equilibration of the diastereomeric ion pair forms.[19] Hence methylation by dimethyl sulfate at −78 °C is so slow that equilibration can proceed to a significant extent (run 2b, Table III).

The above effects, in particular the effects of reaction stoichiometry and the temperature–time profile of the reaction, have not been observed in the analogous dimerization reactions involving the addition of α-lithio-2-ethylpyridine to 2-vinylpyridine in THF followed by methylation.[7] These reactions resulted in the stereoselection formation of *meso*-2,4-di(2-pyridyl)butane (>99% at −78 °C) and were found to be only dependent on the temperature of methylation. As seen in **7a** and **8a**, coordination of the metal ion by the lone pair of the penultimate nitrogen atom brings about a difference in stability of the two diastereomeric ion pairs with ion pair **7** being strongly favored over **8**. Attempts to differentiate between **7** and **8** by NMR techniques[20] have failed, presumably as a result of their rapid interconversion.

In conclusion, the methylation stereochemistry of **4** is dependent upon the method of generation of the carbanion, the stoichiometry and optical purity of **2** and **3**, and the time–temperature profile of the carbanion solution. In most cases, it reflects the relative rates of formation, depletion, and slow interconversion of the diastereomeric ion pairs. If one warms the carbanion solution, the interconversion of the *pro-R* and *pro-S* diastereomeric ion pairs becomes rapid, and upon cooling the thermodynamic mixture is frozen out. Thus, the methylation stereochemistry can be determined either kinetically or thermodynamically by controlling the time–temperature profile of the carbanion solution and the stoichiometry and optical purity of the reagents.

(19) Such effects for monomeric sulfinyl carbanions have been observed. Solladie, G.; Zimmerman, R.; Bartsch, R. *Tetrahedron Lett.* **1983**, *24*, 755.
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Acknowledgment. Support by the National Science Foundation, Division of Materials Research, Polymers Program, is gratefully acknowledged. We also acknowledge the use of the Chemistry Department Nicolet NT-300 NMR spectrometer supported by the instrument program of the NSF Chemistry Division. Thanks are also due to Dr. R. Sheardy (University of Rochester, Rochester, NY) for his help in obtaining the 400-MHz NMR spectra, and to Dr. G. Palenik and Dr. V. Lynch (University of Florida) for the X-ray data.

Registry No. (*R*)-(+)-**1**, 51207-25-1; (±)-**1**, 67529-33-3; (±)-**2**, 96614-05-0; (*R*)-(+)-**2**, 88180-52-3; (*R*)-(+)-**3**, 89299-86-5; (±)-**3**, 88180-53-4; (±)-(*R,S,S*)-**4**, 96556-01-3; (±)-(*R,S,R*)-**4**, 96614-06-1; *meso*-(*R,S,R,S*)-**5**, 96614-09-4; (±)-(*R,S,S,S*)-**5**, 96614-10-7; (±)-(*R,S,S,R*)-**5**, 88243-86-1; (±)-(*R,S,R,R*)-**5**, 96614-11-8; (±)-(*R,R,R,R*)-**5**, 96646-21-8; *meso*-(*R,R,S,S*)-**5**, 88180-51-2; (±)-(*R,S,S*)-**6**, 96614-07-2; (±)-(*R,S,R*)-**6**, 96614-08-3; (*l*)-menthol, 2216-51-5; benzenesulfonyl chloride, 4972-29-6; (*l*)-1-menthylbenzene sulfinate (isomer 1), 34513-32-1; (*l*)-1-menthylbenzene sulfonate (isomer 2), 96614-12-9; ethylmagnesium iodide, 10467-10-4; (±)-ethyl benzenesulfonate, 96556-00-2; vinylmagnesium bromide, 1826-67-1.

Solvolysis of 1-Arylethyl Tosylates. Kinetic and Stereochemical Tests for Solvent Participation

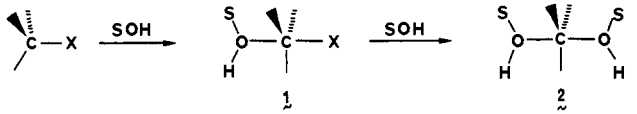
Annette D. Allen, V. M. Kanagasabapathy, and Thomas T. Tidwell*

Contribution from the Department of Chemistry, University of Toronto, Scarborough Campus, West Hill, Ontario, Canada M1C 1A4. *Received December 26, 1984*

Abstract: Solvolytic studies of the 1-arylethyl tosylates **8a** (Ar = 3-BrC_6H_4), **8b** (Ar = 3-$CF_3C_6H_4$), and **8c** (Ar = 3,5-$(CF_3)_2C_6H_3$) show that in relatively nonnucleophilic solvents all three substrates have polarimetric rates markedly faster than rates of product formation. These products are largely racemic, but solvolysis of **8c** in CF_3CO_2H gives 6% net retention. In the more nucleophilic solvents the rates of product formation are close to the polarimetric rates and the products show extensive inversion of configuration. The results are interpreted in terms of an ion-pair mechanism in which nucleophilic solvent attack on the ion pair plays a major role. In the less nucleophilic solvents this attack is rate limiting, whereas attack of the more nucleophilic solvents is fast and initial ionization is rate limiting. Direct displacement by the solvent could contribute to the reactions in the more nucleophilic solvents but is not required by any of the results. The ion-pair mechanism provides a single consistent explanation for the results in all the solvents with all the substrates, and also readily accommodates a variety of other results in the literature, particularly the findings of oxygen and deuterium scrambling, and elimination during solvolysis.

The classic description of solvolytic reactivity in terms of discrete S_N1 and S_N2 pathways became highly developed in the 1930's and was summarized by Ingold in 1953.[1a] Since that time this area has attracted continuous attention and has been frequently reviewed.[1b,c] Recently the specific role of nucleophilic agents in the rate-limiting transition states in the "borderline" or "combat zone"[1b] region where these mechanisms (designated k_c and k_s, respectively, for solvolysis[1d]) become competitive has been the topic of particularly strong interest. As described below, these developments have prompted us to carry out a systematic test of the simultaneous effect on both reaction rates and product stereochemistry of changing electron demand in 1-arylethyl tosylates, a system of invariant steric requirement which is well suited to elucidate behavior in this region.

Scheme I



1 2

A provocative early proposal by Doering and Zeiss[2a] that appeared in 1953 was that pentacovalent intermediates could in-

(1) (a) Ingold, C. K. "Structure and Mechanisms in Organic Chemistry", 1st ed.; Cornell University Press, Ithaca, NY, 1953. (b) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345–375. (c) Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1–67. (d) This classification is due to Winstein; see footnote 2 of Schleyer, P. v. R.; Fry, J. L.; Lam, L. K. M.; Lancelot, C. J. *J. Am. Chem. Soc.* **1970**, *92*, 2542–2544.

