natural compounds were indistinguishable after conversion into the 9-methyl ether as previously described (0.5% tosic acid in methanol at 25 °C for 20 min).[1]

With the completion of the first total synthesis of an optically active maytansenoid in natural form by a sequence of highly selective and efficient steps, the stage is now set for the synthesis of maytansine and related active anti-tumor agents.[16]

References and Notes

(1) Corey, E. J.; Weigel, L. O.; Floyd, D.; Bock, M. G. *J. Am. Chem. Soc.* **1978,** *100,* 2916.
(2) A second synthetic route to (±)-**1** has been described by Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimizu, K. *Ibid.* **1979,** *101,* 4734.
(3) The crystalline methoxy mercuration product **2** possesses the axial (α) orientation of methoxy at C-1, in consonance with a previous report. See Inglis, G. R.; Schwarz, J. C. P.; McLaren, L. *J. Chem. Soc.* **1962,** 1014. Methoxy mercuration of tri-*O*-acetyl-D-glucal under the same conditions affords a mixture of α- and β-anomeric methoxy triacetates in a ratio of 55:45. Although the mixture of anomeric methoxy triacetates was obtained in high yield (>95%) and in principle can be used for the synthesis, in practice the β anomer was found to be unsatisfactory in a later step of the synthesis (epoxide opening by methylcopper reagent). See also, Manolopoulos, P. T.; Mednick, M.; Lichtin, N. N. *J. Am. Chem. Soc.* **1962,** *84,* 2203 for the mercuration step.
(4) Satisfactory infrared, proton magnetic resonance and mass spectral data were obtained using chromatographically homogeneous samples of each synthetic intermediate. All reactions involving air or moisture sensitive components were performed under an atmosphere of dry argon.
(5) This procedure represents a modification of the method described by Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974,** 203, which uses tosyl imidazole as reagent. The reaction of trityl ether diol **4** with this reagent was found to produce not only the desired α-oxide **5** but also (in approximately equal amount) the corresponding β-oxide.
(6) Interestingly, the reaction of **5** with lithium dimethylcuprate in ether–THF at −50 °C afforded in high yield the allylic alcohol which results from elimination of a proton from C-2 and oxygen from C-3 if halide-free CH_3Li was used.
(7) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976,** 809.
(8) Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V.; Floyd, D.; Lipschutz, B. *Ibid.* **1978,** 1051.
(9) Rigby, W.; Hunt, B. J. *Chem. Ind. (London)* **1967,** 1868.
(10) For the original use of this reagent see: Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S. Jr.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978,** *100,* 4620. The reagent was prepared form equimolar amounts of borane-dimethyl sulfide complex in toluene and *n*-butyllithium in hexane (under Argon). The solvent and dimethyl sulfide were removed in vacuo and dry toluene added to give a 0.25 M solution of reagent.
(11) The R_f values found for **10** and the C-10 epimer using silica gel plates with ether as solvent were 0.37 and 0.32, respectively; rotations for **10** and the C-10 epimer were $[\alpha]^{20}_D$ +39.6° and −3.3° (*c* 0.7 in $CHCl_3$), respectively.
(12) Kelley, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977,** 3859. Lithium thiopropoxide in DMF or HMPT was found to be less satisfactory.
(13) Corey, E. J.; Enders, D.; Bock, M. G. *Tetradedron Lett.* **1976,** 7.
(14) Circular dichroism data (CD) in ethanol for **16:** $\Delta\epsilon_{293}$ −2.1°, $\Delta\epsilon_{278}$ −7°, $\Delta\epsilon_{265}$ −23°, $\Delta\epsilon_{238}$ +13°, $\Delta\epsilon_{223}$ −7°; λ_{max} (ethanol) 210 (30 000), 247 (51 000), 275 (25 000) nm; ^1H NMR in (deuterioacetone) 3.90 (s, 3 H), 3.25 (s, 3 H), 320 (s, 3 H), 1.35 (s, 3 H), 1.30 (s, 3 H), 1.05 (d, 3 H) ppm and other peaks as expected.
(15) ^1H NMR data for **1** (at 80 MHz in $CDCl_3$, ppm): 1.27 (d, 3 H), 1.48 (br s, 3 H), 1.70 (br s, 3 H), 3.25 (s, 3 H), 3.30 (s, 3 H), 3.51 (d, 1 H), 4.00 (s, 3 H), 4.18 (m, 1 H), 5.33 (dd, 1 H), 5.40 (d, 1 H), 5.60 (br d, 1 H), 6.03 (d, 1 H), 6.32 (br s, 1 H), 6.38 (dd, 1 H), 6.61 (d, 1 H), 6.79 (d, 1 H), 7.23 (d, 1 H).

