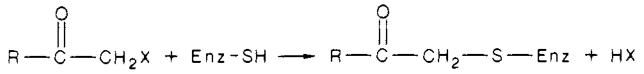

$$R-C(=O)-CH_2X + Enz\text{-}SH \longrightarrow R-C(=O)-CH_2-S-Enz + HX$$

26

can be ascertained by comparison of the ^{13}C NMR spectra of papain inactivated with 1 equiv of Z-Phe-Gly-CH_2X (X = Cl, $OCO(2,4,6\text{-}Me_3)Ph$, or OC_6F_5), labeled as $-{}^{13}C(=O)-CH_2X$ and as $-C(=O)-{}^{13}CH_2X$. The resonances of the inactive enzyme adduct ($C{=}O$, 214.7 ppm; CH_2, 38.1 ppm) are identical for all three inactivators Z-Phe-Gly-CH_2X and are entirely consistent with an active-site bound thiomethyl ketone structure (**26**).

In summary, peptidyl acyloxymethyl ketones can be designed to be potent and specific cysteine proteinase inhibitors that are active-site-directed and irreversible in their action. The aryl carboxylate leaving group offers considerable variation as a design element and with the appropriate peptide component, affinity labels possessing exquisite specificity can, in principle, be constructed. This type of reagent bearing a quiescent nucleofuge lends scope to the affinity label concept and holds forth the prospect of a practical clinical endpoint.

Acknowledgment. We are grateful to Dr. Christopher S. Jones for his contributions to the enzymology, to Sheila L. Donnelly, Cathy J. Streutker, and Lia Stait-Gardner for their synthetic support, and to Dr. C. A. Rodger and Bruker (Canada) for use of NMR instrumentation. We thank the Natural Sciences and Engineering Research Council of Canada for an Industrial Research Fellowship to H.W.P. and an Undergraduate Research Award to S.B.H.

Supplementary Material Available: Physical data for all compounds and synthetic information for **20** and **21** (1 page). Ordering information is given on any current masthead page.

Evidence for Activation of the C–O Bond of Methanol on the Pd{111} Surface after Low-Temperature Adsorption

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Direct evidence, using secondary ion mass spectroscopy (SIMS) supported by X-ray photoelectron spectroscopy (XPS), has been obtained for the activation of the C–O bond of methanol after adsorption at 110 K on the Pd{111} surface. In our experiments we find that the C–O bond dissociates after heating to 175 K leaving CH_{3ads} (methyl) and H_2O_{ads}, as evidenced by prominent SIMS signals at *m/e* 15 and 18, respectively. Methoxide (CH_3O_{ads}) is produced simultaneously and has been identified by its carbon 1s photoelectron binding energy. In addition to reporting the first observation of methanolic C–O bond activation on a well-defined transition-metal surface[1] we also report the discovery of a stable methyl species on Pd{111} as the surface is heated from 175 to 400 K. This observation has mechanistic implications for the uniquely selective formation of methanol from CO and H_2 on Pd catalysts.[2] Previously, only CH_3O_{ads} has been found on single-crystal transition-metal surfaces[3-6] exposed to CH_3OH at low temperatures and subsequently heated between 140 and 200 K. Additionally, the formation of CH_3O_{ads} at low temperatures was found to be enhanced by predosing the transition-metal surface with O_2 at 300 K.[7-9]

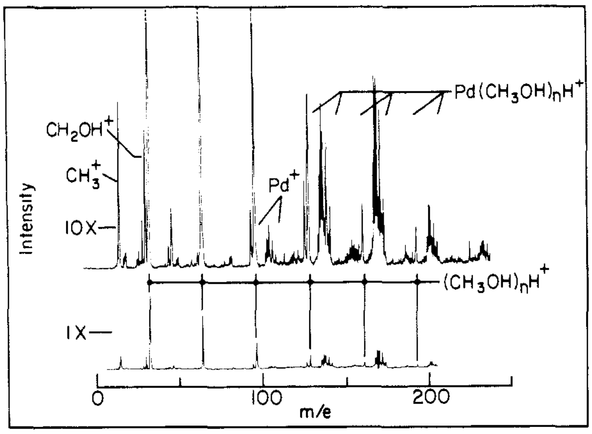

Figure 1. The SIMS spectrum for a 5 L methanol exposure to Pd{111} at 110 K. The primary ion current is 0.4 nA/cm².

