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Electrochemical Peak Potentials of Typical Substrates Used for Coupling Reactions with Organocuprates: Effects of Solvent

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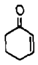
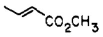
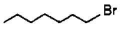
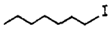
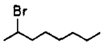
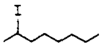
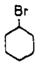
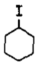
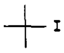
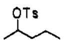
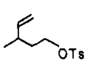
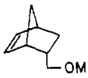
Using cyclic voltammetry, we have measured cathodic peak potentials for a variety of substrates that are routinely used as coupling partners with organocuprate reagents under consistent conditions of solvent(s), working electrode, and supporting electrolyte (SE). Hence, enones, enoates, primary and secondary cyclic and acyclic halides, tosylates, and mesylates have all been examined in DMF, CH_3CN, and THF. It is reported here that the solvent plays a pivotal role in determining the reduction potentials, with significant negative shifts observed upon going from DMF to CH_3CN to THF. In an ethereal solvent, in which most reactions of cuprates are carried out, n-Bu_4NBF_4 is found to be an acceptable SE. Interestingly, in THF, secondary iodides gives two individual waves at potentials considerably more positive than the corresponding bromides, each of which gives rise to only a single wave. The relationship between these observations and the stereochemical outcome (at carbon) in substitution reactions at secondary centers is discussed.

In a recent report[2] it was established that the stereochemical outcome of substitution reactions at secondary, unactivated centers bearing halogen (iodides or bromides) via either lower or higher order cuprates is a function of the nature of the leaving group. Iodides couple to afford racemic products, whereas bromides react with complete inversion of stereochemistry at carbon. Although these observations are of value in terms of devising strategy in synthesis, they say little about the actual mechanism of the coupling process. The implication, however, is that iodides react by way of a free-radical process, whereas bromides presumably do not. Ashby et al.[3] have very recently documented the involvement of radical intermediates in reactions of 6-halo-1-heptenes that lead to methylcyclopentane derivatives for iodides, whereas the corresponding bromides afford products characteristic mainly of substitution.

Table I

entry	substrate	peak potentials, $-E_p$, V		
		DMF	CH_3CN	THF
1		2.05	2.15	2.47
2		2.32	2.51	3.08
3		2.61	>2.90	3.47[b]
4		c	d	2.54
5		2.59	>2.90	3.33[b]
6		f	g	2.26, 2.58[h]
7		2.57	>2.90	3.01
8		i	j	2.18, 2.27[h]
9		2.31, 2.53[h]	2.53	2.77
10		k	l	1.83, 2.49[h]
11		2.19[n]	2.33	2.89
12		2.19[m]	2.32	o
13		2.69	p	2.85

[a] No wave is observed more anodic than electrolyte discharge (−2.60V). [b] Observed wave is on the edge of electrolyte discharge. [c] Current maximum observed at −2.19V. [d] Current maximum observed at −2.13V. [e] No wave observed more anodic than electrolyte discharge (−2.60V). [f] Current maximum observed at −2.15V. [g] Current maximum observed at −2.23V. [h] Two waves of unequal height observed. [i] Current maximum observed at −2.30V. [j] Current maximum observed at −2.45V. [k] Current maximum observed at −1.80V. [l] Current maximum observed at −1.79V. [m] A second smaller wave is also present at −2.69 V. [n] A second smaller wave is also present at −2.63 V. [o] Not determined. [p] No wave observed more anodic than electrolyte discharge (−2.80 V).

In an effort to shed light on the inherent differences between these two halides we have carried out a detailed study of the reduction potentials for common types of substrates that participate in reactions with cuprate reagents. This investigation was deemed necessary as inspection of a number of treatises on electrochemical data points to a disappointing lack of consistency associated with the conditions used to determine these values.[4] Furthermore, while others have previously reported on enones and enoates[5] and, most recently, primary and secondary halides,[6] those studies were routinely conducted in DMF solution. While they may serve, in the former case, as a predictive guide by which to anticipate ligand delivery from copper in a conjugate sense, the values are purely of a relative nature and give no clues as to the capability of cuprates to act as one-electron-transfer reagents in THF. Hence, in this paper we present our results on the determination of peak potentials ($-E_p$, using cyclic voltammetry) on organic substrates under controlled conditions of working electrode[7a] and supporting electrolyte (n-Bu_4NBF_4). Each value has been measured in three

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(1) Recipient of an American Cancer Society Junior Faculty Research Award, 1981-1983.

