mediately after reduction, were isolated in small quantity by C18 reverse phase flash chromatography eluting with a step gradient of methanol and 1.5% aqueous formic acid, and they were characterized as stereoisomers of leucodaunomycin, (8*S*-*cis*)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxohexopyranosyl)-oxy]-6a,7,8,9,10,10a-hexahydro-5,8,12-trihydroxy-1-methoxy-6,11-naphthacenedione (**4**), from spectroscopic, chemical, and kinetic data. The major isomers (A and C) gave UV-vis absorptions as shown in the inset of Figure 1, and isomer C was further characterized from mass spectral and NMR data.[13]

Isomer A was reacted anaerobically in aqueous solution by adjusting the pH to 7.4 with Trizma buffer, and the course of the reaction was monitored spectrophotometrically. The spectra showed a rise (Figure 1) and a fall in the absorption at 618–622 nm consistent with slow back tautomerization to daunomycin hydroquinone (**5**) followed by rapid elimination of daunosamine to form the quinone methide **6** and slow tautomerization of **6** to 7-deoxydaunomycinone (**3**) as shown in Scheme I. The absorption at 618–622 nm versus time data for the early part of the reaction were fit by nonlinear least squares to a consecutive first-order rate law correcting for end absorption by **3**. Absorption at later times was obscured by precipitation of **3**. The integrated rate law was as follows:

$$A_t = \frac{[4]_0}{k_1 - k_2}\{(k_1\epsilon_6 - k_2\epsilon_3)e^{-k_1 t} + (k_1\epsilon_3 - k_1\epsilon_6)e^{-k_2 t} + \epsilon_3(k_2 - k_1)\}$$

where A_t is the absorbance at 618–622 nm at time t, $[4]_0$ is the initial concentration of **4**, k_1 is the pseudo-first-order rate constant for tautomerization of **4**, k_2 is the pseudo-first-order rate constant for tautomerization of **6**, and ϵ_6 and ϵ_3 are the molar extinction coefficients for **6** and **3** at 618–622 nm. The calculated rate constants k_1 and k_2 were $(1.0 \pm 0.1) \times 10^{-2}$ and $(3.3 \pm 0.02) \times 10^{-2}$ s^{-1}, respectively, where the errors are given as the average deviation from the mean of two measurements. Reverse phase HPLC analysis of the product mixture showed 97% 7-deoxydaunomycinone (**3**) and 3% daunomycinone (**7**). In a separate experiment the rate constant for decay of quinone methide **6** generated by anaerobic reduction of **1** at pH 7.4 with sodium dithionite was determined to be 3.2×10^{-2} s^{-1}. Reverse phase HPLC analysis of this reduction showed 98% **3** and 2% **7**.

Similar spectroscopic monitoring of reaction of isomer C of **4** at pH 7.4 did not show the build up of absorption at 618–622 nm but only decay of the leucodaunomycin bands with formation of predominantly the quinone band of **3**. A sharp isosbestic point appeared at 454 nm. The decay of the 440-nm band of **4** was first order, and least-squares treatment of $\ln(A - A_\infty)$ versus time data gave k_1 equal to 1.3×10^{-3} s^{-1} with a correlation coefficient of 1.00. Reverse phase HPLC analysis showed 96% **3** and 4% **7**. The quinone methide band was not observed because the rate constant for tautomerization of isomer C to hydroquinone **5** is too small, 25 times smaller than the rate constant for destruction of **6**.

Isomer A was also reacted with a 60-fold excess of *N*-acetyl-L-cysteine at pH 7.4 to give 86% **3** and 14% of a 2:1 mixture of the diastereomers from quinone methide nucleophilic trapping followed by oxidation, 7-(*N*-acetyl-L-cystein-*S*-yl)-7-deoxydaunomycinone (**8**). The structure for **8** was established by comparison with authentic material produced by reduction of daunomycin in the presence of *N*-acetyl-L-cysteine.[14]

The leucodaunomycins **4** were also produced by reduction of daunomycin with the organic reducing agent bi(3,5,5-trimethyl-2-oxomorpholin-3-yl) (TM-3 dimer)[5,15] in the aprotic solvent anhydrous acetonitrile. Formation of **4** from daunomycin hydroquinone (**5**) in acetonitrile solvent and in protic solvent at low pH in preference to glycosidic cleavage is consistent with glycosidic cleavage occurring at an anionic state of **5**.