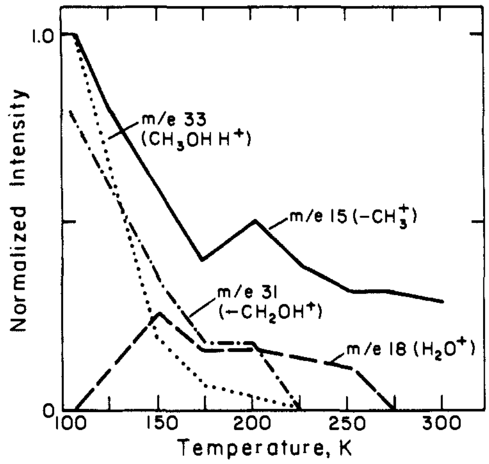

Figure 2. Secondary ion intensity versus surface temperature for a 2 L methanol exposure to Pd{111} initially at 110 K. The primary ion current is 0.4 nA/cm².

The apparatus used for these experiments has been described in detail previously.[10] The Pd{111} surface was rigorously cleaned by cycles of argon ion sputtering (2 $\mu A\ cm^{-2}$) for 5 min followed by annealing to 1200 K prior to each experiment. After this treatment the surface then proved to be free of impurities as determined by SIMS and XPS. The methanol was distilled and subjected to several freeze–pump–thaw cycles before use. The exposures listed throughout this letter are in units of Langmuirs (1 L = 1 × 10^{-6} Torr-s) and are reported as corrected ion gauge readings.

The SIMS spectrum for 5 L CH_3OH on Pd{111} at 110 K is shown in Figure 1. The prominent peaks, marked in the figure, are assigned to CH_3^+ at *m/e* 15, CH_2OH^+ at *m/e* 31,[11] and CH_3OHH^+ at *m/e* 33 as well as to additional hydrogenated n-mers observed at higher mass. In Figure 2, the intensities of

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[1] Steinbach, F.; Krall, R.; Cai, J. X.; Kiss, J. In *Proceedings of the 8th International Congress on Catalysis*; Berlin, July 1984; Vol. 3 (Verlag Chemie: Weinham, 1984) p III-359. The dissociation of the CO bond of methanol on a Ni foil under a high flux of methanol molecules (1 × 10^{16} CH_3OH cm^{-2} s^{-1}) at 190 K is reported. A subsequent study by Russell et al. (Russell, J. N.; Chorkendorff, I.; Yates, J. T. *Surf. Sci.* **1987**, *183*, 316) proved that under similar conditions, the Ni{111} surface does not dissociate the CO bond of methanol.

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[11] A similar experiment using CD_3OH revealed an ion at *m/e* 33 rather than an ion at *m/e* 34 implying the presence of CD_2OH^+ rather than CD_3O^+.

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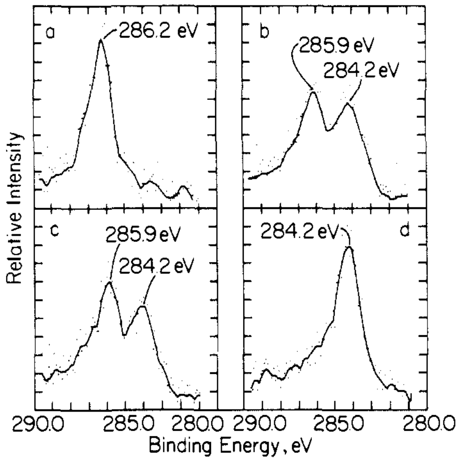

Figure 3. Carbon 1s XPS spectra for a 1.5 L exposure of methanol to Pd{111}: (a) 110 K; (b) heated to 225 K; (c) heated to 300 K; (d) heated to 400 K.

several ions resulting from a 2 L CH_3OH exposure are shown as the surface is heated from 110 K. This picture reveals that the intensity of the methanol-related secondary ions, CH_2OH^+ and CH_3OHH^+, decrease to zero at 225 K, while the CH_3^+ and the H_2O^+ ions signals increase and then eventually decrease at higher temperatures. These trends, along with the corresponding XPS C 1s intensity measurements for a 2 L exposure,[14] suggest that as the surface is heated, approximately $^1/_4$ of the CH_3OH desorbs from the surface while the remaining $^3/_4$ of the CH_3OH dissociates at the C–O or O–H bond. By 300 K the only SIMS signal apparent is at m/e 15. Since the CH_3^+ ion yield from CH_3O_{ads} on O/Pt{111}[4] has been reported to be negligible, this ion almost certainly arises from a surface methyl species. We note that oxygenated species such as O_{ads} and CH_3O_{ads} are suggested by the XPS experiments but are not directly detected in the SIMS measurements. The fact that only CH_3^+ ions are observed with SIMS implies that CH_{3ads} does not decompose to $CH_{n(n=0-2)}$ during the primary ion impact and ion ejection event. By 450 K the CH_3^+ SIMS signal is no longer detected in agreement with previous TPD experiments[12] which show a CO thermal desorption peak denoting recombination and desorption of adsorbed carbon and oxygen. At no time during the decomposition of methanol are SIMS (or XPS) signals attributable to CO formation[13] observed. This suggests that until 450 K, CO plays *no* part in the thermal decomposition mechanism of methanol adsorbed at 110 K on the Pd{111} surface.

