilon'_{\mathrm{i}0}$ and $\epsilon'_{\mathrm{f}w}$ are the corresponding fractions of the total vibrational energies.

The vibrational overlap integrals (in brackets) will in general be less than unity. This is due to shifts in the frequency and/or equilibrium position for various "dependent"[33] modes (those which differ between initial and final states). For example, in $\mathrm{I}^{-}\cdot/\mathrm{K}^{+}$, the nitrile stretching modes are of sufficiently high frequency to be included among these terms, and their frequencies are known to change upon addition of an electron.[34] As noted, some motion of the K^{+} ion may also be required; however, this would involve changes in low-frequency modes and, as such, would influence E_a but not A.

To our knowledge, in only one other situation has a nonadiabatic mechanism for electron transfer been established. Ingenious pulse radiolysis experiments have been employed by Miller and coworkers[31] to investigate electron transfer between pairs of organic

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molecules dissolved in a glass at low temperature. Their studies yield rates of reaction as a function of distance (edge to edge) between donor and acceptor down to about 14 Å. Their data appear to be in good accord with the quantum-mechanical model for a nonadiabatic system.[31] The edge-to-edge distance between aromatic rings in $I^-\cdot/K^+$ is about 7 Å. Miller's results for electron transfer from acridine radical anion to ethylanthraquinone in methyltetrahydrofuran glass may be extrapolated to the same distance to give 5×10^9 s^{-1}.[35] That particular intermolecular reaction is slightly exothermic and believed to proceed with negligible activation energy; therefore, the rate may be directly compared with the preexponential factor for intramolecular transfer in $I^-\cdot/K^+$ (4.6×10^7 s^{-1}). The 100-fold discrepancy may be due to differences in either H_{if} or the vibrational overlap terms or both. In Miller's experiments, the rate represents an average for various different relative orientations of the two components. Among these may be some for which electronic coupling is somewhat stronger than in $I^-\cdot/K^+$. A possible difference in the vibrational overlap terms may stem from the fact that there are four high-frequency nitrile stretching modes for $I^-\cdot/K^+$ but only two comparable carbonyl stretching modes in the quinone of Miller's example.

Note Added in Proof. Solutions of II$^-\cdot$, in the presence of a large excess of II, gave rise to ESR signals substantially broadened due to intermolecular electron transfer. These spectra differ qualitatively from those of dilute solutions of $I^-\cdot/K^+$ in DME, further substantiating an intramolecular mechanism for the latter.

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(36) Optical spectra are uncorrected for background absorption from cell.

(37) Laboratorium für Organische Chemie der Eidgen, Technischen Hochschule, Zürich.

Active-Site Interactions in Fluorine-19 Labeled [Methionine-192]-α-chymotrypsin[1]

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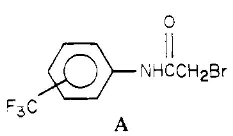
Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. Received October 8, 1979

Abstract: Fluorine-labeled derivatives of α-chymotrypsin were prepared by specific alkylation at the active-site Met-192 by *o*-, *m*-, and *p*-(trifluoromethyl)bromoacetanilides (*o*-, *m*-, and *p*-A), respectively. Their chemical shifts were sensitive to the pH-dependent oligomerization equilibria at pH 5.7 and to the binding of the specificity pocket directed competitive inhibitor indole. In all cases an upfield shift was observed with indole that approached the (pH independent) chemical-shift values in 6 M urea. The K_{dissoc} (= K_D) for indole binding at pH 4.2 from the ^{19}F NMR titrations were as follows: *o*-A, 5.3 ± 2.3 mM; *m*-A, 3.2 ± 0.7 mM; *p*-A, 3.7 ± 0.5 mM. These latter constants were in reasonably close agreement with the K_I values obtained for indole vs. the substrate Ac-Tyr-OEt (B. H. Landis and L. J. Berliner, *J. Am. Chem. Soc.*, following paper in this issue). The extrapolated chemical shifts for infinite indole binding were indicative of a shift of the CF$_3$ moiety toward the solvent environment but still retained a significant degree of nonsolvated character as compared with the corresponding 6 M urea denatured derivative. A partition coefficient or "intramolecular competitive inhibition constant" was derived for the equilibrium between binding by the trifluoromethylacetanilido moiety in the "tosyl pocket" and a second environment outside this pocket where tosyl pocket binding was 23, 51, and 23% for *o*-, *m*-, and *p*-A, respectively.

Previous structural and chemical modification studies have indicated a role for the side chain of Met-192 in both the activation of α-chymotrypsin from its zymogen, chymotrypsinogen, and in the binding and orientation of α-chymotrypsin substrates during catalysis.[3] Particularly for smaller substrates, the Met-192 side chain acts as a "lid" over the hydrophobic side chain binding pocket, the "tosyl hole".[4] Of particular interest has been the kinetic consequences of specific alkylation of this side chain with α-halo ketones or amides as shown, for example, by Schramm and Lawson[5] and Kẽzdy et al.[6] Furthermore, it has seemed reasonable that an aromatic moiety on Met-192 might, in fact, bind favorably in the "tosyl pocket".

Fluorine NMR studies of biological systems are advantageous from two principal viewpoints: the high sensitivity of ^{19}F and the simplicity of no more than a few lines in the NMR spectrum. The broad chemical-shift range and sensitivity of ^{19}F can render an appropriately designed active-site probe a sensitive indicator of active-center interactions.[7a] In particular, Bittner and Gerig[7b,c] first reported the synthesis of the *o*-, *m*-, and *p*-(trifluoromethyl)bromoacetanilides, *o*-, *m*-, *p*-A, and ^{19}F relaxation times



A

for these reagents as their Met-192 sulfonium derivatives on native and denatured α-chymotrypsin. The transverse relaxation times (T_2) of the labeled alkylated derivatives decreased in the order *o*-A > *m*-A > *p*-A-chymotrypsin, respectively, which they sug-

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(1) Portions of this work were presented at the 11th Jerusalem Symposium on Quantum Chemistry and Biochemistry, Apr 3–7, 1978.

(2) Armour Pharmaceuticals Co., Kankakee, IL 60901.

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