(2) Lipshutz, B. H.; Wilhelm, R. S. *J. Am. Chem. Soc.*, **1982**, *104*, 4996.

(3) Ashby, E. C.; DePriest, R. N.; Tuncay, A.; Srivastava, S. *Tetrahedron Lett.* **1982**, *23*, 5251.

(4) Meites, L.; Zuman, P. "Organic Electrochemistry"; CRC Press: Boca Raton, FL, 1976; Vol. 1-4.

(5) (a) House, H. O.; Umen, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 5495. (b) *Ibid.* **1972**, *94*, 8471. (c) *J. Org. Chem.* **1973**, *38*, 3893. (d) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.

(6) (a) McNamee, G. M.; Willett, B. C.; La Perriere, D. M.; Peters, D. G. *J. Am. Chem. Soc.* **1977**, *99* 1831. (b) La Perriere, D. M.; Willett, B. C.; Carroll, W. F., Jr.; Torp, E. C.; Peters, D. G. *Ibid.* **1978**, *100*, 6293. (c) Carroll, W. F., Jr.; Peters, D. G. *J. Org. Chem.* **1978**, *43*, 4633. (d) Mbarak, M. S.; Peters, D. G. *Ibid.* **1982**, *47*, 3397.

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different media,[7b] including an ethereal solvent (THF) in which most cuprate reactions are carried out.[8] To our knowledge, this is the first general study of its kind.

Table I lists the peak potentials observed in DMF, CH_3CN, and THF for 11 substrates that are common electrophilic partners in cuprate coupling reactions. For completeness, tertiary halides[9,11] have also been included. Perhaps the most striking feature of the data is the large dependence of reduction potential on the solvent. The values, in general, reflect significant negative shifts of up to 0.86 V (on the order of 25% or more) on going from DMF through CH_3CN to THF. Such solvent effects have been previously recorded, although for individual situations.[10] A fundamental explanation for these findings has yet to be established although it is reasonable to propose that more energy is required to break up a tight ion pair (i.e., R_4NX) in a poorly solvating medium (e.g., THF) than in a solvent of high dielectric constant.[11] Measurements made on three substrates in DME,[12] which has a dielectric constant (7.20) similar to that of THF (7.58) likewise show values more negative than those seen in either DMF or CH_3CN. Attempts to determine potentials in dioxane ($\epsilon = 2.21$) with n-Bu_4NBF_4 were fruitless as no current flow occurred.

On the basis of electrochemical measurements, the House model[5] continues to serve as an excellent guide for assessing the likelihood of a desired conjugate addition between a cuprate and an unsaturated carbonyl derivative. However, the original studies were performed in DMF and, hence, the values obtained cannot reflect the true ability of cuprates to function as one-electron donating species. That the $-E_p$ values for all entries are much more negative in THF than in DMF suggests that *cuprates may be far more powerful reducing agents than one would have surmised from earlier work using solvents that are traditionally not acceptable media for cuprate formation.*[13]