(2) (a) Doering, W. v. E.; Zeiss, H. H. *J. Am. Chem. Soc.* **1953**, *75*, 4733–4738. (b) For prior discussions of this idea see: Winstein, S.; Grunwald, E.; Jones, H. W. *Ibid.* **1951**, *73*, 2700–2707, and references therein. See also Streitwieser, A., Jr. "Solvolytic Displacement Reactions"; McGraw-Hill: New York, 1962; pp 66–69.

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tervene in solvolysis processes. These authors found that the methanolysis of 3,5-dimethyl-3-hexyl phthalate occurred with net 54% inversion of configuration and 46% racemization, and they concluded that the process in Scheme I occurred, where X is the solvated leaving group, SOH is the solvent, and **1** is a reaction intermediate that could undergo solvent displacement to give the symmetrical species **2**. Product formation from **1** would give inverted products whereas formation of **2** would result in racemization. Electrophilic coordination of the solvent to X was also shown,[2a] and is clearly significant, but is omitted for clarity.

These authors rejected an alternative explanation that the partial net inversion of configuration arose from solvent displacement on an unsymmetrically solvated tricovalent intermediate with the statement: "With the extent of inversion being in fact so surprisingly large in the tertiary case investigated here, it seems unconvincing to us that a shielding effect operating at a comparatively large distance could be the responsible factor."

The possibility of covalent interaction of solvent with the intermediate ion in the S_N1 reaction had already been considered by Hughes, Ingold, Winstein, and others,[2b] and the Doering–Zeiss proposal has continued to receive serious attention,[3] but not universal acceptance.

Consideration of the dependence of the rates of solvolyses on the solvent ionizing power parameter Y and the nucleophilicity parameter N has led to the proposal[4a,b] of an "S_N2-intermediate" mechanism that closely resembles Scheme I. Particular importance in this proposal was ascribed to the occurrence of intermediate rate dependence on ionizing power as reflected by the parameter m; thus values of m in the range 0.6 to 0.8 that were intermediate between those for S_N1 and S_N2 reactions were ascribed to a mechanism intermediate between these two.[4a,b] A clear affinity between the Doering–Zeiss and "S_N2-intermediate" proposals was recognized,[4a,b] and although the latter uses a dotted-rather than solid-line convention to show the nucleophilic interaction at the central carbon in **1** and **2**, a strong, specific effect is clearly implied. This proposal has recently been invoked in some remarkably different contexts.[4c,d]

Other relevant results include the isolation of a stable salt assigned a structure possessing the features of the S_N2 transition state with pentacoordinate carbon,[5] and recent theoretical calculations[6] have dealt with the formally pentacoordinate species CLi_5,[6a] as well as the transition states for S_N1 and S_N2 reactions.[6b-d] Ion pairs[7] and borderline solvolysis have recently been of great interest,[8-13] and it appeared to us that the study of optically active 1-arylethyl tosylates would provide a critical test of reaction mechanisms in the borderline region.

Chart I

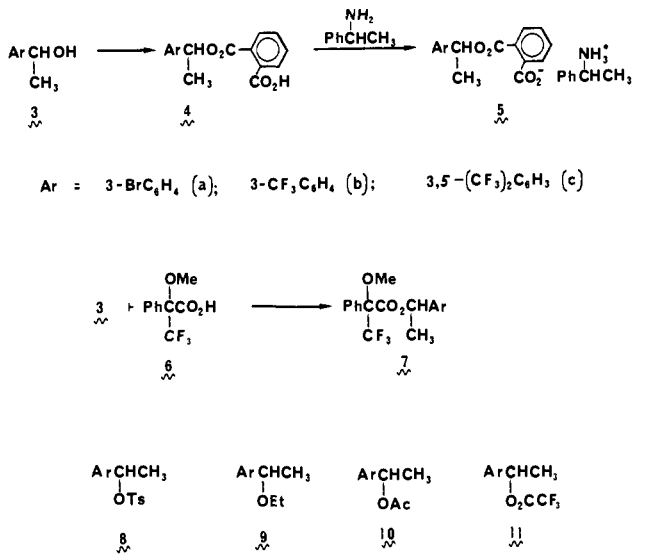

Table I. Optical Rotations, ^{19}F Chemical Shifts, and Optical Purities of 1-Arylethyl Derivatives

$[\alpha]_{436}$ ($CHCl_3$, 25 °C)[a]	3-BrC_6H_4 (**a**)	3-$CF_3C_6H_4$ (**b**)[c]	3,5-$(CF_3)_2C_6H_3$ (**c**)[c]
3	+51.4 ± 0.2[b]	−64.1 ± 0.5	−43.8 ± 0.2
4	−3.80 ± 0.8[b]	+13.8 ± 0.2	+15.1 ± 0.2
8	−78.4 ± 0.3[c,h]	−70.9 ± 1.8	−65.5 ± 0.6
9	+105.0 ± 2.0[b]	−125.9 ± 1.8	−101.8 ± 4.2
10	+126.9 ± 0.8[b]	−144.1 ± 0.4	−103.7 ± 1.5
11			−124.8 ± 5.3
$\delta(^{19}F)$ **7**[d]	4.94,[e] 4.41[f]	4.67,[e] 4.27[f]	5.29,[e] 4.60[f]
e.e.[g]	77.6 ± 8.4[c,h]	92.6 ± 2.6	99.6 ± 7.2

[a] Average of two determinations at 436 nm; rotations also measured at 546, 578, and 589 nm. [b] *R* absolute configuration (ref 17) from (+)-1-phenylethylamine. [c] *S* absolute configuration (ref 17) from (−)-1-phenylethylamine. [d] In ppm downfield from internal CF_3CO_2H in $CDCl_3$. [e] Major. [f] Minor. [g] Enantiomeric excess. [h] (*S*)-(−)-**3**, $[\alpha]_{436}$ −49.8 ± 0.1, used to prepare the **7a** and (−)-**8a** cited.