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Aromatic Hydroxylation by O(^{3}P) Atoms

Sir:

Oxidations of aromatic compounds yielding phenols can be considered as important biological reactions. As a typical example, oxidations induced by monooxygenase can be mentioned which are accompanied by characteristic intramolecular migrations and retentions of substituents of the aromatic ring, commonly referred to as NIH shift.[1,2] An oxygen-transfer mechanism involving cationoid or arene oxide intermediates has been proposed by several investigations for hydroxylations induced by microsome and nonenzymatic model systems.[3-5] However, the elementary reactions of this mechanism are not known with certainty.

During our investigations, oxidations were achieved via O(^{3}P) atoms produced during the γ radiolysis of liquid carbon dioxide.[6] Upon the oxidation of toluene-*2,4,6-d*$_3$, cresol is formed.[7] In this case we observed a pronounced retention of deuterium atoms on the aromatic ring. This result resembled that obtained during oxidations induced by microsomes.[4,8] These observations prompted us to investigate the mechanism of oxidations initiated by O(^{3}P) atoms. These results are considered being of a model character with respect to the understanding of NIH shift in compounds of biological importance.

The γ radiolysis of liquid CO_2 (1.4 mol) in the presence of toluene-*3,5-d*$_2$ (**1**) and -*2,4,6-d*$_3$ (**2**) (5 mmol, respectively) was carried out at 0 °C for 1 h in a stainless steel autoclave (65 mL) using a ^{60}Co source. Product cresols were analyzed by GLC and mass spectrometry after treatment with water to exchange the phenolic deuterium completely by hydrogen. The results are shown in Table I.

Table I. Retention of Deuterium in Cresols Formed by the Hydroxylation of Deuterated Toluenes with O(^{3}P) Atoms

substrate[a]	products[b]	*G* value[c]	distribution of D, % d_3	d_2	d_1
toluene-*3,5-d*$_2$ (**1**)	*o*-cresol	1.89		90	10
	m-cresol	0.14		*d*	*d*
	p-cresol	0.68		75	25
toluene-*2,4,6-d*$_3$ (**2**)	*o*-cresol	1.86	33	67	*e*
	m-cresol	0.14	*d*	*d*	*d*
	p-cresol	0.70	52	48	*e*

[a] Toluene-*3,5-d*$_2$ and -*2,4,6-d*$_3$ were prepared by the method of Howe et al.: Howe, I.; McLafferty, F. W. *J. Am. Chem. Soc.,* **1971,** *99,* 93. Best, A. P.; Wilson, C. L. *J. Chem. Soc.,* **1946,** 239. The deuterium contents of the substrates were determined by mass spectrometry and NMR spectrometry. The mole fraction of two deuterium atoms in the substituted positions of **1** was >0.95 and the mole fraction of three deuterium atoms in the substituted positions of **2** was >0.93. [b] Trace amounts of phenol was also observed as the products. Cresols were analyzed by GLC (UCON LB 550X and silicon DC 550 after trimethylsilylation) and mass spectrometer (Hitachi RMU-4). [c] Molecules per 100 eV absorbed. The conversion was kept lower than 10% to prevent the further reactions. [d] The measurement of a mass spectrum of *m*-cresol was not successful because the yield was low and the separation from *p*-cresol was not complete. [e] Negligibly small.

During our investigations, oxidations were achieved via O(^{3}P) atoms produced during the γ radiolysis of liquid carbon dioxide.[6] Upon the oxidation of toluene-*2,4,6-d*$_3$, cresol is formed.[7] In this case we observed a pronounced retention of deuterium atoms on the aromatic ring. This result resembled that obtained during oxidations induced by microsomes.[4,8] These observations prompted us to investigate the mechanism of oxidations initiated by O(^{3}P) atoms. These results are considered being of a model character with respect to the understanding of NIH shift in compounds of biological importance.