Insofar as halides are concerned, primary iodides are found to give current maxima (CM) in both DMF and CH_3CN, whereas in THF a single wave is observed. This contrasts with a literature[6a,b] report in which two waves have been noted in DMF; this most likely reflects the difference in supporting electrolyte (Me_4NClO_4) and attests to the lack of correlation between potentials recorded under dissimilar circumstances. Primary bromides behave as expected in DMF,[6a,b] whereas in both CH_3CN and THF the wave shifts very close to or completely into the region where solvent discharge occurs. Both cyclic and acyclic secondary iodides behave in a fashion analogous to primary iodides.[6c,d] More interesting in this series, however, is the realization that two waves are clearly visible in THF.[14] Secondary bromides, however, afforded only a single wave detected at considerably more negative potentials (compare entries 5 vs. 6, 7 vs. 8). The two individual waves seen in entries 6 and 8 at relatively positive E_p suggest that a substrate of this type (i.e., a secondary iodide) readily forms a radical and eventually a carbanion at potentials that are separated to a far greater degree than are those of the corresponding bromides. Hence, to the extent that one can draw inferences from these data, it is not surprising that secondary iodides in THF react with cuprates via a radical process affording racemized products. Unfortunately, it is still not clear in the case of bromides whether a single two-electron (oxidative addition) mechanism[15] or two one-electron-transfer steps are involved, since the first and second potentials for secondary bromides are so close.

The electrochemistry of sulfonates was briefly studied as these substrates also raise interesting mechanistic questions in their reactions with cuprates owing to their (1) tendency not to undergo metal-sulfonate exchange, (2) preferred substitution reactions in Et_2O over THF,[16] (3) electrochemical mode of cleavage as a function of the sulfonate. Tosylates have been reported to undergo electrochemical cleavage of the S-O bond,[17] and our results (Table I) on both primary and secondary systems likewise indicate cleavage at sulfur at E_p values that again became more negative in going from DMF to THF for this two-electron process. As sulfonates, in general, have been found not to give synthetically useful reactions with 1-2 equiv of $R_2Cu(CN)Li_2$ in THF or Et_2O,[18] we repeated these experiments on the tosylate of 2-octanol (with both 1.11 and 10 equiv of n-$Bu_2Cu(CN)Li_2$[19]) and scrutinized the crude reaction mixture for 2-octanol. Since it was not found, it appears that this pathway is not competitive with displacement in terms of consumption of starting material. Furthermore, it suggests that, for the level of substitution that does occur, a direct S_N2-like process is probably involved.[20]

Mesylates similarly followed the trend toward more negative reduction potentials in THF vs. DMF, although to a lesser degree. The norbornene derivative shown (Table I, entry 13) is, however, a special case and does not mirror typical $-E_p$ for C-O cleavage.[21]

In summary, cyclic voltammetry has been used to measure cathodic peak potentials for substrates commonly

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[7] (a) All measurements listed in Table I were made with a hanging mercury drop electrode (HMDE), a Pt wire anode, and a saturated calomel reference electrode (SCE). (b) The effect of liquid-junction potentials has not been taken into account in these measurements. Although differences between solvents in this regard are anticipated, literature data derived from both aqueous and nonaqueous media suggest that these variations are minimal (1-40 mV) relative to the several hundred millivolt fluctuations recorded in Table I; cf. Bard, A. J.; Faulkner, L. R. "Electrochemical Methods"; Wiley: New York, 1980; pp 62-72. Sawyer, D. T.; Roberts, J. L. "Experimental Electrochemistry for Chemists"; Wiley: New York, 1974.

[8] Posner, G. H. *Org. React.* **1975**, *22*, 253; 1972, *19*, 1.

[9] Hoffmann, A. K.; Hodgson, W. G.; Maricle, D. L.; Jura, W. H. *J. Am. Chem. Soc.* **1964**, *86*, 631. Breslow, R.; Goodin, R. *Ibid.* **1976**, *98*, 6076.

[10] See for example: (a) Zavada, J.; Krupicka, J.; Sicher, J. *Collect. Czech. Chem. Commun.* **1963**, *28*, 1664. (b) Fry, A. J.; Britton, W. E. *J. Org. Chem.* **1973**, *38*, 4016.

[11] For an alternative explanation, see: Fry, A. J.; Krieger, R. L. *J. Org. Chem.* **1976**, *41*, 54.

[12] Peak potentials for substrates in entries 2, 5, and 8 were also measured in DME. Methyl crotonate gives a single wave at -2.59 V, as does 2-bromooctane at -2.77 V. This latter value is considerably more positive than was expected. Cyclohexyl iodide gives two waves at -2.29 and -2.51 V. In this case the values are more negative than those seen in THF (Table I).

