Phosphinyl-Substituted Dienophiles: Their Synthesis and Directive Effects

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The unilateral directive influence of the carbonyl group in the Diels-Alder reaction can be negated by a diphenylphosphinyl group. The dienophile 4-(diphenylphosphinyl)-3-buten-2-one (4) was synthesized. Products isolated as a result of the addition of 4 to isoprene or acetoxybutadiene proved to be 1,3-substituted (6) and 1,5-substituted (8) cyclohexenes, as opposed to the 1,4-substituted (5) and 1,2-substituted (7) cyclohexenes which are commonly reported.

Reviews of the Diels-Alder reaction²⁻⁴ suggest that the carbonyl group exercises one of the strongest directing effects on the adduct formation. Isoprene and methyl vinyl ketone, for example, have been reported to produce overwhelmingly the 1,4-disubstituted cyclohexene, with only traces of the 1,3-disubstituted product.⁵ Similarly, the Diels-Alder reaction between 1-acetoxy-1,3-butadiene and citraconic anhydride produced a mixture of the 1,2- and 1,6-disubstituted cyclohexenes in a ratio of 1.5:1.⁶

Many theories have been proposed to explain regioselectivity in the Diels-Alder reaction. The frontier molecular orbital (FMO) approach with primary and secondary orbital interactions has been foremost among them.⁷ However, none of the programs presently in use are able to treat the third-row elements and their compounds correctly. A determination of the Hammett σ constants for the diphenylphosphinyl group indicates that it is equivalent to the carbethoxy group in resonanceelectron-withdrawing power.⁸ An examination of the σ constants for the sulfinyl group indicates that the phosphinyl and sulfonyl groups are similar in electronic properties.⁹ One interesting dienophile with carboxyl and sulfinvl groups has been used recently in synthesis. Although the stereochemistry of the dienophile is unknown, the carboxyl group still retained regioselective control.¹⁰

Notably absent in Diels-Alder reactions is the phosphinyl group. We proposed to introduce this group on a dienophile, creating a vinylogous acyl phosphine oxide with which to explore the directing effects of the phosphinyl group. The reactions of 4-(diphenylphosphinyl)-3-buten-2-one (4) as a dienophile showed it to be a good partner in the reaction, yielding crystalline homogeneous products. Contrary to the long-standing tradition of carbonyl dominance in the Diels-Alder reaction, the products from the reaction of 4 with dienes showed that the phosphinyl group took precedence in controlling the orientation of the reaction (vide infra).

Results and Discussion

The dienophile employed, 4-(diphenylphosphinyl)-3buten-2-one (4) was synthesized in a series of relatively

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facile reactions (Scheme I).

The lithium diphenylphosphide was prepared by using the procedure of Vedejs and Fuchs.¹¹ In preparing the 1-(diphenylphosphine)-2-butene, the method of Issleib and Tschach¹² was employed. Crotyl chloride, consisting of a mixture of cis and trans isomers, was added to the lithium diphenylphosphide solution, and after subsequent oxidation and purification, 1-(diphenylphosphinyl)-2-butene (1) was obtained as a mixture of geometrical isomers.

The addition of *m*-chloroperoxybenzoic acid to 1 yielded 1-(diphenylphosphinyl)-2,3-epoxybutane (2). The reaction was monitored by removing aliquots and scanning, in the NMR, for the vinyl hydrogen signal.

A catalytic amount of potassium tert-butoxide was sufficient to convert 2 to 3. The completion of the slightly exothermic reaction was conveniently checked by TLC.

Finally, 4 was obtained by addition of an excess of Jones reagent¹³ to 3.

The reaction of 4 with isoprene or acetoxybutadiene could result, in each case, either in a mixture of isomers or in exclusively one isomer (Scheme II).

The products obtained from reactions 1 and 2 were found to be exceedingly nonvolatile and crystalline. Gas

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Figure 1. ORTEP drawing of 2-acetyl-1-(diphenylphosphinyl)-4methylcyclohex-4-ene.

chromatographic analysis of these products for mixtures was not possible. The crude product of reaction 1 showed only one spot on TLC in the region for the expected phosphine oxides and some isoprene polymer. The yield of crystalline material was 80%. The sporting methods of spectroscopy did not indicate which isomer(s) had been obtained, and, therefore, X-ray crystallography was utilized. A single crystal suitable for X-ray analysis was obtained from a solution of tetrahydrofuran and ether. The structure was determined by direct methods from data collected on a Nicholet P2₁ diffractometer and proved to be 6. An ORTEP¹⁴ plot of compound 6 is given in Figure 1.