The rather high retention of deuterium indicates that in these cases the hydroxylation does not proceed via direct insertion of oxygen atoms into the aromatic C–H bonds and that intramolecular migration takes place to a significant extent. It becomes, therefore, very probable that a mechanism is operative involving a 2,4-cyclohexadienone intermediate which undergoes aromatization to cresol. By Jerina et al.[9] and Bruice et al.[10] it has been assumed that such an intermediate is formed during the aromatization of arene oxides to phenols. Scheme I shows the formation of *p*-cresol from toluene-*2,4,6-d*$_3$ (**2**), as a typical example.

On the basis of the two sets of data, i.e., the deuterium retentions in *p*-cresol formed from **1** and **2,** the isotope effect for the aromatization of 2,4-cyclohexadienone (**4**) to *p*-cresol was calculated to be k_H/k_D = 2.1. Thus, for the relative ratio of path a to path b one obtains 77:23. It is clear that the main course of the hydroxylation by O(^{3}P) atoms is path a which causes a significant NIH shift, although the direct path (path b) is contributing to the oxidation process to a small extent.

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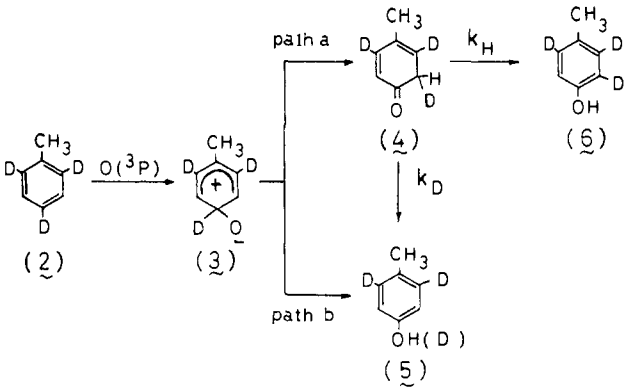
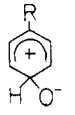
Scheme I



The rate-determining step during the hydroxylation seems to be the addition of an O(^{3}P) atom to the aromatic ring. This conclusion is arrived at due to the fact that the intermolecular deuterium isotope effect for the competitive hydroxylation of benzene and benzene-d_6 is very low (k_H/k_D = 1.1). To further clarify the reaction mechanism, substituent effects were studied with various alkylbenzenes, halobenzenes, and anisole. Figure 1 shows a plot of relative rate constant, k, for the formation of phenols vs. Hammett σ^+ constants. The correlation of the relative rate is better with a σ^+ than with a σ constant. A ρ^+ of -1.6 (correlation factor, 0.95) was obtained from the slope, consistent with a value ($\rho^+ = -1.28$) reported by Grovenstein et al. for the gas-phase reaction of O(^{3}P) atoms generated photochemically.[11] The large negative value demonstrates the O(^{3}P) atoms are of electrophilic nature and that the transients involved in the rate-determining step are stabilized by dipolar resonance structure. The complex **3**, which is also stabilized to some extent by a dipolar structure, may be formed by addition of O(^{3}P) to the aromatic ring followed by spin inversion, or by electron transfer between O(^{3}P) and the aromatic substrate followed by combination of the ion pair. Such a dipolar structure probably promotes the following hydride shift leading to the formation of **4**. Therefore, path a, i.e., hydride shift in complex **3**, should be affected by the introduction of a substituent to the phenyl ring. In **7** electron-donating



(7)

substituents R should stabilize the cationic character of the dipolar structure and thus suppress the hydride (deuteride) shift to form (**4**), leading to the low NIH shift. To study the substituent effects on the NIH shift, anisole-*4-d* and chlorobenzene-*4-d* were synthesized and oxidized by O(^{3}P) atoms. The results are shown in Table II, together with the value obtained with **2**. Table II also includes the values obtained during the microsomal oxidation of these substances for comparison.[8]

Table II. Retention of Deuterium in the Hydroxylation of 4-Deuterated Benzene Derivatives by O(^{3}P) Atoms

substrate[a]	product	retention of D, % O(^{3}P)	retention of D, % microsome[b]
anisole-*4-d*	*p*-methoxyphenol	48	60
toluene-*2,4,6-d*$_3$	*p*-cresol	52	54
chlorobenzene-*4-d*	*p*-chlorophenol	55	54

[a] Anisole-*4-d* and chlorobenzene-*4-d* were synthesized by the hydrolysis of Grignard reagents prepared from 4-bromoanisole and 4-bromochlorobenzene with D_2O, respectively. The isotopic purities measured by NMR and mass spectra were >95%. [b] See ref 8.

