$\delta$  7.77–7.84 (m, 24 H, ArH), 7.97–8.02 (m, 6 H, ArH), 8.09–8.15 (m, 4 H, ArH). Anal. Calcd for  $C_{44}H_{34}F_6O_6P_2S_2$ : C, 58.79; H, 3.82. Found: C, 58.93; H, 3.89.

Reaction of (p-Phenylene)bis(aryliodonium) Ditriflate 8a with Diphenyl Sulfide. A mixture of 8a (789 mg, 1 mmol), Cu(OAc)<sub>2</sub> (9 mg, 0.05 mmol), and diphenyl sulfide (1.36 mL, 8.2 mmol) was gradually heated with stirring to 200 °C. After being stirred for 30 min at 200 °C the mixture was cooled to room temperature and was triturated with ether to give 771 mg of (*p*-phenylene)bis(diphenylsulfonium) ditriflate (12) (100%) as white crystals: mp 103-125 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.72-7.75 (m, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  124.26, 131.12, 131.75, 132.45, 134.81, 140.83. Anal. Calcd for C<sub>44</sub>H<sub>34</sub>F<sub>6</sub>O<sub>6</sub>S<sub>4</sub>: C, 51.46; H, 3.25. Found: C, 51.32; H, 3.35.

## Nucleophilic Reactions of Molybdate

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Although molybdate ( $MOQ_4^{2-}$ ) is over 1000 times less basic than the phosphate dianion it is 35 times more nucleophilic toward *p*-nitrophenyl acetate (pNPA) and *p*-nitrophenyl thioacetate (pNPTA) at 27 °C (Wikjord, B.; Byers, L. D. J. Am. Chem. Soc. 1992, 114, 5553). Based on Bronsted relationships for the reaction of a series of phosphonate dianions with these esters ( $\beta_{nuc} = 0.3$  at 37 °C), molybdate ( $pK_{a2} = 3.9$ ) is as reactive as a phosphonate with  $pK_{a2} = 12$ . The activation parameters are  $\Delta H^* = 15.8 (\pm 0.1)$  kcal/mol and  $\Delta S^* = -17.4 (\pm 0.4)$  eu for the reaction with pNPA and  $\Delta H^* = 16.0 (\pm 0.2)$  kcal/mol and  $\Delta S^* = -15.0 (\pm 0.6)$  eu for the reaction with pNPTA. The second-order rate constant for the reaction of  $MOQ_4^{2-}$  with a series of 13 acyl-substituted *p*-nitrophenyl esters at 27 °C shows nearly identical sensitivity to substitutent effects ( $\rho^* = 2.8$ ) as does the rate of alkaline hydrolysis or the equilibrium addition of hydroxide to aldehydes (Shames, S. L.; Byers, L. D. J. Am. Chem. Soc. 1981, 103, 6170), suggesting that the transition state for the molybdenolysis reaction closely resembles the tetrahedral intermediate. In addition to the reaction with activated carboxylic esters, molybdate catalyzes the hydrolysis of a variety of electrophiles. The second-order rate constants ( $M^{-1} \min^{-1}$ , 27 °C,  $\mu = 1.5$  M) for the reactions of molybdate are 0.25 ( $\pm 0.01$ ) with ethyl pyruvate, (2.10  $\pm 0.08$ )  $\times 10^{-2}$  with 2,4-dinitrofluorobenzene, and (7.2  $\pm 0.4$ )  $\times 10^{-5}$  with methyl iodide.

We have recently reported our observations on the remarkable nucleophilic reactivity of the molybdate dianion toward *p*-nitrophenyl acetate (pNPA) and *p*-nitrophenyl thioacetate (pNPTA).<sup>1</sup> Although molybdate ( $pK_{a2} = 4.1$ , 25 °C) is over 3 orders of magnitude *less basic* than the phosphate dianion it was found to be 35 times *more reactive* toward these esters than is phosphate and significantly more (20–500-fold) reactive toward pNPA than nucleophiles (e.g., aniline, acetate) of comparable basicity.<sup>2</sup> This study was undertaken in order to get a clearer picture of the mechanism of the molybdate-catalyzed ester hydrolysis reaction and to see if the unusual nucleophilic reactivity is a unique feature of acyl-transfer reactions.