Table II. Solvolytic Rate Constants for Product Formation from $ArCH(OTs)CH_3$ at 25 °C[a]

	R		
solvent	3-BrC_6H_4 (**8a**)	3-$CF_3C_6H_4$ (**8b**)	3,5-$(CF_3)_2C_6H_3$ (**8c**)
TFA		0.146^e	2.69×10^{-4} [e]
100% HFIP		1.31×10^{-2}	1.79×10^{-5}
97% HFIP	0.267	2.19×10^{-2}	1.36×10^{-5}
100% TFE	1.84×10^{-2} [b]	1.95×10^{-3}	
97% TFE	1.90×10^{-2} [b]	2.22×10^{-3} [f]	4.19×10^{-6} [h]
HOAc	1.02×10^{-4} [c]	2.04×10^{-5} [g]	1.48×10^{-7} [i]
60% EtOH	1.12×10^{-2} [d]		
80% EtOH	1.57×10^{-3} [d]	5.30×10^{-4} [d]	1.08×10^{-5} [j]
90% EtOH	5.99×10^{-4} [d]	1.88×10^{-4} [d]	
100% EtOH	1.43×10^{-4} [d]	4.80×10^{-5} [d]	1.17×10^{-6} [k]

[a] At least duplicate runs ±5% measured by UV at 240 nm unless noted. [b] UV, 235 nm, rate in TFE containing 5% Et_2O: 1.28×10^{-2} s^{-1}. [c] UV, 258 nm. [d] UV, 245 nm, and conductivity. [e] UV, 274 nm. [f] UV, 265 nm. [g] UV, 255 nm. [h] Extrapolated from rate constants ($s^{-1} \times 10^5$): 4.48 (47.0 °C), 25.5 (65.3 °C), 57.7 (74.3 °C); $\Delta H^* = 19.9$ kcal/mol, $\Delta S^* = -16.3$ eu; UV 250 nm. [i] Extrapolated from rate constants ($s^{-1} \times 10^5$): 0.683 (54.1 °C), 2.63 (65.4 °C), 7.10 (74.8 °C); $\Delta H^* = 25.0$ kcal/mol, $\Delta S^* = -6.1$ eu; UV 260 nm. [j] Extrapolated from rate constants ($s^{-1} \times 10^4$): 1.06 (47.0 °C), 5.44 (65.4 °C), 13.1 (75.0 °C); $\Delta H^* = 15.0$ kcal/mol, $\Delta S^* = -17.4$ eu. [k] Extrapolated from rate constants ($s^{-1} \times 10^4$): 0.150 (47.0 °C), 1.01 (65.4 °C), 2.47 (75.0 °C); $\Delta H^* = 21.4$ kcal/mol; $\Delta S^* = -13.7$ eu.

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Table III. Polarimetric Rate Constants, Rate Ratios $k_\alpha/k_{\text{product formation}}$ (in Parentheses), and Net Stereochemistry of Substitution [in Brackets] at 25 °C for $ArCH(OTs)CH_3$ (**11**)[a]

solvent[b]	3-BrC_6H_4 (**8a**)	3-$CF_3C_6H_4$ (**8b**)	3,5-$(CF_3)_2C_6H_3$ (**8c**)
TFA			3.77×10^{-4} (1.4) [6% ret][e]
HFIP		3.14×10^{-2} (9.2)[d] [rac]	3.77×10^{-5} (2.1) [*l*]
TFE	2.40×10^{-2} (1.9)[c] [rac]	2.78×10^{-3} (1.4) [*k*]	
HOAc	1.13×10^{-4} (1.1) [40% inv][f]	2.20×10^{-5} (1.1) [46% inv][g]	[77 inv][h]
EtOH	1.58×10^{-4} (1.1) [72% inv][i]	4.64×10^{-5} (1.0) [74% inv][j]	[87 inv][h]

[a] At least duplicate runs in each case ±5%, invariant with wavelength of rate measurement. [b] 100% solvents unless noted. [c] Rate measured in the presence of 5% Et_2O. [d] 8.7 ± 0.1 °C, $k_{UV} = 3.41 \times 10^{-3}$ s^{-1}. [e] 6.3 and 5.6% from isolated product and k_α, respectively. [f] 42 and 38% from isolated product and k_α, respectively. [g] 48 and 45% from isolated product and k_α, respectively. [h] From rotations of samples heated for 10 half-lives for solvolysis. [i] 76 and 68% from isolated product and k_α, respectively. [j] From final rotation of k_α. [k] Authentic product not available, measured rotation changed from −0.82 to 0.15° during the reacion. [l] Authentic product not available, measured rotation changed from −0.88 to −0.15 during the reaction.

The 1-arylethyl system has been intensively studied over the years,[8a,11b-e,14] including optically active substrates,[12c,14a,b,d,h,j] and it clearly possesses reactivity in the region where unimolecular and bimolecular mechanisms can become competitive. By the use of a variety of aryl substituents and solvents it appeared this system could be fine-tuned to display the gamut of mechanistic possibilities. Tosylate leaving groups were chosen because solvent effects with this group have been extensively studied,[4b,15a] because these derivatives can be prepared without cleaving bonds at the chiral center, and because a comparison could be made with results obtained using ^{18}O labeling.[15b,c]

Results

Optically active alcohols **3** were obtained by conversions of their Mg(II) salts to phthalate half-esters **4** which were treated with the separate enantiomers of 1-phenylethylamine to give the salts **5** which were converted with HCl back to the half-esters and then to **3** with NaOH (Chart I).[16] The alcohols and the acid chloride of optically active Mosher's acid (**6**) gave the esters **7** whose ^{19}F NMR spectra were used to determine the optical purities.[17] Racemic and optically active **3** was converted to tosylates **8** (NaH or KH/TsCl), ethyl ethers **9** (KH, EtI), acetates **10** (AcCl, pyridine), and trifluoroacetates **11** (trifluoroacetic anhydride, pyridine). Optical rotations of **3**, **4**, and **8–11**, and ^{19}F chemical shifts and calculated optical purities are given in Table I. Authentic trifluoroethyl and hexafluoroisopropyl ethers of the optically active alcohols were not prepared because of the difficulties of carrying out such reactions stereospecifically.

The first-order rates of solvolysis of the tosylates **8** were measured in different solvents by UV or conductivity, as recorded in Table II. Polarimetric rate constants k_α for the same substrates are given in Table III, along with ratios k_α/k_p where k_p is the rate constant for product formation as measured by UV or conductivity. With one exception the polarimetric rate constants and k_α/k_p comparisons were measured at 25 °C, but in several cases the rates for particular substrates in certain solvents were too slow or too fast for measurement of k_α at or near 25 °C so are not available.