The XPS results for this system are in agreement with the mechanism presented above with one addition. The carbon 1s region for surface temperatures above 175 K reveals the presence of a methoxide adsorbate which is approximately equal in intensity to the methyl surface species. The carbon 1s photoelectron spectra for a 1.5 L CH_3OH exposure on Pd{111} at 110 K are shown in Figure 3a. The C 1s binding energy of 286.2 eV is that of methanol on Pd{111}.[14] After heating the surface to 175 K the carbon 1s spectrum contains two peaks as shown in Figure 3b. The peak at 284.2 eV is consistent with a methyl species and the peak at 285.9 eV is assigned to the methoxide adsorbate. This assignment was determined by a comparison to methanol adsorbed on Pd{111} precovered with oxygen and heated to 175 K,[14] a procedure known to produce methoxide.[8] The presence of methoxide on clean Pd{111} is reasonable in our case since this species typically forms on an oxygen site, and an oxygen site is created, as OH_{ads}, every time CH_3OH dissociates at the C–O bond. It should be noted, however, that a mechanism wherein the methoxide is first formed, and then decomposes to methyl and hydroxyl, has not yet been ruled out. At 300 K the methyl and methoxide still exist on the surface, Figure 3c, but by 400 K the methoxide species has decomposed completely to CH_{3ads} as shown in Figure 3d.

In summary, we propose the following mechanism for the thermal decomposition of methanol on the Pd{111} surface from the evidence presented herein

$$2CH_3OH_{ads} \xrightarrow{175\ K} CH_{3ads} + CH_3O_{ads} + H_2O_{ads} \xrightarrow{300\ K}$$
$$CH_{3ads} + CH_3O_{ads} + O_{ads} \xrightarrow{400\ K} CH_{3ads} + O_{ads} \xrightarrow{450\ K} CO_{gas}$$

The SIMS and XPS evidence suggests that methyl is an unusually stable adsorbate on the Pd{111} surface. The lack of C^+, CH^+, or CH_2^+ SIMS signals at 400 K suggests that the methyl group is the only surface hydrocarbon present at this temperature. The fact that CH_4 and CH_3OH are[15] the major hydrocarbon products from palladium catalysts is consistent with a mechanism wherein only CH_{3ads} can combine with H_{ads} or OH_{ads}.

Acknowledgment. We acknowledge the financial support of the National Science Foundation and the Office of Naval Research.

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(13) Experiments determining the SIMS spectra as a function of CO exposure revealed two trends. First the Pd^+ signal was enhanced several orders of magnitude with exposures of <0.5 L CO. Second, a $Pd(CO)^+$ peak was always detected, even at the lowest exposures. In the methanol decomposition experiments neither phenomena was observed.

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Stereoselective Alkylation of Chiral α-Nitro Keto Imine Dianions. Observations on the Role of Amide Bases

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In the context of our investigations on the use of nitroalkenes as 4π components in [4 + 2]-cycloadditions,[1] we recently developed a new, general method for the synthesis of 3-substituted 1-nitrocycloalkenes[2] (Scheme I). The key step is the alkylation of an α-nitro imine or α-nitro hydrazone *dianion*. Since the reduction–elimination of the nitro imines occurs under mild conditions ($NaBH_4/CeCl_3$/room temperature) to afford nitroalkenes and the amine conjugate, we felt that this process was ideally suited for auxiliary based asymmetric alkylation. We report the following in this communication: (1) the stereoselective alkylation of chiral α-nitro imine dianions, (2) the influence of the amide base on stereoselectivity, and (3) the production of optically active 1-nitrocyclohexenes.

Stereoselective carbon–carbon bond formation with imines and hydrazones derived from chiral adjuvants through their metalloenamine forms has been a fertile and rewarding area of asymmetric synthesis.[3] The importance of coordinating appendages in the auxiliary for high selectivity has been amply demonstrated.[3b,c,d] Thus, our efforts were first directed at the common amino ether auxiliaries.[4] To survey auxiliary structure we employed

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