Since isoprene and methyl vinyl ketone have repeatedly been found to give predominantly 1,4-cyclohexene adducts of type 5, this would suggest a very strong directing influence by the diphenylphosphinyl group. The trans relationship of the acetyl and phosphinyl groups was expected, since the starting dienophile exhibited IR absorption at 1690 and 970 cm⁻¹, indicative of a trans alkene.

The NMR spectrum of the crystalline product obtained in 79% yield from reaction 2 indicates the formation of the unexpected isomer 8. The two protons of the allylic methylene were found merged with the two singlets for the methyl protons. The two protons, one α to the phosphinyl group and one tertiary and α to the ketone are found at approximately the same chemical shift as they were found in the isoprene adduct. The only remaining protons which had not been assigned were the vinyl protons and the proton on the carbon bearing the acetoxy group. The envelope in the vinyl region gave an integration for three protons. A 300-MHz spectrum resolved this envelope into an apparent doublet of two protons and a singlet of one proton. Examination of the ¹³C NMR spectrum of compound 8 indicated clearly each carbon of the structure. The phosphorus atom was coupled to five of the carbon atoms, including the phenyl carbons. From off-resonance decoupling the doublets centered at 29.8 ppm ($J^{P-C} = 3.6$ Hz), 49.79 ppm ($J^{P-C} = 0.12$ Hz), and 64.89 ppm ($J^{P-C} =$ 0.40 Hz) were assigned respectively to CH-P, CH-C=O and CH-OAc. From the coupling by phosphorus of the methine carbon bearing the acetoxy group we can conclude that the orientation assignment for compound 8 is correct. The problem to be resolved is why the single proton appears at δ 5.76 instead of δ 4.6.

Examination of a molecular model in which the acetoxy, acetyl, and phosphinyl groups are equatorial (8) indicates that the proton probably occupies space in the deshielding zone of one of the phenyl rings on the diphenylphosphinyl oxide. The triequatorial relationship of the groups would be expected from the endo approach of the carbonyl group

to the diene for maximum π overlap and an exo approach of the large diphenylphosphinyl group to minimize steric hinderance. In the other possible isomer 7, no such deshielding was apparent from examination of the models. No abnormal deshielding was apparent in the isoprene adduct, compound 6. We therefore concluded that the three equatorial substituents substantially lock the molecule into one conformation, and the buttressing of the acetoxy and acetyl groups prevents free rotation of the phosphinyl group. The preferred conformation of the molecule must also be responsible for the apparent lack of large coupling constants between most of the protons with each other and the phosphorus atom. Unfortunately, attempts so far to obtain a single crystal for an X-ray structure determination have produced only twined crystals.

Conclusion

Neither isoprene nor acetoxybutadiene has been found to be selective with most dienophiles: a preponderance of one isomer may be obtained, but it is seldom formed exclusively. In reactions 1 and 2, no evidence for the formation of isomer 5 or 7 was apparent from exhaustive TLC analysis and the examination of other physical properties. The high yields (80%) of the one isomer isolated in each case indicates an almost complete reversal of the usual directive effects by the acyl group. Previous series of directing groups have placed the acyl group as the most influential in the orientation of the Diels-Alder cycloaddition.² The data presented here would suggest that the phosphinyl group heads this list as the most influential. Further work to elucidate the competitive effects of the phosphinyl group is anticipated.

Experimental Section

Nuclear magnetic resonance spectra were recorded on Varian EM-360, FT80A, and 300-MHz spectrometers. Infrared spectra were obtained on Perkin-Elmer 337 or 597 infrared spectrometers. Melting points, which are uncorrected, were determined on a Thomas-Hoover capillary melting point apparatus. Molecular weights were determined on a Finnigan 3300 mass spectrometer. Microanalysis were performed by Micro-Tech Laboratories, Inc., Skokie, IL.