### **Experimental Section**

**Materials.** p-Nitrophenyl acetate, propionate, n-butyrate, and trimethylacetate were obtained from Aldrich Chemical Co., and p-nitrophenyl thioacetate was obtained from U.S. Biochemical Corp. The other p-nitrophenyl esters were from previous studies.<sup>3,4</sup> o-Nitrophenyl acetate, ethyl pyruvate, 2,4-dinitrofluorobenzene, bis(p-nitrophenyl) phosphate, HEPES<sup>5</sup> buffer, NADH,<sup>5</sup> and lactate dehydrogenase (rabbit muscle, specific activity = 860 units/mg) were obtained from Sigma Chemical Co. Sodium molybdate (dihydrate), 2,4-dinitrochlorobenzene, and methyl iodide were obtained from Matheson, Coleman, and Bell. Molybdate stock solutions (0.5 M) were prepared by dissolving  $Na_2MoO_4$  in buffer solutions (0.01 M HEPES) and adjusting the pH to 7.5 with HCl (or DCl in  $D_2O$ ). At this pH there is negligible polymerization of molybdate.<sup>6</sup>  $D_2O$  (99.8%) was from Sigma Chemical Co.

Methods. pH measurements were made with a Metrohm (Brinkmann) combititator. pD values were estimated by adding 0.41 to the pH meter reading.<sup>7</sup> For the ester hydrolysis reactions, kinetics were followed by measuring the absorbance ( $\lambda = 400 \text{ nm}$ for p-nitrophenoxide or 412 nm for p-nitrophenylthiolate) on a Hewlett-Packard Model 8452A diode array spectrophotometer equipped with a circulating water bath (Endocal) to maintain temperatures  $(\pm 0.1^{\circ})$  in the sample (determined with a calibrated digitally monitored thermocouple). The reactions were initiated by adding 10  $\mu$ L of the ester (10 mM in CH<sub>3</sub>CN) to 1 mL of a thermally equilibrated buffer solution (ionic strength maintained at 1.6 M with  $Na_2SO_4$  and, for the reactions with the esters only, 0.1 M NaCl). In general, the increase in the absorbance was typically followed for at least 4 half-lives and the data were analyzed by nonlinear regression to a first-order curve.<sup>8</sup> The internal standard deviations of the pseudo-first-order rate constants were consistently less than 1%. Rate constants were determined at least in triplicate for each reaction. The kinetics for the hydrolysis of ethyl pyruvate (pH = 7.5, 0.01 M HEPES,  $\mu$ = 1.5 M maintained with  $Na_2SO_4$ ) was obtained by coupling the reaction to the lactate dehydrogenase reaction (pyruvate + NADH  $\rightarrow$  L-lactate + NAD) and monitoring the decrease in absorbance at 340 nm due to NADH. The reaction was initiated by adding  $10 \,\mu\text{L}$  of an ethanolic solution of ethyl pyruvate (10 mM) to a 1-mL thermally equilibrated solution containing the desired concentration of molybdate, NADH (0.2 mM), and lactate dehydrogenase  $(25 \,\mu g/mL)$ . The absorbance followed a single exponential decay

Wikjord, B.; Byers, L. D. J. Am. Chem. Soc. 1992, 114, 5553-5554.
 Jencks, W. P.; Carriuolo, J. J. Am. Chem. Soc. 1960, 82, 1778-1786.

<sup>(3)</sup> Shames, S. L.; Byers, L. D. J. Am. Chem. Soc. 1981, 103, 6170-6177.

 <sup>(4)</sup> Knowlton, R. C.; Byers L. D. J. Org. Chem. 1988, 53, 3862-3865.
 (5) Abbreviations used: 2,4-DNFB, 2,4-dinitrofluorobenzene; HEPES, N-(2-hydroxyethyl)piperizine-N'-2-ethanesulfonic acid; NADH, reduced

N-(2-hydroxyethyl)piperizine-N'-2-ethanesulfonic acid; NADH, reduced form of nicotinamide adenine dinucleotide; pNPA, p-nitrophenyl acetate; pNPTA, p-nitrophenyl thioacetate.

<sup>(6)</sup> Aveston, J.; Anacker, E. W.; Johnson, J. S. Inorg. Chem. 1964, 3, 735-746.

<sup>(7)</sup> Covington, A. K.; Paabo, M.; Robinson, R. A.; Bates, R. G. Anal. Chem. 1968, 40, 700-706.