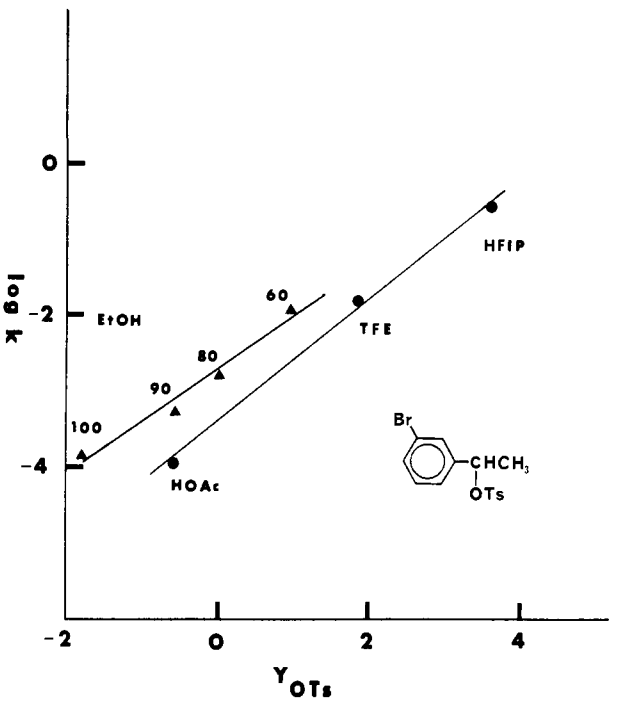

Figure 1. Solvolysis rates of **8a** as a function of solvent.

The stereochemistries of product formation were measured in two ways, the first being comparison of the observed final rotations in the kinetic experiments with the rotations of the authentic optically active products in the reaction solvents. The zero rotations of the final solvolysis product mixtures for reactions of **8a** in TFE and of **8b** in HFIP were taken as indicating the reactions gave complete racemization. In addition whenever sufficient material was available the solvolysis products were isolated and purified, and their optical rotations measured and compared with those of authentic samples. For determination of the product stereochemistry by either method, two to six separate measurements were made in each case, and the indicated stereochemistries were reproducible to ±5% of the net result. There was good agreement between the product stereochemistries as determined by the two methods, as listed in Table III.

The optical stabilities of the product acetates and ethyl ethers were tested in the appropriate solvents containing an added equivalent of TsOH, and in all cases there was no change in rotation after 10 half-lives.

The possibility that racemization might occur through an elimination–addition pathway was checked for solvolysis of **8c** in CF_3CO_2D. No deuterium incorporation was visible in the product **11c** by ^1H NMR of the reaction mixture or by mass spectral analysis of the isolated product. Similarly no deuterium incor-

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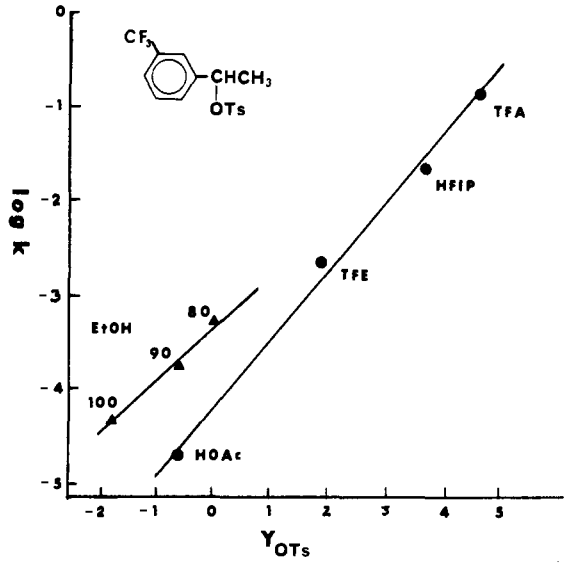


Figure 2. Solvolysis rates of **8b** as a function of solvent.

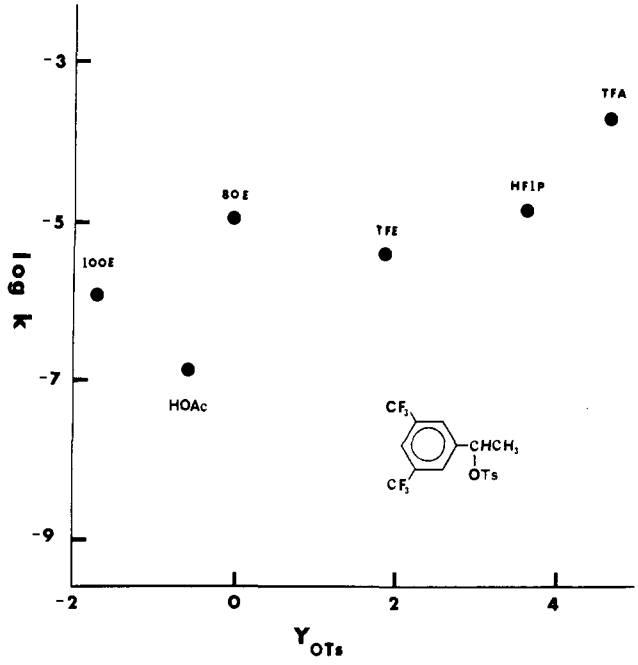


Figure 3. Solvolysis rates of **8c** as a function of solvents.

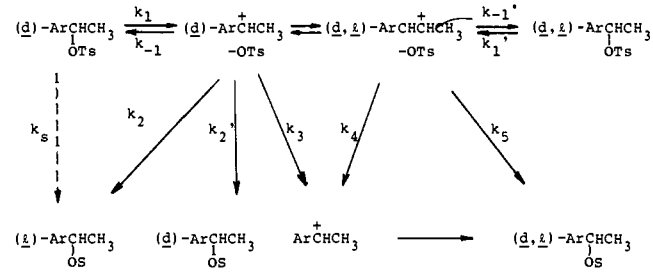
poration in **10a** from solvolysis of **8a** in CD_3CO_2D was detectable by ^1H NMR.

The solvolysis of **8b** in trifluoroethanol gave a change in rotation from −0.82 to +0.15°, and **8c** in hexafluoroisopropyl alcohol gave a change from −0.88 to −0.15°. However, as authentic samples of the optical active ethers were not available, the stereochemical outcome of these processes could not be assessed.