Starting materials and solvents were obtained from commercial sources and were used without further purification with the exception of crotyl chloride and chlorodiphenylphosphine, which were distilled, and potassium *tert*-butoxide, which was sublimed twice [160–170 °C (0.015 mmHg)].

1-(Diphenylphosphinyl)-2-butene. To a system which had been dried and placed under static helium pressure were added 17 mL (0.126 mol) of diphenylphosphinous chloride and 250 mL of tetrahydrofuran. Lithium wire (1.86 g 0.268 mol, 2 equiv, plus a 6% excess) was cut directly into the reaction vessel, and the resulting mixture was refluxed approximately 5 h. In order to monitor the progress of the reaction, a 5-mL aliquot of the solution was removed by syringe and cooled in ice. A known excess of 1.000 N HCl was quickly added to the aliquot and, after addition of 4 drops of phenolphthalein indicator, was back titrated with 1.000 N NaOH. After the complete formation of the phosphide, the solution was cooled to room temperature, and 12.8 mL (0.131 mol) of crotyl chloride was added by syringe. The mixture was stirred for 15 min and the majority of the solvent evaporated. The residue was redissolved in methylene chloride and stirred with an icewater slurry adjusted to pH 7. Hydrogen peroxide (30%) was added until starch-iodine paper tested positive. The aqueous phase was extracted with methylene chloride, the separated organic phase was dried over MgSO₄, and the solvent was evaporated. The crude product, obtained in 84.6% yield, was recrystallized from hexanes. The purified material was obtained in 44% yield: mp 118-119 °C; ¹H NMR (CDCl₃) δ 1.4-1.7 (overlapping d, 3 H), 2.7–3.9 (dd, 2 H), 5.2–5.5 (m, 2 H), 7.1–7.8 (m, 10 H); IR (CH₂Cl₂) 1200 (P=O), 1440 (PPh), 1690 and 970 cm⁻¹ (trans-

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HC=CH); mass spectrum (for $C_{16}H_{17}OP$), m/e 256. Anal. Calcd for $C_{16}H_{17}OP$: C, 74.99; H, 6.69. Found: C, 75.13; H, 6.69.

1-(Diphenylphosphinyl)-2,3-epoxybutane. To a solution of 5.9 g (0.034 mol) of m-chloroperoxybenzoic acid in 70 mL of ethyl acetate was added 7.00 g (0.027 mol) of 1-(diphenylphosphinyl)-2-butene. The mixture was refluxed until its NMR spectrum indicated, through the complete disappearance of the vinyl hydrogen signal, the completion of the reaction (approximately 3 h). The solution was cooled, and 10% aqueous NaHSO3 was added to decompose the excess peracid (exothermic reaction). The mixture was diluted with 100 mL of methylene chloride, and the organic phase was separated and washed with 5% aqueous KOH until the aqueous layer was basic to indicator paper. The separated organic phase was dried with MgSO4 and the solvent evaporated. The crude solid product (obtained in 95.7% yield) was purified by using, with modification, the method devised by Still et al., flash chromatography.¹⁵ Better separation was obtained in the chromatography by increasing the published R_{f} value of 0.35 for the desired compound to 0.50. The solvent system employed was 60% acetone-40% hexanes. The purified compound was obtained in 72.2% yield and was further purified by recrystallizing from hexanes: mp 81 °C; ¹H NMR (CDCl₂) δ 1.1 (d, J = 5 Hz, 3 H) 2.0-3.1 (m, 4 H), 7.1-7.9 (m, 10 H); IR (paraffin)oil) 1200 (P=O), 1440 (PPh), 915 (epoxide 11-μm band), 753 cm⁻¹ (epoxide 12-μm band); mass spectrum (for C₁₄H₁₇OP), m/e 272. 1-(Diphenylphosphinyl)-1-buten-3-ol. To a 50-mL round-