<sup>(8)</sup> Leatherbarrow, R. J. Enzfitter: A Non-linear Regression Data Analysis Program for the IBM PC; Elsevier Science: New York, 1987.



Figure 1. Correlation between the rate constants  $(M^{-1} \text{ min}^{-1})$  for molybdate-catalyzed and specific base-catalyzed hydrolysis for a series of *p*-nitrophenyl esters. The slope of the line is 1.07 (±0.06). The acyl substituents are as follows: (a) Me<sub>3</sub>C-, (b) nPr-, (c) Et-, (d) CH<sub>3</sub>-, (e) BrCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, (f) Cbz-NHCH<sub>2</sub>CH<sub>2</sub>-, (g) BrCH<sub>2</sub>CH<sub>2</sub>-, (h) (MeO)<sub>2</sub>P(O)CH<sub>2</sub>CH<sub>2</sub>-, (i) Cbz-NHCH<sub>2</sub>-, (j) CH<sub>3</sub>OCH<sub>2</sub>-, (k) ICH<sub>2</sub>-, (l) ClCH<sub>2</sub>-, and (m) BrCH<sub>2</sub>-.

(typically from 1.2 to an endpoint of 0.6). In a control reaction where the ester was replaced with pyruvate (final concentration = 0.1 mM) the rate constant (~18 min<sup>-1</sup>) for the enzymatic reaction was at least 100-fold larger than that obtained when the ester was converted to pyruvate at the highest  $[MOQ_4^{2-}]$  used. The reaction of methyl iodide (50 mM) with molybdate (0.5 M) was followed in D<sub>2</sub>O (10 mM phosphate, pD = 7.8) by <sup>1</sup>H-NMR (200 MHz) by monitoring the relative intensities of the signals at 2.07 ppm (CH<sub>3</sub>I) and 3.25 ppm (CH<sub>3</sub>OD).

#### Results

Ester Hydrolysis. The molybdate-catalyzed hydrolysis of pNPA and pNPTA (pH = 7.5, 0.01 M HEPES) was followed as a function of temperature (10-69 °C). The activation parameters were evaluated by a fit to the Eyring equation

$$\ln (k_2/T) = -(\Delta H^*/R)(1/T) + \Delta S^*/R + \ln(k_B/h) \quad (1)$$

where  $k_2$  is the second-order rate constant,  $k_B$  is Boltzmann's constant, and h is Planck's constant. It is interesting to note that the 2-fold faster hydrolysis rate of the thioester than of the oxygen ester is a result of a more favorable entropy of activation [= -15.0 (±0.6) eu for pNPTA, -17.4 (±0.4) eu for pNPA]. The enthalpies of activation [16.0 (±0.2) kcal/mol for pNPTA and 15.8 (±0.1) kcal/mol for pNPA] are identical for the two reactions.

The reaction of molybdate with a series of acyl-substituted p-nitrophenyl esters was examined at 27 °C ( $\mu = 1.6$  M). These reactions all followed pseudo-first-order kinetics ( $0.2 \text{ M} \leq [\text{MOO}_4^{2-}] \leq 0.5 \text{ M}$ ). When the second-order rate constants for the molybdate-catalyzed reactions are plotted logarithmically against those for the hydroxide-catalyzed hydrolysis<sup>4</sup> a linear relationship is obtained (Figure 1). The correlation equation is

$$\log k_{\rm Mo} = 1.07 \ (\pm 0.06) \ \log k_{\rm OH} - 3.9 \ (\pm 0.2) \\ n = 13, r = 0.981$$
 (2)

indicating nearly equal sensitivities of the two reactions to acyl substituent effects.

At 27 °C the second-order rate constant for the molybdate-catalyzed hydrolysis of o-nitrophenyl acetate is 0.130 ( $\pm 0.003$ ) M<sup>-1</sup> min<sup>-1</sup> which is 50% of the value for the pnitrophenyl ester. This can be compared to the ratio of rate constants for the specific base-catalyzed reactions in which case the o-nitrophenyl ester is 77% as reactive as the p-nitrophenyl ester. The hydrolysis of ethyl pyruvate, an ester with a poor leaving group, was examined with the