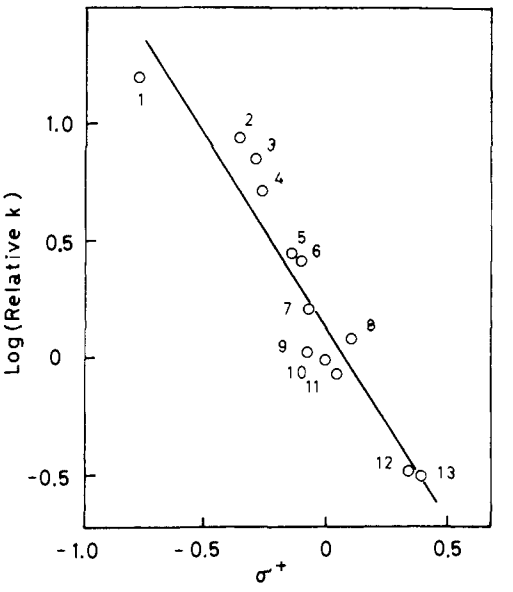


Figure 1. A Hammett plot of relative k values for the formation of phenols vs. σ^+ substituents. The code is as follows: 1, *p*-OMe; 2, *m*- + *p*-Me; 3, *p*-Me; 4, *p*-*t*-Bu; 5, *m*- + *m*-Me; 6, *m*-*t*-Bu; 7, *p*-F; 8, *p*-Cl; 9, *m*-Me; 10, H; 11, *m*-OMe; 12, *m*-F; 13, *m*-Cl.

Consistent with the substituent effect expected from the above mechanism is the finding that the retention values slightly increase with the σ^+ values of the substituents. It is noteworthy the NIH shift of deuterium observed in the present system is almost identical with that found for the liver microsomal induced oxidation as shown in Table II.[12]

The present results demonstrate that oxidations of aromatic compounds by O(^{3}P) atoms proceed via the following mechanism: (i) addition of O(^{3}P) atoms to phenyl rings to form dipolar complexes—O(^{3}P) atoms show a significant electrophilicity, $\rho^+ = -1.6$; (ii) hydride shift within the complex leading to a 2,4-cyclohexadienone intermediate—this step is responsible for the NIH shift which is enhanced by the introduction of an electron-withdrawing substituent; (iii) aromatization to phenol accompanied by a deuterium isotope effect of 2.1.

Acknowledgment. The authors express their thanks to Professor W. Schnabel, Hahn-Meitner-Institute für Kernforschung, Berlin, for helpful discussion.