Discussion

The rate dependence of the tosylates **8** on the solvent ionizing power parameter Y_{OTs}[18a] is shown in Figures 1–3. For the 3-bromo- and 3-trifluoromethylphenyl substrates **8a** and **8b** it appears that separate correlations best accommodate the data for ethanol solvents (**8a**: $\log k = 0.70Y_{OTs} - 2.71$, $r = 0.989$; **8b**: $\log k = 0.59Y_{OTs} - 3.32$, $r = 0.993$) and the other solvents (**8a**: $\log k = 0.82Y_{OTs} - 3.36$, $r = 0.993$; **8b**: $\log k = 0.78Y_{OTs} - 4.17$, $r = 0.997$). Single correlations of the data for these two substrates

Scheme II



are obtained with the additional parameter N[18a] for solvent nucleophilicity included (**8a**: $\log k = 0.90Y_{OTs} + 0.26N - 2.60$, $r = 0.994$; **8b**: $\log k = 0.91Y_{OTs} + 0.37N - 3.14$, $r = 0.994$).

In the case of the 3,5-bis(trifluoromethyl) derivative **8c** the deviations from a single correlation with Y_{OTs} is unmistakable (Figure 3), and even the correlation with Y_{OTs} and N gives only a fair correlation coefficient ($\log k = 0.93Y_{OTs} + 0.72N - 4.67$, $r = 0.977$). The coefficient l, which measures the dependence on solvent nucleophilicity, is thus 0.26, 0.37, and 0.72 for **8a**, **8b**, and **8c**, respectively. For the less hindered benzyl tosylate this parameter has been reported as 0.75[18a] and 0.90.[18b,c] Together the results for **8a–c** fulfill our intention of spanning the range of reactivity where solvent nucleophilicity takes on significant kinetic importance.

As discussed below we believe that all our results are consistently explained using an abbreviated version of the Winstein–Robinson ion-pair mechanism,[7] as shown in Scheme II. This scheme omits the differentiation of initially formed intimate ion pairs and solvent-separated ion pairs, as our data do not directly elucidate the respective roles of these entities. Also our results do not exclude some contribution in some of the systems of backside covalent attachment of solvent during the breaking of the bond to the leaving group, whether or not this process (designated k_s, Scheme II) involves an intermediate. However, such a process is not required by the data, which can be adequately explained with its omission. Solvation is very important for all of the ionic species in Scheme II, but is composed of numerous weak interactions of many solvent molecules, and not specific interaction with a single nucleophilic solvent molecule as shown in **1**.

In all cases in which polarimetric rates could be measured in the less nucleophilic fluorinated solvents, the rate constants exceeded those for product formation, by factors of 1.4 to 9.2. This corresponds in Scheme II to ion-pair return via k_{-1}', and is evidently a consequence of the low solvent nucleophilicity so that product formation via k_2 through k_5 is rate limiting.

In the more nucleophilic solvents the rates of product formation are close to the polarimetric rates, indicating that the product-determining steps (k_2–k_5) in Scheme II are fast and that substrate racemization by k_{-1}' is not significant. Return with retention (k_{-1}) may still contribute, so ionization (k_1) is not necessarily strictly rate limiting. The correlation of the rates with the dual parameters N and Y_{OTs} arises from a combination of ion-pair return in the less nucleophilic solvents, giving diminished rates of product formation, and any enhancement in the rates of product formation in the least ionizing solvents through the k_s route.

The occurrence of little or no net inversion in the solvolysis products from **8** in the fluorinated nonnucleophilic solvents is readily explained by Scheme II, as backside attack of solvent on the initial ion pair is too inefficient to compete with symmetrical solvation of the cation. Interestingly in **8c** in TFA 6% net retention occurs. Such retentive solvolysis has been observed before,[14d,g,h,19] and has been plausibly attributed to electrophilic coordination of the solvent to the departing anion which promotes frontside substitution.[19] The importance of such electrophilic solvent assistance has been receiving increased recognition,[19c] and provides

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a satisfactory explanation for the results for **8c** in TFA (path k_2'). It has been proposed that such retentive solvolysis "probably" occurs on solvent-separated ion pairs.[19a]

The occurrence of substantial net inversion from **8** in the more nucleophilic HOAc and EtOH is also readily accommodated by Scheme II by attack of solvent from the backside of the initial optically active ion pair before racemization occurs. Nucleophilic solvent attack during bond-breaking to the leaving group is an alternative pathway, but the occurrence of some racemization even for **8c** in EtOH shows this is not the only path in any example.

Correlations of the rates with the aryl substituent parameters σ^+ gives ρ values as a function of solvent: CF_3CO_2H, −4.9; 100% HFIP, −5.1; 97% HFIP, −5.9; 100% TFE, −6.3; 97% TFE, −5.1; CH_3CO_2H, −3.9; 80% EtOH, −3.0; 90% EtOH, −3.3; and 100% EtOH, −3.4.[20] The correlation coefficients for the rather small data sets are all at least 0.999 except for 100% EtOH, which gives $r = 0.992$. The ρ values in the fluorinated solvents are comparable to values of 1-arylethyl derivatives of −5.0 to −6.3 compiled by Richard and Jencks[11d] and attributed to carbocation-forming reactions. The ρ values in the ethanolic solvents are comparable to that of −2.9 for the S_N2 reaction of 1-arylethyl derivatives with azide.[11d] These ρ values provide further evidence for the carbocation character of the intermediates in the tosylate reactions in the fluorinated solvents, and for the nucleophilic role of the ethanolic solvents in either assisting in the tosylate displacement or rapidly capturing an ion pair. The intermediate ρ value in CH_3CO_2H shows transitional behavior in this solvent. For comparison ring-substituted benzyl mesylates in HFIP give a ρ^+ value of −12[21] and 1-aryl-2,2,2-trifluoroethyl tosylates gives values of −6.7 to −11.9 depending on the solvent.[13a] The greater magnitude of these values is consistent with the much greater electron demand of the cations formed.

As already mentioned Scheme II is analogous to the mechanisms we have proposed for the solvolysis of 2-butyl tosylate,[13a] 1-aryl-2,2,2-trifluoroethyl sulfonates,[13b] and 2-trifluoromethyl-2-propyl triflate[13c] and readily accommodates the observations that for the first substrate specifically labeled with deuterium that hydrogen scrambling in the tosylate occurred during trifluoroacetolysis,[22] while for the latter (and others[21]) elimination from the ion pair became rate limiting.

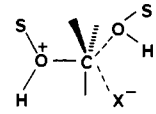
Scheme II also accounts for the observation that many secondary aryl sulfonates undergo ^{18}O scrambling in the sulfonate moiety during solvolysis,[15b,c] although **8** has not itself been tested specifically for this phenomenon. Ion-pair return also may be the cause of m values less than 1.0 for **8a–c** and a number of other substrates believed to react through carbocation intermediates.[13b,21] Thus if the initial ionization of these substrates (k_1) is no longer rate limiting because of ion-pair return in the less nucleophilic solvents, then the observed rates of product formation in these solvents will underestimate the rates of ionization and the m values will be lower than if true rates of ionization were available.