bottomed flask which had been dried and placed under static nitrogen pressure were added 2.00 g (7.4 mmol) of 1-(diphenylphosphinyl)-2,3-epoxybutane and 20 mL of absolute ethanol. A catalytic amount of potassium tert-butoxide (0.10 g, 0.89 mmol) was added to the solution, the temperature of the mixture rising to 31 °C. The mixture was maintained at this temperature and the reaction monitored by TLC on silica gel until disappearance of the spot corresponding to the epoxide was noted (approximately 1.5 h). The solution was diluted with 60 mL of methylene chloride and washed with 5% aqueous HCl until the aqueous layer was acidic to indicator paper. The organic phase was separated and dried with MgSO4 and the solvent evaporated. The crude product (obtained in 91% yield) was purified by using flash chromatography (60% acetone-40% hexanes). The suggested R_f value of 0.35 was altered to 0.42, a modification which was still unsatisfactory, as much of the alcohol remained on the column. It was recovered by flushing the column with acetone. The purified product, an oil, was obtained in 70% yield and was not purified further but was used in the subsequent oxidation: ¹H NMR $(CDCl_3) \delta 1.2 (d, J = 7 Hz, 3 H), 4.1-4.6 (m, 1 H), 4.8-5.5 (s, 1 H)$ H), 6.3-6.5 (m, 1 H), 6.7-6.9 (m, 1 H), 7.0-8.0 (m, 10 H); IR (neat) 3312 (OH), 1200 (P=O), 1440 (PPh), 1690 and 970 cm⁻¹ (trans-HC=CH)

4-(Diphenylphosphinyl)-3-buten-2-one. The solution resulting from the addition of 1.4 g (5.15 mmol) of 1-(diphenylphosphinyl)-1-buten-3-ol to 10 mL of acetone was cooled to -10 °C by use of an acetone/dry ice bath. Jones reagent¹³ was added dropwise to the solution until an excess had been added, as indicated by the solution's orange color. The rate of addition was controlled so that the mixture's temperature did not rise above 0 °C. The final solution was allowed to warm over a 10-min interval to 10-15 °C, and more Jones reagent was added, if necessary, to maintain the solution's orange color. The mixture was cooled to 0 °C, and aqueous, acidified (to a pH of approximately 4), saturated sodium bisulfite was added to decompose the excess oxidant. The solution was extracted with ether, the separated organic phase dried with MgSO₄, and the solvent evaporated. The crude product obtained in 80% yield was recrystallized from tetrahydrofuran and ether. The purified product was obtained: 66% yield; mp 128–129 °C; ¹H NMR (CDCl₃) δ 2.3 (s, 3 H), 6.8-8.0 (m, 12 H); IR (paraffin oil) 970 (trans-HC=CH), 1200 (P=O), 1440 cm⁻¹ (C=O); mass spectrum (for C₁₆H₁₅O₂P), m/e 270. Anal. Calcd for C₁₆H₁₅O₂P: C, 71.11; H, 5.59. Found: C, 71.05; H, 5.54

2-Acetyl-1-(diphenylphosphinyl)-4-methylcyclohex-4-ene. In a glass-lined steel bomb were combined 0.65 g (2.4 mmol) of 4-(diphenylphosphinyl)-3-buten-2-one and 1.02 g of isoprene (15.0

Table I. Crystal Data

mol formula	C., H., O. P	V_c	1838.88 ų
mol wt	338.38	Z	4
crystal system	monoclinic	$d_{\mathbf{c}}$	1.222 g cm ⁻³
space group	$P2_1/C$	d_{0}	1.216 g cm ⁻³
a	15.423 (4) Å	μ	1.6 cm^{-1}
ь	13.042 (4) A	F(000)	720
с	9.142 (3) A	λ (Mo K α)	0.71069 Å
в	96.16 (2)°	· · ·	

mmol). The mixture was heated at 110–120 °C for 24 h. The crude product obtained was recrystallized from tetrahydrofuran and ether in 69% yield. The mother liquor was purified by using flash chromatography with a solvent system of 50% acetone–50% hexanes. The oil obtained yielded, upon recrystallization, an additional 0.09 g of material. This increased the refined yield to a total of 80%: mp 162–163 °C; ¹H NMR (CDCl₃) δ 1.63 (s, 3 H), 2.07 (s, 3 H, superimposed on m, 4 H), 2.8–3.4 (m, 2 H), 5.27 (br s, 1 H), 7.1–8.1 (m, 10 H); IR (CHCl₃) 1200 (P=O), 1440 (PPh), 1700 cm⁻¹ (C=O); mass spectrum (for C₂₁H₂₃O₂P), *m/e* 338. Anal. Calcd for C₂₁H₂₃O₂P: C, 74.54; H, 6.85. Found: C, 74.69; H, 6.79.

