The k_{cat} and K_m values for the deuterated substrate **7** are 6.5 × 10^{-3} h^{-1} and 0.90 mM, respectively, resulting in an isotope effect (k_{catH}/k_{catD}) of 3.3.[12] This suggests that the rate-determining transition state for the reaction involves some degree of α C-H bond breaking. For comparison, $(k_{AcOH})_H/(k_{AcOH})_D$ = 1.8. Treatment of antibody with diazoacetamide had no effect on catalytic activity, suggesting either that glutamate or aspartate residues do not play a key catalytic role or that they are sequestered from the reagent.[13] In contrast, treatment of antibody with 4′-nitro-2-bromoacetophenone led to complete inactivation, consistent with the presence of histidine, cysteine, serine, or lysine in the active site.[14] Interestingly, antibody 43D4, which was generated to hapten **8** and catalyzes the elimination of HF from substrate **6**,[1] does not accelerate the dehydration of water from **2** (although it binds **2** with K_D = 4.7 mM). This result is consistent with the notion that hapten **1** stabilizes an oxonium ion like transition state. Further experiments are being carried out to more precisely define the mechanism and stereochemistry of this antibody-catalyzed dehydration reaction and to generate an antibody combining site containing a catalytic dyad.

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Registry No. 1, 57548-40-0; **2**, 142160-94-9; D_2, 7782-39-0; dehydratase, 9044-86-4.

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[12] The deuterated substrate **7** was synthesized from 4′-nitrobenzaldehyde and acetone-d_6.[11]

[13] 20A2F6 was dialyzed against 20 mM borate and 150 mM $NaClO_4$ buffer, incubated with 0.4 M diazoacetamide at pH 5.5 at 25 °C for 8 h, and then dialyzed exhaustively against assay buffer. Grosberg, A. L.; Pressman, D. *J. Am. Chem. Soc.* **1960**, *82*, 5478–82.

[14] 20A2F6 was treated with 2 mM 4′-nitro-2-bromoacetophenone at room temperature for 50 h, pH 7, and dialyzed exhaustively against assay buffer. The control experiment with 4′-nitroacetophenone was carried out in a similar manner, and 20A2F6 showed no loss of catalytic activity.

Electron-Density Analysis of the Transition States of Substitution Reactions of 17- and 18-Electron Hexacarbonyl Complexes

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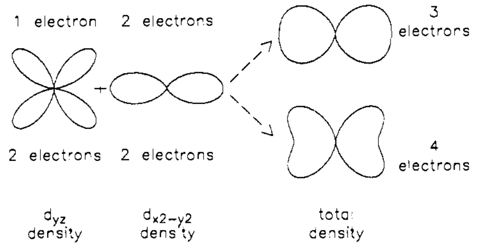
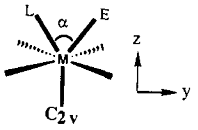
It is well known that 17-electron metal carbonyl radicals such as $Mn(CO)_5$ and $Re(CO)_5$ are substitution labile.[1-3] Kinetic studies have shown that the first CO substitution of the vanadium hexacarbonyl, $V(CO)_6$, by phosphine ligands is about 10^{10} times faster than that of the analogous 18-electron chromium complex, $Cr(CO)_6$.[4] Usually, the substitutional lability of 17-electron metal complexes has been explained qualitatively in terms of formation of a 2-center, 3-electron bond in the 19-electron transition state or intermediate. However, the extremely large magnitude of the rate enhancement is not yet satisfactorily understood through this simple bonding picture. In this communication, we provide an electron-density analysis of the 19-electron and 20-electron transition states and observe how the single electron difference leads to a significant difference in the valence-electron charge concentrations.

Scheme I



Restricted Hartree–Fock (RHF) ab initio calculations were used to obtain the electron density. The effective core potentials (ECP2s) and double-ζ basis sets of Hay and Wadt were employed for transition-metal atoms.[5] For ligand atoms, the ECPs and basis sets with a double-ζ representation of Stevens, Basch, and Krauss were used.[6] Although we have shown that the electron correlation is extremely important for determining the transition states and activation energies of the substitution reactions of 17-electron and 18-electron carbonyl complexes, it is much less important for metals in the third transition series than in the first or second transition series.[7] Therefore, for theoretical simplicity, we studied the transition states for carbonyl exchange reactions of $M(CO)_6$ + CO (M = Ta and W) at the RHF level. The transition state (or intermediate if one exists) for an exchanging reaction can be easily obtained by optimizing structures with a symmetry (mirror or C_2) restriction relating the entering and leaving ligands, since the principle of microscopic reversibility requires that in the transition state (or intermediate) of an exchange reaction the entering and leaving groups have a like geometric relation to the rest of the structure.[8,9] For nucleophilic attack on an octahedral face, the assumed transition state with a C_{2v} symmetry is shown in **1**. In the geometry optimization of the C_{2v} transition states, all degrees of freedom were optimized, except the M–C–O angles which were assumed to be linear for the four equivalent carbonyls.



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For these assumed transition states, $M(CO)_7$ (**1**), the structural parameters α and M—E (= M—L, E = L = CO) are found to be 70.0° and 2.3 Å for M = Ta and 54.7° and 3.9 Å for M = W. The assumed associative transition state for $W(CO)_6$ + CO, in fact, resembles an I_d transition state since both entering and leaving ligands are far from the metal center in the calculated transition-state geometry. The activation energies are calculated to be 20.8 kcal/mol for the $Ta(CO)_6$ + CO exchange reaction and 35.8 kcal/mol for the $W(CO)_6$ + CO exchange reaction (the latter is close to the reported dissociation energy[10]). The significant activation energy difference (15.0 kcal/mol) can account for the extremely large magnitude of the rate enhancement, since the 10^{10} multiplicative difference in the substitution reaction rates corresponds to a difference of 12–13 kcal/mol in the activation energy if we assume an Arrhenius expression for the rate constant

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Figure 1. Plots of $-\nabla^2\rho$ in the E–M–L plane of the assumed transition states in the $Ta(CO)_6$ + CO (a) and $W(CO)_6$ + CO (b) carbonyl exchange reactions. ρ is the valence-electron density.

and similar preexponential factors.