Figure 2. Spectral change when 2,4-DNFB (67  $\mu$ M) is incubated with 0.4 M MoO<sub>4</sub><sup>2-</sup> (pH = 7.5,  $\mu$  = 1.5 M, 27 °C). The blank contains no DNFB (at  $\lambda$  < 286 nm the absorbance of the blank is >1 od). The increasing spectra were obtained at 0.75, 4, 7, 15, 30, 45, and 150 min and 6 and 27 h.

intention of looking at the influence of molybdate on a reaction expected to undergo general-base catalysis. This ester, however, was found to be very labile even in buffer containing no molybdate (0.5 M SO<sub>4</sub><sup>2-</sup>, 0.01 M HEPES, pH = 7.5). Under these conditions (27 °C) the hydrolysis occurred with a rate constant of 0.04 min<sup>-1</sup>. Molybdate was found to be a catalyst for this reaction with a second-order rate constant of 0.25 (±0.01) M<sup>-1</sup> min<sup>-1</sup>. When the reaction was carried out in D<sub>2</sub>O (pD = 7.8) the rate constant was unchanged. Molybdate is a poor catalyst for the hydrolysis of bis(*p*-nitrophenyl) phosphate. In the presence of 0.5 M MOO<sub>4</sub><sup>2-</sup> the half-life for the reaction (corrected for the spontaneous hydrolysis in the presence of 0.5 M SO<sub>4</sub><sup>2-</sup>) is estimated to be 1.7 years.

Reaction with Other Electrophiles. Molybdate is very effective in catalyzing the hydrolysis of 2.4-DNFB.<sup>5</sup> Figure 2 shows the spectral change with time when 2,4-DNFB is incubated with molybdate. The developing spectrum of the product is identical with that of 2,4-dinitrophenolate, with no indication of the accumulation of an intermediate. The observed first-order rate constants for the reaction show a linear dependence on molybdate concentration (0.05–0.50 M) with a slope of (2.10  $\pm$  0.08)  $\times 10^{-2}$  M<sup>-1</sup> min<sup>-1</sup>. In the absence of molybdate (0.5 M  $SO_4^{2-}$ ) the hydrolysis rate constant is  $8.1 \times 10^{-6}$  min<sup>-1</sup>. The reaction of molybdate with 2,4-dinitrochlorobenzene is very slow. In the presence of 0.475 M  $MoO_4^{2-}$  (pH = 7.5, 0.2 mM dinitrochlorobenzene, 10% v/v ethanol, 27 °C) the half-life for the hydrolysis reaction is about 11 months, corresponding to a second-order rate constant of  $(3.0 \pm 0.2)$  $\times 10^{-6} \text{ M}^{-1} \text{ min}^{-1}$ .

The reaction of molybdate with methyl iodide is slow. In the presence of 0.5 M molybdate at room temperature (~24 °C) the half-life for conversion to methanol is 13 days corresponding to a second-order rate constant of  $(7.2 \pm 0.4)$ × 10<sup>-5</sup> min<sup>-1</sup>. In the course of the reaction the only signals apparent in the <sup>1</sup>H-NMR were those of methyl iodide (2.07 ppm), methanol (3.25 ppm), and HOD (4.65 ppm). No signals at >4.7 ppm, corresponding to a methyl molybdate ester, were detectable. In the absence of molybdate no methanol was detected after 23 days.

#### Discussion

As was previously shown,<sup>1</sup> molybdate is an effective nucleophilic catalyst for the hydrolysis of activated esters. Molybdate ( $pK_{a2} = 4.1$  at 25 °C<sup>9</sup>) is over 30 times more

<sup>(9)</sup> Sasaki, Y.; Lindquist, I.; Sillen, L. G. J. Inorg. Nucl. Chem. 1959, 9, 93-94.

Table I. Reactions with p-Nitrophenyl Acetate

	$k_2$ (37 °C) $M^{-1}$ min <sup>-1</sup>	∆H*, kcal/mol	$\Delta S^*$ , eu
imidazole <sup>a</sup>	80	8.7	-30
Me <sub>3</sub> N <sup>b</sup>	20	12.3	-21
MoO <sub>4</sub> <sup>2-</sup>	0.48	15.8	-17
CH <sub>3</sub> PO <sub>3</sub> <sup>2-</sup>	0.035	19.5°	-10 <sup>c</sup>
CH <sub>3</sub> CO <sub>2</sub> <sup>-d</sup>	0.002	15.7	-29