Richard and Jencks[11d] reached similar conclusions to ours in their study of 1-(4-nitrophenyl)ethyl tosylate, which they reported reacted in water "with little or no nucleophilic assistance" to form a carbocationic intermediate. In the presence of the much more nucleophilic agent azide ion a concurrent S_N2 reaction was proposed to occur. These authors[11c] also concluded that 1-(4-methylphenyl)ethyl derivatives reacted by ion-pair mechanisms and suggested that "reactions of all less stable carbocations must also proceed by ion-pair intermediates, until the point is reached that the cation does not have a significant lifetime to exist as a reaction intermediate". Our results indicate that even for the 3,5-bis(trifluoromethyl)phenyl compound ion pairs still occur to some extent even in ethanol.

As already noted solvent participation (k_s) can contribute significantly to some of the reactions here, and should be given serious consideration whenever rate accelerations and stereochemical inversion occur. However, it appears to us that objective criteria for the occurrence of the "S_N2-intermediate" variation of this process are much less clear cut.

To illustrate the difficulties, two recent examples in which this process was proposed to be involved may be cited. In methanolysis of $(Me_3Si)_3CSiMe_2I$ there was stereochemical evidence for solvent participation (lack of rearrangement) but kinetic corroboration was lacking (NaOMe caused no acceleration). This was proposed[4c] to implicate the "S_N2-intermediate" mechanism. However, the same process was invoked in the solvolysis of some β-substituted bicyclic tosylates where it was suggested there was kinetic evidence for phenyl assistance (taking the place of solvent assistance), but the products were indicative of an open carbocation intermediate.[4d] The fact that the disparate behaviors in these two systems were explained by the same process suggests that objective tests of this concept will be hard to design.

The authors who have considered the intermediate **1**[2,4] have also proposed that this intermediate could undergo solvent displacement to produce the symmetrically solvated pentacoordinate species **2**. The transition state **12** was suggested[2] for this process,



12

but this six-coordinated species is severely crowded, and its formation is competing with bond formation by the strongly coordinated solvent molecule already present.

Pseudorotation in **1** as a alternative to explain the observed racemization seems highly improbable, as the importance of this process is debatable even for silicon.[23]

Scheme II with rate-limiting product formation also provides a satisfactory alternative explanation for the recent proposal[24] that the secondary deuterium isotope effects for trifluoroacetolysis of 2-propyl tosylate indicated the occurrence of "nucleophilic solvent attachment in the transition state" for tosylate departure. Thus less than maximal isotope effects are expected for ion-pair mechanisms if solvent attack on the carbocation of the ion pair is rate limiting, and this appears to be the case in trifluoroacetolysis. It may seem paradoxical, but it is quite logical that nucleophilic solvent participation plays a significant kinetic role in the least nucleophilic solvents, as evidenced by polarimetric rate measurements, ^{18}O- and ^2H-scrambling, and the occurrence of elimination.

It has also been argued in support of the "S_N2-intermediate" mechanism that there is "no indication of . . . major shifts in magnitudes of ion-pair return" and "internal return of substantial magnitude (>fivefold effect on k_t) is absent."[4b] However, for both **8b** (Table III) and other examples[7b,13b,14g,21b] polarimetric rates exceed rates of product formation by more than a factor of 5, and furthermore internal return should exceed k_α.

In summary we believe that the observation of substrate racemization prior to product formation, retentive solvolysis, and ρ values of large magnitude for **8a–c** in fluorinated solvents provides strong evidence for formation of ion pairs which undergo rate-limiting attack by solvent, as shown in Scheme II. Nucleophilic

(20) σ^+ values used were 0.405 (3-Br), 0.56 (3-CF_3), and 1.12 (3,5-$(CF_3)_2$). The value for 3-CF_3 is from ref 26e, and gives somewhat better correlations than the usual value of 0.52 (Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979–4987). A rate for $PhCH(OTs)CH_3$ in 100% EtOH of 8.35×10^{-3} s^{-1} from ref 14i is included in the data. In 100% EtOH the correlation is better represented as two lines with $\rho = -4.4$ for the two most reactive compounds, and $\rho = -2.9$ for the three least reactive, but with such a small data set the quantitative validity of these values should not be overemphasized.

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(24) Yamataka, H.; Tamura, S.; Hanafusa, T.; Ando, T. *J. Chem. Soc., Chem. Commun.* **1984**, 362–363.

solvent participation becomes more effective in the ethanols, and is either involved in displacement of the tosylate or in rapid attack on the ion pair. The latter path makes at least a small contribution even for **8c** in 100% EtOH, as evidenced by the occurrence of 13% racemization of the product. The ion pair interacts with solvent, but not by strong covalent bonding. The "S_N2 intermediate" cannot be objectively disproved to intervene in some cases, but we subscribe to the view of Olah and Prakash[25] that "the S_N2 intermediate indeed can best be characterized as a trivalent carbocationic center solvated from both sides by the negatively charged nucleophile and the leaving group." This view deemphasizes the covalent character of the solvent–carbocation interaction, and is operationally equivalent to an ion pair.[28]

Experimental Section

Reagents and fluorinated solvents were usually obtained from Aldrich with the exception of 1-bromo-3,5-bis(trifluoromethyl)benzene (Saber Laboratories) and (+)- and (−)-1-phenylethylamine (Norse Laboratories). Reactions were carried under N_2 in glassware that had been oven-dried. Chromatographic purifications were carried out using a Chromatotron centrifugal radial thin-layer chromatograph from Harrison Research. ^1H and ^{19}F NMR spectra were run using Varian T-60 and XL-200 instruments, respectively. Elemental analyses are by Galbraith Laboratories.

Preparative studies, resolutions, and product studies are described for the 3-trifluoromethylphenyl derivatives. Procedures for the 3-bromo- and 3,5-bis(trifluoromethyl)phenyl compounds were analogous.

Tables of spectral and analytical data for **3**, **4**, **7**, **8**, **9**, **10**, and **11** are available as supplementary material. Compounds **3a**,[26a] **3b**,[26a,b] **3c**,[26c] **10a**,[26d] and **10b**[26e] have been reported previously.

