On the Allylic Rearrangements in Metal Oxo Complexes: Mechanistic and Catalytic Studies on $MoO_2(allyloxo)_2(CH_3CN)_2$ and Analogous Complexes

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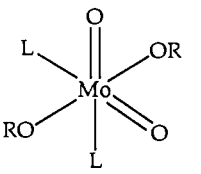
The 1,3 transposition of a hydroxy group on an allyl moiety using metal oxo catalysts is of both fundamental and practical importance. The isomerization of allyl alcohols can be catalyzed by complexes such as $VO(OR)_3$[1] or $WO(OR)_4$[2] (R = alkoxy or siloxy) at 130–200 °C, or by $VO(acac)_2$ or $MoO_2(acac)_2$ at 25 °C when activated by $Me_3SiOOSiMe_3$.[3] Similar rearrangements have also been invoked in the mechanism of acrolein (and acrylonitrile) formation through the oxidation of propene on heterogeneous bismuth molybdate catalysts at 350–450 °C (Sohio process).[4] The determination of the detailed mechanism of these processes has been hampered by the absence of *well-defined molecular complexes* in which such a rearrangement takes place under mild conditions. We report herein studies on the complexes $MoO_2(allyloxo)_2L_2$ (allyl = $CMe_2CH{=}CH_2$ or $CH_2CH{=}CMe_2$) and their imido analogues for which such allyl arrangements can be readily observed. Further, these complexes also effect the catalytic isomerization of allyl alcohols at 25 °C.

By treatment of MoO_2Cl_2 with lithium allyloxide (2 equiv) in CH_3CN at −10 °C, followed by filtration to remove the LiCl formed, the complexes $MoO_2(allyloxo)_2L_2$ (L = CH_3CN, **a**; pyridine; or $^1/_2$ bipyridyl, **b**) can generally be isolated as white crystals after the addition of L. Their molecular structure (Figure 1) is analogous to that found for the corresponding alkoxo complexes,[5] according to their ^1H NMR and IR spectra. When, however, $MoO_2(OCMe_2CH{=}CH_2)_2(CD_3CN)_2$ (**1a**)[6] is synthesized in this fashion in CD_3CN and then studied by ^1H NMR at 25 °C, the growth of new resonances indicates the progressive conversion of **1a** into complexes **2a** and **3a**[6] containing the rearranged $OCH_2CH{=}CMe_2$ ligands (Scheme I).

Scheme I

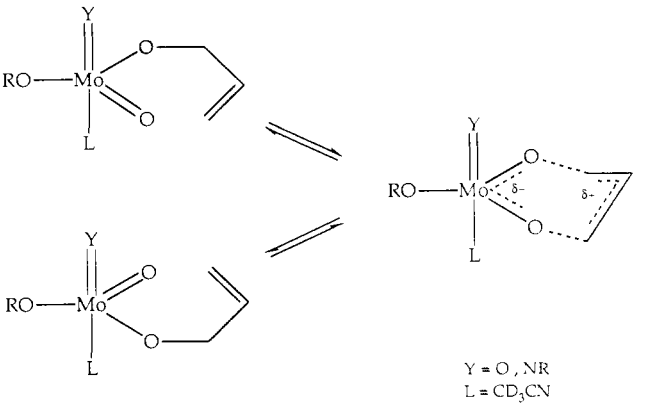
$$MoO_2(OCMe_2CH{=}CH_2)_2(CD_3CN)_2 \rightleftharpoons \underset{\mathbf{1a}}{} $$
$$MoO_2(OCMe_2CH{=}CH_2)(OCH_2CH{=}CMe_2)(CD_3CN)_2 \rightleftharpoons \underset{\mathbf{2a}}{}$$
$$MoO_2(OCH_2CH{=}CMe_2)_2(CD_3CN)_2 \quad \mathbf{3a}$$

At equilibrium (after ca. 5 h), the ratio of the ^1H resonances of the ligands $OCMe_2CH{=}CH_2$ to those of $OCH_2CH{=}CMe_2$ is ca. 1:3, but the relative concentrations of the complexes **1a**, **2a**, and **3a** cannot be determined. On addition of bipyridyl to this solution, **3b**[6] can be isolated quantitatively. The same equilibration takes place (albeit more slowly) when starting from **3a**. By measurement of the initial rate of conversion of **1a** to **2a** for varying concentrations of **1a** ($3.6–10 \times 10^{-2}$ M) we find that $-d[\mathbf{1a}]/dt = k_1[\mathbf{1a}] + k_2[\mathbf{1a}]^2$, with $k_1 = 3 \times 10^{-5}$ s^{-1} and $k_2 = 10^{-3}$ M^{-1} s^{-1}.