[13] This study is not meant to equate the values in Table I with the precise reducing strength of organocopper species. Rather, we do suggest, based on the trends observed between solvents, that those potentials measured in ethereal media are more closely related to the reactions carried out with these reagents.

[14] After the peak potentials for cyclohexyl iodide in THF were recorded, DMF was added (20% of the original volume) and the measurement retaken. A current maximum at essentially the same potential given in Table I for DMF alone was observed.

[15] (a) Johnson, C. R.; Dutra, G. A *J. Am. Chem. Soc.* **1973**, *95*, 7783. (b) Luche, J. L.; Barreiro, E.; Pollat, J. M.; Crabbe, P. *Tetrahedron Lett.* **1975**, 4615. (c) Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 112.

[16] Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777.

[17] (a) Yousefzadeh, P.; Mann, C. K. *J. Org. Chem.* **1968**, *33*, 2716. (b) Horner, L.; Schmitt, R.-E. *Phosphorus Sulfur* **1978**, *5*, 223. (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y. *Tetrahedron Lett.* **1979**, 2157.

[18] Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672.

[19] Interestingly, whereas 1-1.5 equiv of n-$Bu_2Cu(CN)Li_2$ affords moderate yields of substitution product, this experiment with 10 equiv of reagent leads to a ca. 80% yield of 5-methylundecane.

[20] The stereochemical outcome (inversion) of a coupling process between a secondary tosylate and a cuprate has been elucidated; cf. ref 15a.

[21] Experiments on the reduction of the mesylate of 2-octanol in DMF, CH_3CN, and THF showed no waves prior to solvent discharge.

involved in cuprate coupling reactions. The values are highly sensitive to solvent polarity; waves that are considerably more negative are observed in nonpolar media. A true indication of the reducing power of organocuprates, routinely employed in ethereal solvents, has been determined. In THF, secondary iodides give two distinct values, whereas the corresponding bromides afford only a single wave at far more negative potentials. This finding is in line with the anticipated propensity of an iodide to undergo a one-electron reduction to afford an intermediate (free) radical that can racemize at carbon. The results also indicate that with tosylates *in THF* the electron sink is at sulfur. As it is the S-O bond that ultimately is broken electrochemically, this suggests that, in their substitution reactions, these substrates participate in a direct two-electron (oxidative addition) process with organocopper(I) reagents.

Experimental Section

Procedures. Tetramethylammonium tetrafluoroborate (TMAF, electrometric grade, Southwest Analytical Co.) was used without further purification. Tetra-*n*-butylammonium tetrafluoroborate (TBAFB, electrometric grade, Southwest Analytical Co.) was recrystallized (200 mmol) once from 180 mL of ethyl acetate and 100 mL of pentane; the resulting white crystals were dried in a vacuum oven (8 torr, room temperature) for 48 h: mp 162-162.5 °C (lit.[22] mp 162.5 °C). Both salts were stored in a desiccator over Drierite (50:50 mixture of indicating and nonindicating, W.A. Hammond Drierite Co., 8 mesh). *N*,*N*-Dimethylformamide (DMF, Mallinckrodt) was first magnetically stirred over calcium hydride (Alfa) under a nitrogen atmosphere for at least 36 h. Stirring was discontinued and the calcium hydride allowed to settle (ca. 24 h) under a nitrogen atmosphere. The supernatant liquid was decanted and then distilled at reduced pressure (55 °C, 19 torr) from anhydrous copper sulfate (Aldrich, used as received and stored in a vacuum desiccator) onto activated 3A molecular sieves. This distillate was then passed through a column of activated alumina and stored over 3A molecular sieves and activated alumina under an argon atmosphere in the dark.

Dioxane (Aldrich), 1,2-dimethoxyethane (DME, Aldrich), and spectral-grade acetonitrile (CH_3CN, Mallinckrodt) were distilled from calcium hydride at atmospheric pressure and then passed through a column of activated alumina under an argon atmosphere in the dark. Tetrahydrofuran (THF, Mallinckrodt) was distilled from a calcium hydride prestill and finally from sodium benzophenone ketyl.