<sup>a</sup> Akiyama, M.; Hara, Y.; Tanabe, M. J. J. Chem. Soc., Perkin Trans. 2 1978, 288–292. <sup>b</sup> Bruice, T. C.; Benkovic, S. J. J. Am. Chem. Soc. 1963, 85, 1-8. <sup>c</sup> Shames, S. L.; Byers, L. D. J. Am. Chem. Soc. 1981, 103, 6177–6184. The values reported here were obtained by extending the temperature range (5-70 °C) over that used by Shames and Byers and can be compared to their values of  $\Delta H^* = 18.7$  kcal/mol and  $\Delta S^* = -13$  eu. <sup>d</sup> Gaetjens, E.; Morawetz, H. J. Am. Chem. Soc. 1960, 82, 5328–5335.

reactive toward pNPA and pNPTA than is the phosphate dianion<sup>2</sup> or phosphonate dianions<sup>3</sup> with  $pK_{a2} \sim 7$ . From an earlier study<sup>3</sup> it was found that the reactivity of pNPA and pNPTA with a series of phosphonates ( $4.8 \leq pK_{a2} \leq 8.7$ ) at 37 °C can be correlated with the basicity of the oxydianions yielding a  $\beta_{nuc}$  of 0.3. The rate constants for the reaction of molybdate with pNPA and with pNPTA at 37 °C are 0.48 (±0.1) and 1.08 (±0.02) M<sup>-1</sup> min<sup>-1</sup>, respectively. From these values and the correlation equations in ref 3,  $MOQ_4^{2-}$  is about 300 times more reactive than a phosphonate with  $pK_{a2} \approx 12$ .

One explanation<sup>1</sup> for this enhanced reactivity is that the larger molybdate dianion is not as strongly solvated as the phosphorous oxydianions. Consistent with this is the observation that the entropy of activation for the reaction of molybdate with pNPA is more in line with the values typical of bimolecular reactions involving neutral or monoanionic nucleophiles than is that for the reaction of methylphosphonate (Table I). The methylphosphonate reaction shows an unusually favorable activation entropy. This most likely reflects that a significant fraction of the entropy change in reaching the transition state is due to the disordering of water molecules. This desolvation from a nucleophilic site on the phosphonate dianion would also be expected to be associated with an increase in the enthalpy of activation. It is also possible that the larger enthalpy of activation for the phosphonate reaction reflects a stricter steric requirement for nucleophilic attack by phosphonate (P–O distance<sup>10</sup> = 1.54 Å] than by molybdate  $[Mo-O distance^{10} = 1.83 Å].$ 

Another explanation<sup>1</sup> for the enhanced nucleophilicity of molybdate toward esters is that it may have a chelating effect, stabilizing the transition state by forming a Mo–O bond with the incipient oxyanion of the ester carbonyl (II):



Two of our results, however, tend to rule this out. The first is the near-identity of the sensitivities of the molybdatecatalyzed and hydroxide-catalyzed reactions to acyl substituent effects (Figure 1). The  $\rho^*$  for the reaction of hydroxide with *p*-nitrophenyl esters is 2.65 at 26 °C,  $\mu =$ 1.0 M.<sup>4</sup> Since the slope of the plot of log  $k_{Mo}$  vs log  $k_{OH}$ is the ratio of Taft  $\rho^*$  values for the two reactions, the reaction of molybdate with the esters is characterized by a value of  $\rho^* = 2.8$ . This can be compared to the value of  $\rho^* = 3.0$  for the equilibrium addition of hydroxide ion to aldehydes to form the anionic tetrahedral adduct<sup>11</sup> or the estimated value of  $\rho^* \simeq 3.4$  for the equilibrium addition of a phosphonate dianion to carbonyls.<sup>3</sup> This indicates that the transition state for the reaction of molybdate with the esters closely resembles the presumed anionic tetrahedral intermediate (structure I). If the negative charge on the carbonyl oxygen was delocalized by forming a bond with Mo (structure II), the electrostatic component of the Taft coefficient would be significantly reduced and a  $\rho^*$  of less than 2 would be expected. ( $\rho^*$ = 1.6 for the rate of reaction of neutral nucleophiles with *p*-nitrophenyl esters<sup>4</sup> and  $\rho^* = 1.7$  for the equilibrium addition of water or thiols to aldehydes.<sup>11</sup>)