OR = allyloxo
L = CH_3CN, pyridine, 1/2 bipyridyl

Figure 1.



Y = O, NR
L = CD_3CN

Figure 2.

The analogous imido complexes $MoO(NR)(OCMe_2CH{=}CH_2)_2L_2$ can also be synthesized and shown to isomerize similarly, although significantly more slowly. The following relative rates could be established qualitatively: O > NC_6H_4-4-NO_2 > NC_6H_5 > NBu^t. When R = Bu^t (L = CD_3CN, **4a**[6]), the rearrangement is too slow to be observed before the oxidative dehydrogenation of the allyloxo ligands,[7] which occurs at ca. 80 °C in this case.

The first-order term in the kinetic expression indicates that the allyl rearrangement takes place intramolecularly in a mononuclear complex. Transfer of the allyl groups would occur to a vicinal oxo ligand,[8] probably via a [3,3] sigmatropic shift (Figure 2) similar to a Claisen rearrangement.[1] The greatly reduced rate of this process when one oxo ligand is replaced by a more electron donating imido ligand would indicate that in the transition state some accumulation of negative charge takes place on Mo, with the migrating allyl group possessing some cationic character.[9] The second-order kinetic term can be interpreted as arising from the presence of small quantities of a more rapidly rearranging dimeric species which is in equilibrium with monomer in solution.[10]

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(6) Selected ^1H NMR data (CD_3CN, δ ppm) are as follows. **1a**: 6.18 (dd, 1 H, $^3J_{H_aH_b}$ = 17.3 Hz, $^3J_{H_aH_c}$ = 10.6 Hz, $=CH_a$), 5.24 (dd, 1 H, $^3J_{H_bH_a}$ = 17.3 Hz, $^2J_{H_bH_c}$ = 1.7 Hz, $=CH_bH_c$), 5.06 (dd, 1 H, $^3J_{H_cH_a}$ = 10.6 Hz, $^2J_{H_cH_b}$ = 1.7 Hz, $=CH_bH_c$), 1.48 (s, 6 H, CMe_2). **3a**: 5.66 (t, 1 H, $^3J_{HH}$ = 9.5 Hz, =CH), 4.78 (d, 2 H, $^3J_{HH}$ = 9.5 Hz, CH_2), 1.75 and 1.68 (2 s, 6 H, $=CMe_2$). **3b**: 9.37 (d, 2 H, $H_{6,6'}$), 8.35 (d, 2 H, $H_{3,3'}$), 8.18 (m, 2 H, $H_{5,5'}$), 7.68 (m, 2 H, $H_{4,4'}$), 4.81 (t, 2 H, $^3J_{HH}$ = 8.9 Hz, =CH), 4.27 (d, 4 H, $^3J_{HH}$ = 8.9 Hz, CH_2), 1.46 and 1.28 (2 s, 12 H, $=CMe_2$). **4a**: 6.02 (dd, 2 H, $^3J_{H_aH_b}$ = 17.4 Hz, $^3J_{H_aH_c}$ = 10.7 Hz, $=CH_a$), 5.20 (dd, 2 H, $^3J_{H_bH_a}$ = 17.4 Hz, $^2J_{H_bH_c}$ = 1.7 Hz, $=CH_bH_c$), 5.04 (dd, 2 H, $^3J_{H_cH_a}$ = 10.7 Hz, $^2J_{H_cH_b}$ = 1.7 Hz, $=CH_bH_c$), 1.47 (s, 12 H, CMe_2), 1.42 (s, 9 H, CMe_3).
(7) Belgacem, J.; Kress, J.; Osborn, J. A. Manuscript in preparation.
(8) Studies on the appropriately labeled molecules are underway to confirm this point.
(9) For a simple transformation, this transition state must possess a plane of symmetry to conform with microscopic reversibility. It can be seen that the six-coordinate complexes **1a–3a** cannot themselves satisfy such a demand without drastic reorganization of the other ligands. However, their conversion into a trigonal-bipyramidal (as represented in Figure 2) or tetrahedral structure would surmount this problem. This implies that the reversible dissociation of CD_3CN is necessary to form the active species. Experiments are in progress to verify this point. We note that the less labile bipyridyl (such as **3b**) or pyridine complexes do not readily rearrange. Further, this mechanism implies that the migration would take place suprafacially, which indeed has been shown in one case.[3]