Cyclohexyl iodide, 1-iodoheptane, *tert*-butyl iodide, cyclohexyl bromide, 1-bromoheptane, and *tert*-butyl bromide were all commercially available. 2-Iodo- and 2-bromooctane were both prepared according to the method of Coulson et al. from 2-octanol.[23] All iodides were distilled from neutral alumina at reduced pressure prior to use and protected from light; the bromides were distilled at atmospheric pressure. Methyl crotonate and cyclohexenone were commercially available and were used without further purification.

Mesylates were prepared according to the method of Crossland et al.[24] using the appropriate alcohol, triethylamine, and methanesulfonyl chloride; tosylates were formed from the corresponding alcohols in pyridine containing *p*-toluenesulfonyl chloride.[25]

Apparatus. A three-compartment cell was used for cyclic voltammetry (CV) studies. The reference and auxiliary electrode compartments were separated from the working electrode compartment by fine-porosity sintered-glass frits. The working electrode was a mercury drop suspended on a mercury-plated platinum wire. The reference electrode was a saturated calomel electrode (SCE). The auxiliary electrode was a platinum wire. The solutions analyzed were $1-16 \times 10^{-3}$ M in substrate with 0.1 M TBAFB in either DMF, CH_3CN, or THF as the solvent. Cyclic voltammograms were obtained with a Bioanalytical Systems Inc. CV-II wave generator and a Houston 200 X-Y recorder. Typical scans were run at 100 mV/s.

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Registry No. Cyclohex-2-en-1-one, 930-68-7; methyl crotonate, 623-43-8; 1-bromoheptane, 629-04-9; 1-iodoheptane, 4282-40-0; 2-bromooctane, 557-35-7; 2-iodooctane, 557-36-8; cyclohexyl bromide, 108-85-0; cyclohexyl iodide, 626-62-0; *tert*-butyl bromide, 507-19-7; *tert*-butyl iodide, 558-17-8; 2-pentanol tosylate, 3813-69-2; 3-ethenyl-1-butanol tosylate, 25163-50-2; 5-norbornene-2-methanol mesylate, 86646-41-5; tetra-*n*-butylammonium tetrafluoroborate, 429-42-5.

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[22] House, H. O.; Feng, E.; Peet, N. P. *J. Org. Chem.* 1971, *36*, 2371.

[23] Coulson, E. J.; Gerrard, W.; Hudson, H. R. *J. Chem. Soc.* 1965, 2364.

[24] Crossland, R. K.; Servis, K. L. *J. Org. Chem.* 1970, *35*, 3195.

[25] Fieser, L.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 1180.

Electrophilic Addition of *p*-Nitrobenzenesulfonyl Peroxide to 3,4-Dihydro-2*H*-pyran

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The addition of *p*-nitrobenzenesulfonyl peroxide to 3,4-dihydro-2*H*-pyran (DHP) in alcohols gives high yields of 3-[[(*p*-nitrophenyl)sulfonyl]oxy]-2-alkoxytetrahydropyrans. The stereochemistry of the addition process is dependent on the steric bulk of the attacking alcohol. For small alcohols, trans addition predominates, while bulky alcohols give mostly cis product. The results are compared with analogous haloalkoxylations of DHP.

Our interest in electrophilic additions of sulfonyl peroxides to olefins[1] prompted us to examine their reactions with 3,4-dihydro-2*H*-pyran (DHP). Besides serving as a model for sulfonyl peroxide addition to electron-rich olefins, this system could be used prototypically to develop a method for preparing α-substituted acetals and ketals of current interest from vinyl ethers[2] (eq 1). Furthermore, we hoped to exploit the good leaving properties of the

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[1] Hoffman, R. V.; Bishop, R. D. *Tetrahedron Lett.* 1976, 33.

[2] Creary, X.; Rollin, A. J. *J. Org. Chem.* 1977, *42*, 4231.

0022-3263/83/1948-3308$01.50/0