The other result which tends to argue against a chelating mechanism being responsible for the enhanced nucleophilicity of molybdate is that  $MoO_4^{2-}$  is an effective catalyst for the hydrolysis of 2,4-DNFB. The second-order rate constant for the reaction of methoxide (in CH<sub>3</sub>OH, 25 °C) with 2,4-DNFB<sup>12</sup> is only 14 times larger than that for the reaction of molybdate. In the presence of 0.5 M molybdate the hydrolysis of 2,4-DNFB is 1300 times faster than in the presence of 0.5 M sulfate (pH = 7.5, 27 °C). Clearly, a chelating role for molybdate is implausible for this reaction. The most likely mechanism for the molybdatecatalyzed hydrolysis of 2,4-DNFB is an  $S_NAr$  (i.e.,  $A_N$  +  $D_N$ ) reaction leading to the 2,4-dinitrophenylmolybdate which is rapidly hydrolyzed to the phenolate and molybdate. This mechanism is suggested<sup>12</sup> from the observation that molybdate reacts about 7000 times more rapidly with 2,4-DNFB than with its chloro analogue. The absence of a lag phase for the increase in absorbance (due to 2,4-dinitrophenolate) at even the highest concentration of  $MoO_4^{2-}$  tested (0.5 M,  $k_{obs} = 0.01 \text{ min}^{-1}$ ) indicates that cleavage of the phenylmolybdate (the immediate product of the substitution reaction) is at least 5 times more rapid than the rate of nucleophilic attack (i.e.,  $>0.05 \text{ min}^{-1}$ ). The linear dependence of the pseudo-first-order rate constants on  $[MoO_4^{2-}]$  (0.05–0.5 M) indicates that the Meisenheimer complex does not accumulate (i.e., the dissociation constant of molybdate from this complex must be >2M). There is also no spectroscopic evidence (Figure 2) for the accumulation of either the Meisenheimer complex or the 2,4-dinitrophenylmolybdate, at least in the transparent region  $(\lambda > 290 \text{ nm})$  in the presence of molybdate.

The reaction of molybdate with methyl iodide is relatively slow but appreciably more rapid than the spontaneous hydrolysis rate at pD = 7.8. The second-order rate constant ( $7.2 \times 10^{-5} \text{ M}^{-1} \text{ min}^{-1}$ ) for the reaction of molybdate with CH<sub>3</sub>I (to form CH<sub>3</sub>OD) is 38% of that for the reaction of Cl<sup>-</sup> and 1.8% of that for the reaction of <sup>-</sup>OH with methyl iodide in aqueous solution.<sup>13</sup> Thus, methyl iodide, and related compounds which can undergo S<sub>N</sub>2 reactions, can be hydrolyzed under mild conditions in the presence of molybdate. For example, the rate of hydrolysis of methyl iodide in the presence of 0.1 M MoO<sub>4</sub><sup>2-</sup> at pH = 7.5 should be equal to the hydrolysis rate at pH = 11.3 in the absence of molybdate.

The rapid hydrolysis of ethyl pyruvate in the presence of molybdate shows a solvent kinetic isotope effect of unity. This is consistent with a nucleophilic mechanism in which

<sup>(10)</sup> Sutton, L. E., Ed. Tables of Interatomic Distances and Configuration in Molecules and Ions; The Chemical Society: London, 1958; No. 11.

<sup>(11)</sup> Kanchuger, M. S.; Byers, L. D. J. Am. Chem. Soc. 1979, 101, 3005-3010.

 <sup>(12)</sup> Bartoli, G.; Todesco, P. E. Acc. Chem. Res. 1977, 10, 125-132.
 (13) Bathgate, R. H.; Moelwyn-Hughes, E. A. J. Chem. Soc. 1959, 2642-2648.

molybdate adds to the C-2 carbonyl of the ester and then displaces the ethanol leaving group resulting in a labile cyclic acyl molybdate ester. The rapid first-order production of pyruvate (no detectable lag in the presence of 0.45 M MoO<sub>4</sub><sup>2-</sup>,  $k_{obs} = 0.12 \text{ min}^{-1}$ ) indicates that the half-life of this acyl molybdate intermediate must be <6 s. This can be compared to an estimate of  $t_{1/2} < 0.5$  s for the hydrolysis of the 1-molybdo-3-phosphoglycerate at pH 7.3.14

The results presented here show that molybdate is an effective nucleophilic catalyst for the hydrolysis of a variety of substrates.