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The isomerization of allyl alcohols can also be readily carried out at 25 °C using such complexes as catalysts, the stable and easily prepared $MoO_2(OBu^t)_2$ (**5**)[5] serving conveniently as the catalyst precursor. For instance, using a 2.8×10^{-2} M solution of **5** in CD_2Cl_2, 50 equiv of $Me_2C{=}CHCH_2OH$ is converted in 2.5 h into the equilibrium mixture of this alcohol with $CH_2{=}CHCMe_2OH$ (ca. 37:63), at an initial rate of 35 turnovers/h. We have shown by ^1H NMR that in the presence of excess $Me_2C{=}CHCH_2OH$ the initial replacement of OBu^t ligands and the displacement of rearranged ligand $CH_2{=}CHCMe_2O$ by $Me_2C{=}CHCH_2O$ is rapid ($\ll$ 5 min). Further, the isomerization rate is zero order in allyl alcohol under these conditions. These observations show that the allyl rearrangement step of the type found in complexes **1a-3a** is turnover limiting in the catalytic process.

(10) If we assume the equations (M = monomer), the rate of inversion will

$$\text{inversion} \xleftarrow[k_1]{} M \overset{K}{\rightleftharpoons} \tfrac{1}{2}M_2 \xrightarrow[k'_1]{} \text{inversion}$$

be expressed by $v = k_1[M] + k'_1[M_2]$. If K is small, this tends toward $v = k_1[M] + k'_1K^2[M]^2 = k_1[M] + k_2[M]^2$. Allyl migration in this dimer (built via bridging oxo or allyloxo ligands) may also take place on a single Mo center, as described above. The Lewis acidity of the second Mo center would thereby lower the transition state by stabilizing the developing negative charge on the first Mo, thereby increasing the rate. We also observe that addition of excess $MoO_2(OBu^t)_2$ (**5**)[5] to CD_3CN solutions of **1a**, which will increase the overall concentration of dimeric species, increases the initial rearrangement rate.

$^{11}C/^{14}C$ Kinetic Isotope Effects in Enzyme Mechanism Studies. $^{11}C/^{14}C$ Kinetic Isotope Effect of the Tyrosine Phenol-Lyase Catalyzed α,β-Elimination of L-Tyrosine

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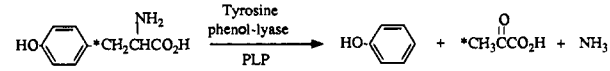
In this paper a method for determination of $^{11}C/^{14}C$ kinetic isotope effects (KIEs) in enzyme-catalyzed reactions is presented. The KIE was determined for the elimination reaction of L-(β-*C)tyrosine (*C = ^{11}C or ^{14}C), catalyzed by tyrosine phenol-lyase (EC 4.1.99.2) from *Citrobacter freundii*; see Scheme I. This reaction was chosen as a model to develop methodology for determination of $^{11}C/^{14}C$ KIEs in enzyme-catalyzed reactions.