t-2-(Diphenylphosphinyl)-c-3-acetyl-5-cyclohexen-r-1-yl Acetate. In a glass-lined steel bomb were combined 1.05 g (3.9 mmol) of 4-(diphenylphosphinyl)-3-buten-2-one and 1.10 g (3 equiv) of acetoxybutadiene. The mixture was heated at 98-114 $^{\circ}\bar{C}$ for 42 h. The acetoxybutadiene was made by following the procedure of Bailey and Barclay.¹⁶ The crude product obtained was recrystallized from tetrahydrofuran and ether in 55% yield. The mother liquor was purified by using flash chromatography with a solvent system of 75% acetone-25% hexanes. This yielded an additional 0.36 g of material and increased the refined yield to a total of 79%: mp 163-164 °C; ¹H NMR (CDCl₃, 300 MHz) δ 1.9-2.5 (2 s. both 3 H. both superimposed on m, 2 H), 3.3-3.6 (m, 2 H), 5.76 (s, 1 H), 5.88 (d with superimposed splitting, 2 H);¹H NMR (60 MHz) 7.3-8.1 (m, 10 H); ¹³C NMR (CDCl₃) 20.87 (q, multiplicity is reported for the off-resonance decoupling), 25.08 (t), 28.02 (d), 30.05 (q), 31.50 (d), 49.73 (d), 49.85 (d), 64.69 (d), 65.08 (d), 123.96-131.31 (aryl and vinyl), 131.60 (s), 131.89 (s), 169.89 (s), 205.53 (s), 205.75 (s); IR (CHCl₃) 1710 (C=O), 1200 (P=O), 1440 cm⁻¹ (PPh); mass spectrum (for $C_{22}H_{23}O_4P$), m/e382. Anal. Calcd for C₂₂H₂₃O₄P: C, 69.11; H, 6.06. Found: C, 69.12; H, 5.84.

X-ray Analysis of 2-Acetyl-1-(diphenylphosphinyl)-4methylcyclohex-4-ene (6). A single crystal of 1-acetyl-2-(diphenylphosphinyl)-5-methylcyclohex-4-ene suitable for X-ray analysis was grown from THF/ether overnight. The approximate size of the crystal used for data collection measured $0.5 \times 0.3 \times$ 0.4 mm. The crystals were clear, colorless rods (elongated parallel to the *a* axis).

The density was measured by flotation in a mixture of bromotrichloromethane and hexanes. The crystal was mounted on a Nicholet P2₁ automatic diffractometer equipped with an incident-beam graphite-crystal monochromator. All measurements were made at 25 °C by using Mo K_{α} radiation. The unit cell constants and the orientation matrix to be used in data collection were obtained from a least-squares refinement of 15 centered general reflections. Crystal data are listed in Table I.

Data Collection. The diffraction data were collected by the θ -2 θ scan technique at room temperature with graphite monochromated Mo K_{α} radiation. The scan rate varied from 2° to 10°/min, dependent on the intensity of diffraction maxima (scan width was based on $\Delta \theta = 1.00 + 0.15 \tan \theta$). No decay was noted for the three standard reflections $(\bar{3}, \bar{2}, \bar{2}, \bar{6}, \bar{1}, \bar{1}, \text{ and } \bar{3}, \bar{3}, \bar{3})$, which were monitored for every 50 reflections. A total of 1870 reflections were collected, comprising the quadrant of reciprocal space where k and l are each nonnegative and h assumed all values. Of the 1870 reflections collected, 1744 were classified as observed for $|F_0|^2 > 2\sigma(|F_0|^2)$, where $|F_0|$ is the observed structure factor amplitude corrected for Lorentz and polarization effects.