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(14) Byers, L. D.; She, H. S.; Alayoff, A. Biochemistry 1979, 18, 2471-2480.

# Homolytic Substitution Reactions of Electron-Rich Pentatomic Heteroaromatics by Electrophilic Carbon-Centered Radicals. Synthesis of $\alpha$ -Heteroarylacetic Acids

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Efficient and selective homolytic substitutions (yields between 55 and 90%) of pyrrole, indole, and some pyrrole derivatives have been carried out using ambiphilic and electrophilic carbon centered radicals, generated in DMSO by  $Fe^{2+}/H_2O_2$  and  $\alpha$ -cyano-,  $\alpha$ -carbonyl-, and  $\alpha, \alpha'$ -dicarbonylalkyl iodides. The reaction is highly successful also with pyrroles substituted by electron-withdrawing groups, which has allowed an efficient synthesis of Tolmetin. A few extensions of this reaction to furan and thiophene are described.

The last decade has witnessed an exceptional development of the synthetic aspects of free radical chemistry. However, as far as we know, few applications of this chemistry to the synthesis of pyrrole derivatives have been carried out.1

Recent studies have shown that efficient homolytic substitution of aromatic and electron-rich heteroaromatic substrates can be accomplished using electrophilic carbon-centered radicals generated by oxidation of 1,3-dicarbonyl compounds with cerium(IV) or manganese(III) salts.<sup>2</sup> The exploitation of these reactions for the synthesis of pyrrole derivatives would seem straightforward since pyrrole is an electron-rich heteroaromatic compound; however, all attempts in this direction have so far failed since pyrrole itself is preferentially oxidized under the reaction conditions.<sup>3</sup> On the other hand, when electrophilic carbon-centered radicals are formed under reductive conditions (i.e. by the atom-transfer method), no homolytic aromatic substitution has been observed,<sup>4</sup> presumably because there is no possibility that the intermediate  $\sigma$ radical is oxidized to products (eq 1).

$$ArH + R^{\bullet} \rightleftharpoons ^{\bullet}Ar < H^{\bullet} Ar = ArR + H^{\bullet}$$
(1)

We wish now to report that the homolytic substitutions of pyrrole and indole and some pyrrole derivatives by both

ambiphilic<sup>5</sup> and electrophilic carbon-centered radicals is a highly efficient and selective process, if the radicals are generated by the corresponding alkyl iodides,  $H_2O_2$ , and catalytic  $Fe^{2+}$  in DMSO<sup>6</sup> (eqs 2-5).

$$H_2O_2 + Fe(II) \longrightarrow OH + OH + Fe(III)$$
 (2)

(2)

$$Me \xrightarrow{-}S \xrightarrow{-} Me \xrightarrow{-} Me^{\bullet} + MeSO_{2}H$$
(4)

$$Me^{\bullet} + RI \longrightarrow MeI + R^{\bullet}$$
 (5)

As alkyl iodides we have used  $ICH(CH_3)CO_2Et$ , ICH<sub>2</sub>CO<sub>2</sub>Me, ICH<sub>2</sub>CO<sub>2</sub>Et, ICH<sub>2</sub>CN, IC(CH<sub>3</sub>)(CO<sub>2</sub>Et)<sub>2</sub>, and  $ICH(CO_2Me)_2$  which provide the radicals  $CH(CH_3)CO_2Et$ ,  $CH_2CO_2Me$ ,  $CH_2CO_2Et$ ,  $CH_2CN$ ,  $CH_3C(CO_2Et)_2$ , and •CH(CO<sub>2</sub>Me)<sub>2</sub>, respectively, whose properties from ambiphilic or borderline to clearly electrophilic should increase in the same order. Some experiments carried out using furan and thiophene as the substrates are also described.

#### **Results and Discussion**

Reactions were carried out, at room temperature, in DMSO by adding 35%  $H_2O_2$  to a solution of substrate, alkyl iodide, and FeSO<sub>4</sub>.7H<sub>2</sub>O. The substrate was in large excess with respect to both alkyl iodide and FeSO<sub>4</sub>.7H<sub>2</sub>O (at least 15:1 and 75:1, respectively) whereas the substrate:  $H_2O_2$  molar ratio was 1.5-4. These conditions turned out to be the most suitable for obtaining only monosub-

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