In summary, daunomycin hydroquinone (**5**) tautomerizes at the B-ring to leuco isomers in competition with glycosidic cleavage when the pH is rapidly reduced from 7 to 3. The leuco isomers are stable at low pH but revert to daunomycin hydroquinone at pH 7.4. If leucodaunomycins are formed in vivo as transient metabolites by reduction of daunomycin in hydrophobic regions or in regions of low pH, subsequent reaction with biological macromolecules would not require reduction but only a change in pH and hydrophobicity. The leucodaunomycins may also be interesting pharmaceutical materials because they are anthracyclines which do not require bioreductive activation to reach the quinone methide state; furthermore, isomer C has a relatively long half-life at biological pH.

(13) FAB (positive ion) m/z 552 (100, M + Na$^+$), 530 (80, M + 1), 401 (27); (negative ion) m/z 529 (100, M); 300 MHz ^{1}H NMR δ 1.22 (d, J = 6.5 Hz, 5′-CH$_3$), 1.79–2.18 (m, 2′-H, 7-H, 9-H), 2.28 (s, 8-COCH$_3$), 3.60 (m, 3′-H, 6a-H), 3.73 (m, 4′-H, 10a-H), 3.98 (s, 1-OCH$_3$), 4.13 (q, J = 6.5 Hz, 5′-H), 4.72 (m, 10-H), 4.94 (m, 1′-H), 7.30 (d, J = 7.6 Hz, 4-H), 7.71 (t, J = 7.7 Hz, 3-H), 7.93 (d, J = 7.4 Hz, 2-H).

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Ligand Substitution Reactions of 17-Electron Transition-Metal Carbonyl Anions: An Electron-Transfer Mechanism

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Seventeen-electron metal complexes have been recognized as intermediates in catalytic, photochemical, and electrochemical reactions.[1] An important aspect of their reactivity is their substitutional lability. In general 17-electron complexes are more reactive than 18-electron complexes and more selective in their reactivity than 16-electron complexes. Reaction of a 17-electron metal complex with a two-electron donor by an associative mechanism usually involves delocalization of electron density from the metal onto the ligands. This avoids a high-energy 19-electron transition state and is postulated to be important in the very facile ligand substitution reactions of $Mn(CO)_5$,[2] for example. We report here facile gas-phase ligand substitution reactions of the isoelectronic $Cr(CO)_5^-$. These reactions provide an interesting example of the selectivity with which 17-electron complexes can react. They proceed selectively with ligands of high electron affinity. This suggests a mechanism in which the metal transfers an electron to the attacking ligand, and the resulting 16-electron metal complex can then accept two electrons from a donor group on the ligand to form a low-energy 18-electron transition state. Charge transfer is thought to be involved in some reactions of more unsaturated metal carbonyl anions,[3,4] but reactions of 17-electron metal carbonyl anions have generally been interpreted in terms of other mechanisms.[4,5]

The gas-phase reactions involve $Cr(CO)_5^-$ and a series of organic ligands. Examination of the reactions has produced two kinds of evidence supporting the charge-transfer mechanism: (1) The variation of rates of the reaction with electron affinity of the ligand and (2) the distinctive nature of the products of certain reactions, in particular the reactions of the bromonitrobenzene isomers.