Preparation of Optically Active Alcohols.[16] 3-Bromotrifluoromethylbenzene (60.7 g, 0.27 mol) in 60 mL of ether was added dropwise over 1.5 h to 10.4 g (0.43 mol) of Mg in a 500-mL three-neck flask equipped with a mechanical stirrer, reflux condenser, and addition funnel. The solution was cooled with ice, and 16 mL (0.29 mol) of acetaldehyde in 30 mL of ether was added over 15 min; the solution was refluxed 1 h. The solution was cooled and phthalic anhydride (39.8 g, 0.27 mol) was added in six batches. The solution was refluxed overnight and poured into ice, acidified with 3 M HCl, and extracted three times with ether; the combined ether layers were washed with water and saturated NaCl, dried over Drierite, and evaporated. Pentane was added to the yellow oily product and white crystals formed. Evaporation and distillation of the pentane layer gave 14.4 g (0.76 mol, 28%) of 1-(3-trifluoromethylphenyl)ethanol. The white crystals were heated to boiling with 250 mL of petroleum ether (80–100 °C), and the hot solution was decanted from the residual solid and cooled. The solution was decanted from the half-ester which crystallized back into the original flask; the procedure was repeated five times leaving phthalic acid in the original flask and 39 g (0.115 mol, 43%) of 1-(3-trifluoromethylphenyl)ethyl phthalate (**4b**) in the other.

(+)-1-Phenylethylamine (6.8 mL, 0.053 mol) was slowly added to the phthalate half-ester **4b** dissolved in 60 mL of acetone; after the exothermic reaction concluded, the mixture was cooled in the refrigerator overnight and the crystals which formed were collected by filtration and washed three times with cold acetone to yield 3.1 g of the amine salt **5b** as a first crop. The acetone solution was evaporated and the residual **4b** recovered by addition of 2 M HCl, three extractions with ether, washing of the ether layers with water and NaCl solution, drying over Drierite, and evaporation. The recovered **4b** was treated with (−)-1-phenylethylamine and **4b** and **5b** were isolated as before. After three repetitions of the procedure with each amine there was obtained a total of 16.8 g of salt **5b** from the (+) amine and 12.9 g from the (−) amine, overall yield 56%. The former salt was recrystallized once from acetone before conversion to the optically active half-ester and the latter was used directly.

The (−)-phenylethylamine salt **5b** (13 g, 0.028 mol) was stirred with 100 mL of ether and 200 mL of cold 2 M HCl until the solid dissolved. The ether layer was extracted three times with cold 2 M HCl and the combined HCl layers were extracted three times with ether. The combined ether layers were extracted twice with H_2O and once with saturated NaCl, dried over Drierite, and evaporated to give 10 g (0.028 mol, 100%) of **4b**, $[\alpha]^{25}_D$ 3.00 ± 0.06°. This material was refluxed overnight with 20 mL of 3 M NaOH, cooled, and extracted three times with ether; the combined ether layers were washed with H_2O and NaCl, dried over Drierite, evaporated, and distilled to give 1-(3-trifluoromethylphenyl)-ethanol (**3**, 3.7 g, 65%).

Mosher's acid [(−)-α-2-methoxy-2-phenyl-3,3,3-trifluoropropionic acid, Aldrich][17] (0.550 g, 2.35 mmol) was refluxed 72 h with 7 mL of $SOCl_2$ and 8 mg of NaCl; the acid chloride (0.295 g, 1.17 mmol, 55%) was obtained by vacuum distillation. To 0.196 g (0.786 mmol) of chloride was added **3b** (0.147 g, 0.784 mmol) followed by 1 mL of CCl_4 and 1 mL of pyridine. The mixture was allowed to stand overnight, after which H_2O was added; the solution was extracted three times with ether which was washed with 2 M HCl and then with saturated $NaHCO_3$, dried, and evaporated. Purification on the Chromatotron using 10% EtOAc and 90% petroleum ether gave 1-(3-trifluoromethylphenyl)ethyl 2-methoxy-2-phenyl-3,3,3-trifluoropropionate (**7b**), analyzed by ^{19}F NMR using a Varian XL-200 instrument in $CDCl_3$ with CF_3CO_2H as internal standard. Spectral data on the esters **7** are recorded in Table I. On the basis of reported stereochemical correlations[17b] it may be concluded that the alcohols **3** with (−) rotation obtained from (−)-1-phenylethylamine have *S* absolute configuration.

Preparation of Other Derivatives. Tosylates **8** were prepared from reaction of **3** with NaH or KH and TsCl as reported[13] and gave the physical properties noted. Optically active tosylates were purified using the Chromatotron.

A solution of (−)-**3b** (0.234 g, 1.24 mmol) in 8 mL of THF was slowly added via a syringe to KH (0.3 g, 2.61 mmol, prewashed with pentane) at 25 °C. The solution was stirred 1 h, 0.1 mL (1.24 mmol) EtI in 10 mL THF was added, and the solution was refluxed overnight. The product was hydrolyzed with EtOH, saturated NaCl was added, and the solution was extracted with ether which was washed with $NaHCO_3$ followed by NaCl, dried, and evaporated. The product contained equal amounts of **3b** and (−)-1-(3-trifluoromethylphenyl)-1-ethoxyethane (**9b**) which was purified by VPC (OV-17 column, 140 °C).

Addition of acetyl chloride (0.084 mL, 1.17 mmol) and pyridine (0.123 mL, 1.52 mmol) to (−)-**3b** (0.200 g, 1.05 mmol) in 5 mL ether was followed by 2 h of reflux. Water was added, the solution was extracted three times with ether, and the ether layer was washed with 2 M HCl, $NaHCO_3$, and NaCl, and was then dried over Drierite and evaporated. Purification by VPC (OV-17, 160 °C) gave (−)-1-(3-trifluoromethylphenyl)-1-acetoxyethane (**10b**).

The trifluoroacetate **11c**, mp 30–31 °C, was prepared from reaction of **3c** with trifluoroacetic anhydride and pyridine.[27]

Kinetic Studies. Polarimetric rates were measured as described[13b] by equilibrating the solvent to the desired temperature in a jacketed 10.0-cm polarimeter cell, injecting the tosylate with a syringe, drawing the solution in and out of the cell for mixing, and monitoring the rotation at 436 nm using a Perkin-Elmer 141 polarimeter. For determination of k_α/k_{uv} rate ratios the rates were measured on the same day using the same batch of solvent.

Product Studies. Comparison of the final rotation of the acetolysis product of **8b** with the rotation of authentic (−)-**10b** in the acetolysis medium indicated the product had a net inversion of 45 ± 3% (average deviation of six runs). In a separate preparative experiment the product **10b** from acetolysis of **8b** was isolated by extraction and purified by VPC; the rotation in $CHCl_3$ was compared with that of authentic (−)-**10b**. The product was found to have a net inversion of 48% after correction for the optical purity of the starting **8b**, which had partially racemized during synthesis.