References and Notes

(1) Daly, J. W.; Guroff, G.; Jerina, D. M.; Udenfriend, S.; Witkop, B. *Adv. Chem. Ser.* **1968**, No. 77, 279.
(2) Guroff, G.; Daly, J. W.; Jerina, D. M.; Renson, J.; Witkop, B.; Udenfriend, S. *Science* **1967**, *158*, 1524.
(3) Jerina, D. M.; Daly, J. W.; Witkop, B. *J. Am. Chem. Soc.* **1967**, *89*, 5488.
(4) Jerina, D. M.; Daly, J. W.; Witkop, B., *Biochemistry* **1971**, *10*, 366. Jerina, D. M.; Yagi, H.; Daly, J. W. *Heterocycles* **1973**, *1*, 267, and references cited therein. Mori, Y.; Toyoshi, K.; Baba, S., *Chem. Pharm. Bull.* **1976**, *24*, 865.
(5) Tomaszewski, J. E.; Jerina, D. M.; Daly, J. W. *Biochemistry* **1975**, *14*, 2024.
(6) The formation of O(^{3}P) atoms by the γ radiolysis of liquid carbon dioxide has been established by the reaction with various kind of organic substrates: Sakurai, H.; Akimoto, K.; Toki, S.; Takamuku, S. *Chem. Lett.* **1975**, 469. Hori, A.; Takamuku, S.; Sakurai, H., *J. Org. Chem.* **1977**, *42*, 2318; *J. Chem. Soc., Chem. Commun.* **1976**, 686. Goto, S., Hori, A.; Takamuku, S.; Sakurai, H., *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1569. Hori, A.; Matsumoto, H.; Takamuku, S.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1978**, 16.
(7) Hori, A.; Matsumoto, H.; Takamuku, S.; Sakurai, H. *Chem. Lett.* **1978**, 467.
(8) Daly, J. W.; Jerina, D. M. *Arch. Biochem. Biophys.* **1969**, *134*, 266. Daly, J. W.; Jerina, D. M.; Witkop, B. *Ibid.* **1968**, *128*, 517.
(9) Boyd, D. R.; Daly, J. W.; Jerina, D. M. *Biochemistry* **1972**, *11*, 1961.
(10) Kasperek, G. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 198; *J. Chem. Soc., Chem. Commun.* **1972**, 784.
(11) Grovenstein, E., Jr.; Mosher, A. J. *J. Am. Chem. Soc.* **1970**, *92*, 3810.
(12) Similar substituent effects on the degree of deuterium retention during

pyridine *N*-oxide photolysis has been reported by Jerina et al., though the oxidizing active species has not been clarified with certainty: Jerina, D. M.; Boyd, D. R.; Daly, J. W. *Tetrahedron Lett.* **1970**, 457-460.

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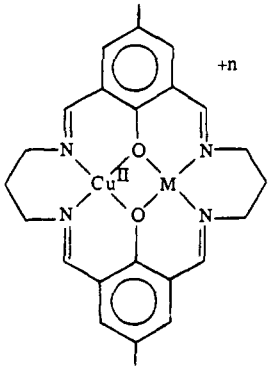
An Electrochemical Method for Measuring Electronic Delocalization in Mixed-Valent Species

Sir:

Binucleating macrocyclic ligands offer attractive opportunities to study electron-transfer processes and metal-metal interactions. For example, the mixed-valent complex, Cu^{I}-$Cu^{II}L^{+}$, **2**, apparently exhibits temperature-dependent intra-



1 M = Cu(II), n = 2
2 M = Cu(I), n = 1
3 M = Mn(II), n = 2
4 M = Fe(II), n = 2
5 M = Co(II), n = 2
6 M = Ni(II), n = 2
7 M = Zn(II), n = 2

molecular electron transfer ($\sim 10^{10}$ s^{-1} at 25 °C).[1,2] The macrocyclic ligand in **2** also permits study of a series of complexes in which the ligand environment, including that of the bridging ligands, remains essentially constant while the metals are varied. Capitalizing on this feature we report here an electrochemical method for directly measuring the electronic delocalization energy in the mixed-valent complex, **2**, and in related materials.

The $Cu^{II}Cu^{II}L^{+2}$ complex, **1**,[3] was prepared by the method of Robson.[4] All of the new heterobinuclear complexes, $Cu^{II}M^{II}L^{+2}$, **3**–**7**, were prepared by a stepwise synthesis, under mild conditions, as follows. Condensation of 2 equiv of 2-hydroxy-5-methylisophthalaldehyde with 1 equiv each of 1,3-diaminopropane and Cu(II) led to isolation of a mononuclear copper(II) complex.[5] Further reaction with 1 equiv of the appropriate divalent metal ion gave a complex with Cu(II) presumably in an N_2O_2 site and the second metal in an O_4 site. Subsequent reaction with 1 more equiv of 1,3-diaminopropane gave the heterobinculear complexes, **3**–**7**.[6] All of the complexes gave satisfactory C, H, N, and M analyses and have been further characterized by X-ray fluorescence spectroscopy, electronic and infrared absorption spectroscopy, and variable-temperature magnetic susceptibility.[7] All complexes also exhibit cyclic voltammograms and differential pulse polarograms, which help to provide further evidence that the new complexes are uniformly heterobinuclear and not mixtures of