The total reaction rate constants for reactions of $Cr(CO)_5^-$ with a series of organic ligands were measured by using FTICR techniques on a Nicolet FTMS-2000 instrument.[6] The anion reactant was formed by low-energy electron attachment to Cr-

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Table I. Rate Constants for Reactions of Ligands with $Cr(CO)_5^-$

ligand	EA[a] (ev)	k[b] (10^{-10} cm^3 s^{-1})	k/k_c[c]
hydroquinone	<0	$<8 \times 10^{-5}$	$<8 \times 10^{-6}$
anthracene	0.57	$<1 \times 10^{-2}$	$<1 \times 10^{-3}$
benzophenone	0.62	$<1 \times 10^{-2}$	$<5 \times 10^{-4}$
m-dicyanobenzene	0.91	$<7 \times 10^{-2}$	$<3 \times 10^{-3}$
nitrobenzene	1.01	1.23	6.42×10^{-2}
o-bromonitrobenzene	1.16	1.26	6.26×10^{-2}
phthalic anhydride	1.21	4.69×10^{-3}	1.81×10^{-4}
p-bromonitrobenzene	1.29	4.32	0.196
maleic anhydride	1.44	8.96	0.447
m-dinitrobenzene	1.65	5.51	0.258
p-naphthaquinone	1.81	2.50	0.178
p-benzoquinone	1.91	14.1	1.33
p-dinitrobenzene	2.00	1.83	0.175
2,3,5,6-tetrachloroquinone	2.78	3.30	0.310
tetracyanoethylene	3.17	4.06	0.446

[a] Electron affinities from the following: Chowdhury, S.; Kebarle, P. Kinetics and Equilibria of Electron Transfer Reactions: $A^- + B = A + B^-$. Determinations of Electron Affinities of A and B and Stabilities of Adducts A_2^- and $(A\ B)^-$. In *Structure/Reactivity and Thermochemistry of Ions*; Ausloos, P., Lias, S. G., Eds.; Reidel: Boston, 1987; pp 321–366. [b] Present results. k is the overall bimolecular rate constant. As discussed in the text only for the bromonitrobenzenes and tetracyanoethylene are products besides those of ligand substitution observed. Estimated uncertainty ±20% resulting primarily from uncertainties on pressure measurement. [c] The capture collision rate is calculated by using formulas In the following: Su, T.; Chesnavich, W. J. *J. Phys.* **1982**, *76*, 5183.

$(CO)_6$.[7] The reactant neutral was introduced to a pressure between 2×10^{-8} Torr and 2×10^{-7} Torr. Mass spectra of the trapped ions were obtained at varying delay times following an initial ionizing electron beam pulse. Decays of $Cr(CO)_5^-$ signal intensity were exponential over at least 3 half-lives for reactive ligands suggesting that the results are unaffected by hot ions. With few exceptions the observed products corresponded to ligand substitution. The ligands and their electron affinities are listed in Table I. Dividing each rate constant by the corresponding ion-molecule capture collision rate gives a reaction efficiency. Unit efficiency corresponds to a reaction that proceeds on every collision. The reaction efficiencies are plotted against ligand electron affinity in Figure 1.

The reactions of species with large electron affinities proceed with near unit efficiency. At an electron affinity near 1 eV, reaction efficiency drops sharply with decreasing electron affinity. This certainly suggests that electron transfer plays a role in the reaction. A general scheme for the reaction consistent with the observed correlation with electron affinity is

$$Cr(CO)_5^- + L \rightarrow [Cr(CO)_5^-\text{-}L] \rightarrow [Cr(CO)_5\text{-}L^-] \rightarrow Cr(CO)_{5-n}L^- + nCO$$

Usually $n = 1$ or 2. In the first step an electrostatically bound complex is formed. Next electron transfer from the metal to the ligand occurs within the complex. The ligand then donates a pair of the electrons to the resulting 16-electron species $Cr(CO)_5$ to form a molecular complex which then loses one or more CO molecules. Charge transfer between $Cr(CO)_5^-$ and most of the ligands is endothermic, but within the complex the energy required for charge transfer is decreased by the binding energy of the complex. Evidently the residual energy barrier exceeds the reactant energy unless the electron affinity of L exceeds ca. 1 eV. An electron affinity greater than that of $Cr(CO)_5$ (>2.0 eV[8]) is required to form free L^- in an outright electron transfer. In fact, free L^- is observed as a product (53% of the total) only for tetracyanoethylene which has the highest electron affinity (3.17 eV) of the ligands studied.