Isotope-effect studies[1] are crucial in enzyme mechanism investigations in that they yield information on the kinetic mechanisms, rate-limiting steps, and chemical mechanisms. In favorable cases, transition-state structures for single steps may also be inferred from KIE data.[2] In carbon KIE studies of enzyme reactions, the isotopes ^{12}C, ^{13}C, and ^{14}C have so far been utilized. The isotope ^{11}C is a short-lived (half-life 20.34 min) accelerator-produced positron-emitting radionuclide. ^{11}C is frequently used in positron emission tomography (PET) studies[3] in biomedical research and clinical diagnosis. This has accelerated the development of rapid labeling synthesis, so that today a large range of ^{11}C-labeled molecules can be synthesized.[4]

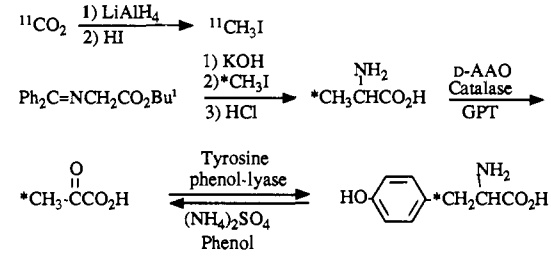
The $^{11}C/^{14}C$ method[5a] is based on internal competition between two radioactive isotopically labeled substrates. The rate constants

Scheme I[a]



[a] An asterisk (*) denotes 11 or 14; PLP = pyridoxal 5-phosphate.

Scheme II. Multienzymatic Synthesis of β-Labeled Tyrosine[a]



[a] An asterisk (*) denotes 11 or 14; D-AAO = D-amino acid oxidase; GPT = glutamic-pyruvic transaminase.

for the two isotopic (^{11}C and ^{14}C) reactions are calculated from the measurements by liquid scintillation counting of substrate and product fractions, isolated from the reaction mixture via a technique of quenching and HPLC separation.

Three different methods have been used earlier to determine KIEs for enzyme reactions:[2a] the direct comparison method, the equilibrium perturbation method, and the internal competition method. The highest accuracy has been achieved by the last method, using an isotope ratio mass spectrometer.

The present method may become an alternative and complement to that based on mass spectrometry and has certain advantages;[5] e.g., the largest practical mass range of carbon isotopes is utilized, resulting in relatively large isotope effects. The kinetic techniques involved in the $^{11}C/^{14}C$ method are quite easy to use. HPLC is a versatile technique which can be applied to many different systems. Moreover, no cumbersome workup or degradation of the samples is required. Neither are the analyses sensitive to unlabeled impurities, as long as these do not cause scintillation quenching. The $^{11}C/^{14}C$ method has recently been demonstrated to be useful in the determination of carbon[5] and deuterium[5b] isotope effects for some organic reactions. In the present study, the $^{11}C/^{14}C$ method described earlier[5a] was used with some modifications.

The synthesis of L-[β-^{11}C]tyrosine was performed using a multienzymatic reaction route;[6] see Scheme II. The radiochemical yield was 30% (decay corrected), and the total synthesis time, including purification, was usually 50 min. The same reaction route was used for the synthesis of L-(β-^{14}C)tyrosine, except that in the ^{14}C-labeling synthesis (^{14}C)methyl iodide was used as starting material.

The KIE experiments were performed under first-order reaction conditions. The conditions were chosen so that the reverse reaction was negligible. In the KIE experiments, the ^{11}C- and ^{14}C-labeled tyrosines were mixed with a standard solution of unlabeled tyrosine. The kinetic experiments were performed in the following way: equal volumes (400-1000 μL) of thermostated enzyme and substrate solutions[8] were mixed and replaced in the thermostat. The reaction mixture was agitated during the entire experiment. At time intervals, small volumes (50-100 μL) of the reaction mixture were withdrawn and immediately added to vials containing trifluoroacetic acid, cooled in an ice bath. During the first 10 min of the reaction, 10-15 samples were withdrawn from the

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(8) The tyrosine phenol-lyase stock solution, purified from *C. freundii*, had a protein concentration of 56.7 mg mL^{-1} and a specific activity of 1.2 (μmol of tyrosine) min^{-1} (mg of protein)$^{-1}$. The enzyme concentration was a 200-fold dilution of the stock solution containing 0.2 mM PLP, and the L-tyrosine concentration was 0.6 mM. The experiment was performed in phosphate buffer at pH 6.8 and 18 °C.

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