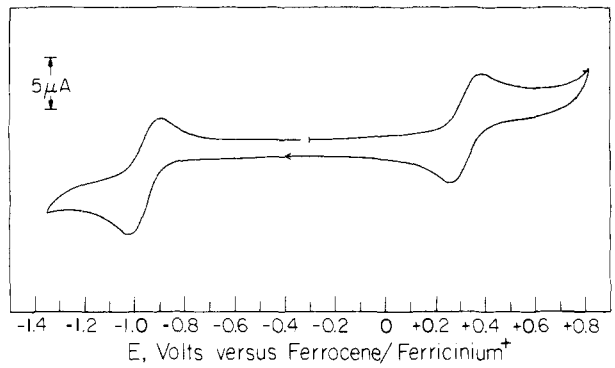


Figure 1. The cyclic voltammogram of $CuMnL^{+n}$, **3**, in methanol. The wave at +0.3 V corresponds to the Mn(III/II) couple. At −1.0 V is the Cu(II/I) wave. The absence of shoulders on each wave indicates little contamination by homonuclear impurities.

homobinuclear species. For example, the $Cu^{II}Cu^{II}L^{+2}$ complex, **1**, exhibits two one-electron redox processes at $E_1 = -0.94$ V and $E_2 = -1.31$ V:[3,8,9]

$$Cu^{II}Cu^{II}L^{+2} + e^{-} \overset{E_1}{\rightleftharpoons} Cu^{I}Cu^{II}L^{+}$$

$$Cu^{I}Cu^{II}L^{+} + e^{-} \overset{E_2}{\rightleftharpoons} Cu^{I}Cu^{I}L \qquad (1)$$

In contrast, only a single reduction of Cu(II) to Cu(I) is observed in the $CuM^{II}L^{+n}$ series, **3**–**7**, as shown in Figure 1 for the complex $Cu^{II}Mn^{II}L^{+2}$, **3**.

Mixed-valent ion stabilization energies can be extracted from the magnitude of the separation of the two one-electron redox processes, $E_1 - E_2$, observed for the homobinuclear complexes. The separation actually reflects several phenomena, which can be considered for any binuclear complex, in the absence of significant coordination geometry changes, as follows. (1) Noninteracting metal sites will have $E_1 - E_2 = 36$ mV, attributable to the simple statistical factor, $RT/F \ln 4$.[11] (2) Electrostatic interactions become important as the metals come closer together yielding $E_1 - E_2 > 36$ mV. If $E_1 - E_2$ is large enough (~100 mV), two one-electron waves can often be resolved.[12] (3) Superexchange interactions may occur in one or more oxidation states, which can either increase or decrease the magnitude of $E_1 - E_2$. (4) Electronic delocalization can stabilize mixed-valent species which will be reflected as an increased separation, $E_1 - E_2$.

The electrochemical behavior of the $Cu^{II}Cu^{II}L^{+2}$ species, **1**, can be analyzed in this context. The measured separation $E_1 - E_2 = 370$ mV is corrected for the statistical factor, 36 mV, to give $E_1 - E_2 = 334$ mV. The measured superexchange stabilization in the $Cu^{II}Cu^{II}L^{+2}$ species ($-3/4\,J = 217$ cm^{-1} = 27 mV)[13] is used to correct $E_1 - E_2$ to 361 mV. No correction need be applied due to the diamagnetic $Cu^{I}Cu^{I}L$ species. The separation $E_1 - E_2 = 361$ mV then reflects electrostatic interactions and covalent stabilization of the mixed-valent $Cu^{I}Cu^{II}$ species relative to the $Cu^{II}Cu^{II}$ and $Cu^{I}Cu^{I}$ species. Previous attempts to separate these contributions have relied on estimating the electrostatic component.[14] In the present case the heterobinuclear complexes, **3**–**6**, permit the covalent factor to be isolated since the electrostatic factor is constant.

Copper(II/I) reduction potentials as a function of the divalent metal ion in the second site

$$Cu^{II}M^{II}L^{+2} + e^{-} \rightleftharpoons Cu^{I}M^{II}L^{+} \qquad (2)$$

$$M^{II} = Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II}, Zn^{II}$$

are listed in Table I. Reduction potentials have been corrected for superexchange stabilization in the $Cu^{II}M^{II}L^{+2}$ species as described above, and as estimated from magnetic susceptibility

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