In Figure 1, we plot the Laplacian of the valence-electron density, i.e., $-\nabla^2\rho$,[11] on the *yz* plane (i.e., E–M–L plane) from the ab initio calculations on these assumed transition states (**1**). In these plots solid lines show regions of local electron concentrations, while dotted lines show regions of local electron depletions. A significant difference in the valence-electron $-\nabla^2\rho$ plots is seen clearly in Figure 1. Two concentrations in the $+y$ and $-y$ directions, 180° apart, are observed for the 19-electron system ($Ta(CO)_7$, Figure 1a), while the 20-electron system ($W(CO)_7$, Figure 1b) gives four concentrations with an angle of about 109.5° between the two concentrations in the $+z$ direction (toward the entering/leaving ligands).

Although this difference seems large, its qualitative origin is easily understood through a simple scheme, where for a C_{2v} ML_7 (**1**) complex we consider the orbital interaction between a square-pyramidal ML_5 fragment and the two entering/leaving ligand σ orbitals in the *yz* plane. The d_{yz} orbital of the "t_{2g}" set of the ML_5 fragment is antibonding and the $d_{x^2-y^2}$ orbital is slightly antibonding. The electron density contributed by the d_{yz} and $d_{x^2-y^2}$ orbitals is of primary importance in comparing the two systems ($Ta(CO)_7$ and $W(CO)_7$) since for a 19-electron ML_7 system the d_{yz} orbital is singly occupied (Scheme Ia), while for a 20-electron ML_7 system it is doubly occupied (Scheme Ib). Scheme I illustrates how the single electron difference leads to a significant difference in the electron density between 19-electron and 20-electron systems.

In summary, the significant difference in the substitution reaction rates of 17-electron and 18-electron transition-metal carbonyl complexes is reflected in the significant difference in the valence-electron distributions of their transition states. This large difference was unanticipated through traditional valence-bond or molecular orbital concepts. In the substitution reaction of an 18-electron metal carbonyl complex, where the transition state corresponds to a 20-electron system, the valence-electron charge concentrations are located along the directions of metal–entering/leaving ligand bonds in the transition state. For a 19-electron system, the two maxima in the charge concentration are not directed toward the entering/leaving ligands. Therefore, a more stable transition state is observed for the substitution reaction of a 17-electron transition-metal complex.

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Can Acyl Transfer Occur via a Concerted Mechanism? Direct Evidence from Heavy-Atom Isotope Effects

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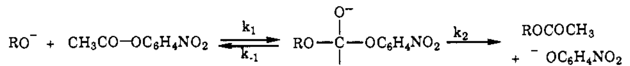
Nucleophilic acyl-transfer reactions most often occur by way of a two-step mechanism with a tetrahedral intermediate, described in the IUPAC system[1] as $A_N + D_N$. Acyl halides can react through an acylium ion intermediate by an S_N1 ($D_N + A_N$) mechanism.[2] There has been interest in the question of whether ester acyl transfers can proceed by a concerted S_N2 (A_ND_N) pathway.[3] On the basis of structure–reactivity studies, Williams et al. proposed that the reaction of phenoxide anions with *p*-nitrophenyl acetate proceeds by such a concerted pathway,[4a] and they proposed a theory predicting when ester acyl transfers will be concerted and when they will go by the limiting stepwise mechanisms.[5] These conclusions have been challenged.[6] Recently, theoretical arguments have been presented in support of a concerted mechanism in reactions of aryl acetates with phenoxide anions.[7]

We have shown that in displacement reactions where *p*-nitrophenol is the leaving group the degree of transition-state bond cleavage is reflected in a measurable ^{15}N isotope effect.[8] The isotope effect arises from bonding changes that occur in the nitro group as a result of the delocalization of charge arising from partial cleavage of the bond to *p*-nitrophenol in the transition state. Because the ^{15}N isotope effect is a secondary one and reaction coordinate motion does not make a contribution, it is a better measurement of transition-state bond cleavage than the primary phenolic oxygen isotope effect. The utility of this method for examining transition-state structure was demonstrated in a study of the hydrolysis reactions of phosphate esters of *p*-nitrophenol.[8]

This technique offers a direct means for distinguishing a concerted mechanism from a tetrahedral one for acyl-transfer reactions with *p*-nitrophenyl acetate. In the tetrahedral mechanism shown here, where the pK_a of the nucleophile is higher than that of the leaving group, nucleophilic attack will be rate-limiting and the intermediate will partition completely forward to products. Only the first step of this process can show isotope effects since it is rate-limiting, and no ^{15}N isotope effect is expected in this step since the bond to the leaving group is scarcely affected. Therefore, this mechanism predicts no significant ^{15}N isotope effect. A concerted mechanism on the other hand will exhibit an isotope effect corresponding to the degree of transition-state cleavage of the bond to the *p*-nitrophenol leaving group.



$$RO^- + CH_3CO{-}OC_6H_4NO_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RO{-}\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}{-}OC_6H_4NO_2 \xrightarrow{k_2} \begin{matrix} ROCOCH_3 \\ + \ ^-OC_6H_4NO_2 \end{matrix}$$

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