It is interesting to note that $Cr(CO)_5^-$ has been observed in solution. The ion can be formed by electrochemical reduction of

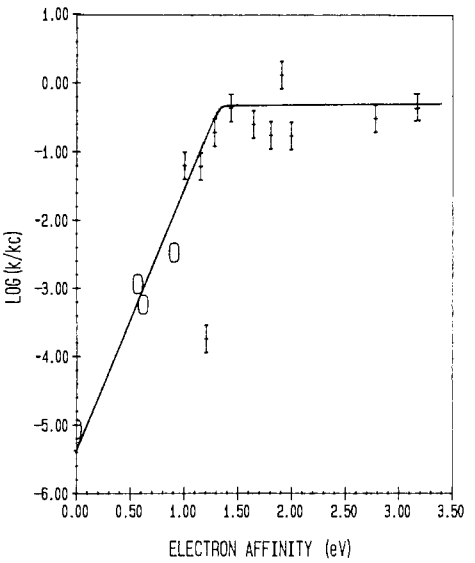

Figure 1. Efficiency (k/k_c) of reactions of $Cr(CO)_5^-$ with organic ligands vs electron affinity of the ligand. Open circles indicate estimated upper limits for reactions in which products were not observed at long reaction time.

$Cr(CO)_6$.[9] Ligand substitution reactions have not been reported in solution, but it has been noted that acetonitrile is unreactive. This is consistent with the present results since acetonitrile does not have a positive electron affinity.

Additional evidence for electron transfer within the reacting complex comes from results with a particular pair of ligands. The bromonitrobenzenes react according to

$$Cr(CO)_5^- + C_6H_4BrNO_2 \xrightarrow{k_1} Cr(CO)_5Br^- + C_6H_4NO_2$$
$$\xrightarrow{k_2} Cr(CO)_{5-n}(C_6H_4BrNO_2)^- + nCO$$

where $k_1/k_2 = 0.53$ for the *o*-bromonitrobenzene and 0.10 for *p*-bromonitrobenzene.[10] This is reminiscent of the results of electrochemical reduction of the bromonitrobenzenes.[11] The ortho isomer yields Br^- efficiently ($k = 110$ s^{-1}),[12] while the para isomer does not ($k = 0.004$ s^{-1}).[13] Together these observations suggest a scheme for $Cr(CO)_5Br^-$ involving steps such as

$$[Cr(CO)_5^-\text{-}C_6H_4BrNO_2] \rightarrow [Cr(CO)_5\text{-}C_6H_4BrNO_2^-] \rightarrow [Cr(CO)_5\text{-}(Br^-\text{-}C_6H_4NO_2)]$$

The role of the $Cr(CO)_5^-$ parallels that of the condensed phase electrode. It provides an electron to the bromonitrobenzene which then behaves in a way similar to the condensed phase radical anion. The ortho isomer loses Br^- more readily than does the para isomer. Just as in the condensed phase this is probably because the distortion from planarity resulting from the interaction between the ring substituents in the ortho isomer provides a driving force for loss of Br^-. The qualitative agreement with the condensed phase result suggests that the bromonitrobenzene radical anion has at least a transient existence in its complex with $Cr(CO)_5$. Thus the interesting stereochemical selectivity of this chemistry again supports an electron-transfer mechanism.

Similar variations of rate constants with electron affinities occur for the 17-electron radical anions $Fe(CO)_4^-$ and $Ni(CO)_3^-$. Sixteen- and 18-electron metal carbonyl anions behave differently. These results will be discussed in a full paper.

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