Final rotations of the ethanolysis product of **8b** with authentic **11b** indicated net inversion of 76 ± 3% (average deviation of five runs).

Product Stability. Solutions of (−)-**9b** (0.0224 g, 0.103 mmol) with $TsOH·H_2O$ (0.0178 g, 0.103 mmol) in 1.1 mL of EtOH and (−)-**10b** (0.0482 g, 0.201 mmol) with $TsOH·H_2O$ (0.0395 g, 0.207 mmol) and 0.207 mmol of Ac_2O in 5 mL of CH_3CO_2H showed no change in optical rotation over 10 half-lives for solvolysis of **8b** in these media. The optical stabilities of **9a** and **10a** in the reaction media were also confirmed.

The reaction of **8c** (0.161 g, 0.47 mmol) in 1.5 mL of CF_3CO_2D for 10 half-lives for solvolysis gave a product with no deuterium incorporation visible by ^1H NMR. Pentane was added and the solution was washed with water and dried; product **11c** was isolated by VPC. Comparison of the mass spectrum with that of authentic material revealed the presence

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(27) Allen, A. D.; Rosenbaum, M.; Seto, N. O. L.; Tidwell, T. T. *J. Org. Chem.* **1982**, *47*, 4234–4239.

(28) **Note Added in Proof**: In a personal communication Professor Schleyer has endorsed the quotation by Olah and Prakash[25] and states that of the present results only those in EtOH and perhaps HOAc would be expected to involve the S_N2 (intermediate) mechanism, as evidenced by low *m* values, inversion of configuration "with some leakage", low ρ values, and k_a/k_p values near unity. It is still our belief that all of our data are best explained without the intervention of such an intermediate.

of 0.0 ± 4% deuterium incorporation. There was 6% of the styrene present in the solvolysis product as indicated by the VPC trace, but based on the known reactivities of substituted styrenes in TFA[26] this material is expected to be inert under these conditions.

The reaction of **8c** in CD_3CO_2D was similarly observed by ^1H NMR and no deuterium incorporation in the $CHCH_3$ of the product was detectable.

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Supplementary Material Available: Tables of ^1H NMR spectra, elemental analysis, and mass spectral data (4 pages). Ordering information is given on any current masthead page.

Electronic Structure and Bonding of the Blue Copper Site in Plastocyanin

Kevin W. Penfield, Andrew A. Gewirth, and Edward I. Solomon*

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. *Received October 10, 1984*

Abstract: Spin restricted self consistent field–Xα–scattered wave (SCF–Xα–SW) calculations are presented for a number of approximations to the blue copper active site in plastocyanin. The results of these calculations indicate that the bonding at the site is quite covalent and that substantial electron delocalization occurs. A comparison of Xα calculations for free imidazole and the blue copper site indicates that the splitting of the imidazole π_1 and π_2 and n and π_2 levels is expected to significantly increase upon complexation. Similarly, the 2e and $3a_1$ valence levels of the methylthiolate ligand split into three levels upon complexation to copper. The energy separation between these levels is calculated to decrease relative to the splitting between the 2e and $3a_1$ levels in free methylthiolate. All three valence levels have significant electron delocalization onto the copper, and the bonding is best described as involving one π- and two σ-type interactions. The $4a_1$ (sulfur p_z) orbital of the axial thioether ligand at the blue copper site is computed to undergo a small but significant bonding interaction with the d_{z^2} orbital on the copper. On the basis of comparison to D_{4h} $CuCl_4^{2-}$ and $CuCl_6^{4-}$ model complexes, this interaction is found to effect the energy of the $d_{z^2} \rightarrow d_{x^2-y^2}$ ligand field transition. Formalisms are developed to calculate g and A values from the output of the Xα calculation. The g values provide an experimental calibration for the amount of delocalization present in the ground state wave function. These calculations indicate that the unpaired electron in the blue copper site spends about 40% of the time in a $d_{x^2-y^2}$ orbital on the copper and about 36% of the time on the p π orbitral of the thiolate sulfur. A rhombic splitting of 0.017 in the g values is calculated, the magnitude of which is confirmed by experimental observation of this splitting in spinach plastocyanin with Q-band EPR. The rhombic character of the EPR appears to relate to electron delocalization of the ground state wave function over the p π orbitals of the sulfur. Hyperfine values are calculated for the blue site and for D_{4h} $CuCl_4^{2-}$. The difference between the values for the two complexes is found to relate in large measure to the increased delocalization in the blue site relative to $CuCl_4^{2-}$. p_z mixing at the blue site is not found and is shown to be insufficient as an explanation for the reduced A_z in the blue site relative to D_{4h} $CuCl_4^{2-}$. These studies provide a reasonable, experimentally calibrated, approximation of the orientation and delocalization of the ground state wave function involved in electron transfer.

I. Introduction

The blue copper active site is found in a number of proteins containing single copper centers, including the plastocyanins, azurins, and stellacyanins.[1] This site is also found in the multicopper oxidases: laccase, ceruloplasmin, and ascorbic acid oxidase. In those proteins where the function of the blue copper site has been clearly determined, it participates in outer-sphere electron-transfer reactions. There has been a great deal of effort focused toward understanding the spectral features and associated electronic structure and bonding of the blue copper site, with the long-range goal of relating the unusual electronic structure properties to active-site reactivity.

Spectroscopy on the blue copper active site has focused on understanding the unique spectral features of the site in terms of its geometry.[2] These spectral features include an unusually small copper hyperfine splitting of the EPR signal in the $g_\parallel$ region ($A_\parallel \leq 70 \times 10^{-4}$ cm^{-1}) and an extremely intense low-energy absorption band ($\nu \approx 600$ nm, $\epsilon \approx 4000$ m^{-1} cm^{-1}). Infrared circular dichroism (IRCD) studies[3] demonstrated that at least three d–d transitions existed in the blue copper proteins at wavelengths as large as 2 μm. A ligand-field analysis[3] of these transitions indicated that the site has a geometry close to tetrahedral and that all d–d transitions would have to occur at energies below 800 nm. Therefore, the intense 600 nm absorption band must involve a charge-transfer (CT) transition, which probably arises from cysteine ligation[4] at the site. High-resolution structures of plastocyanin[5] (to 1.6 Å) and azurin[6] (to 2.7 Å) indicate that the remaining ligands are two imidazoles of histidine and a

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