Structure Determination and Refinement. The diffractometer data were reduced by using a program written at The University of Akron and based on a program made available from the Analytical Instruments Division of Syntex Corp. The structure was solved by direct methods using the program MULTAN 74.¹⁷ The probable phase set, as determined by statistics and based on three origin and three starting reflections, produced an E map containing all 24 of the 24 heavy atoms in the structure. All atoms were varified in difference Fourier maps by using the program set CRYM.¹⁸

Full-matrix least-squares refinement of the heavy-atom positions minimizing the quantity $\sum w(F_o^2 - F_c^2)^2$, where $w = (1/\sigma^2)F_o^2$, was followed by the calculation of all hydrogen atoms except the methyl hydrogens, which were located in difference Fourier maps. At this point, seven cycles of isotropic full-matrix least-squares refinement resulted in a R value $\left[=\sum (||F_{o}| - |F_{c}|) / \sum |F_{o}|\right]$ of 18.8. Further full-matrix least-squares analysis of 309 variables (coordinates and anisotropic temperature factors for 24 heavy atoms, coordinates and isotropic temperature factors for the 23 hydrogen atoms, and a scale factor) led to a final R value of 5.0 and a goodness-of-fit $[=\sum w(F_o^2 - F_c^2)^2/(M - S)^{1/2}]$ for M = 1744 observed reflections and S = 309 parameters of 1.63. The R_w value $[=[\sum w(F_o^2 - F_c^2)^2 / \sum wF_o^4]^{1/2};$ 1645 reflections] was 7.2, and the R factor for the 3σ data set was 3.5. The estimated standard deviations were computed from the inverse matrix of the last full-matrix least-squares cycle. All shifts in parameters were less than their estimated standard deviations in the final refinement cycle. The scattering factors and anomalous dispersion terms were taken from the literature.²² The scattering factors for hydrogen

were taken from the literature.¹⁹

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Registry No. (*E*)-1, 17668-60-9; 2, 80780-91-2; (*E*)-3, 80780-92-3; (*E*)-4, 80780-93-4; 6, 80780-94-5; 8, 80780-95-6; isoprene, 78-79-5; acetoxybutadiene, 1515-76-0.

Supplementary Material Available: Table II, positional parameters for the heavy atoms; Table III, anisotropic thermal parameters for the heavy atoms; Table IV, positional and thermal parameters for the hydrogen atoms; Table V, angles and torsion angles; Table VI, structure factor tables (16 pages). Ordering information is given on any current masthead page.

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Unexpectedly Low Effective Molarity in the Dicarboxylate-Catalyzed Iodine Oxidation of a Sulfide

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The iodine oxidation of N-acetylmethionine methyl ester is strongly accelerated by dicarboxylate anions. For succinate, adipate, suberate, and sebacate dianions at pH 7.0, both first- and second-order catalytic terms are observed. The ratios of the first- to the second-order catalytic constants are 0.85, 0.69, 0.55, and 0.16 M, respectively. The iodide dependence is inverse squared (approaching inverse cubed) at both high and low buffer concentrations. Since the succinate-catalyzed oxidation of sulfides has been suggested to proceed by intramolecular deacylation of an intermediate O-acyl sulfoxide, the observed effective molarities and the dependence on chain length are surprisingly small. It is suggested that the intermediate O-acyl sulfoxides exist largely as sulfuranes, complexed with the intramolecular carboxylate anion, and that the breakdown of this sulfurane is rate limiting, giving rise to the low effective molarities.

The carboxylate-catalyzed iodine oxidation of sulfides is thought to proceed through the formation of an intermediate iodosulfonium ion,¹⁻⁴ or activated sulfur-iodine complex,⁵ which is attacked by carboxylate anions to give an O-acyl sulfoxide. This intermediate can partition by reaction with the solvent or with another mole of carboxylate to give sulfoxide and carboxylate anhydride.^{2,3} In dicarboxylate anions, the intramolecular carboxylate attacks the O-acyl sulfoxide to give cyclic anhydride.² We have recently described the mechanisms of buffer catalysis in the iodine oxidation of N-acetylmethionine and Nacetylmethionine, methyl ester^{3,4} (NAME). For Nacetylmethionine, the intramolecular carboxylate appeared to be a poor nucleophile toward the iodosulfonium ion, relative to intermolecular carboxylate catalysis.^{3,4} In order to more clearly define the role of intramolecular carboxylates in these reactions, we have examined the catalysis of the oxidation of N-acetylmethionine methyl ester by carboxylate dianions interspaced by two, four, six, and eight methylene units.

Experimental Section

Materials. Inorganic salts were reagent grade and were used as supplied. Organic acids were recrystalized prior to use. N-Acetylmethionine methyl ester was prepared by esterification of N-acetylmethionine, as previously described.³ Stock solutions of the ester were prepared at about 0.1 M in methanol. Reactions

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