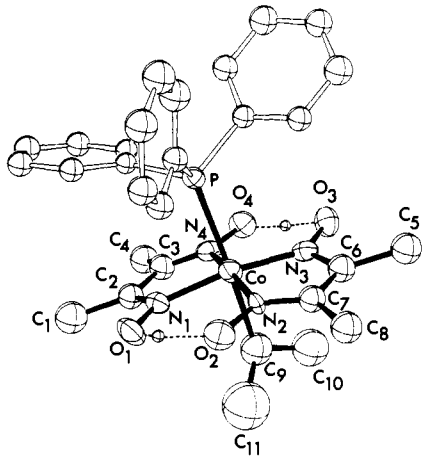

Figure 1. Molecular structure of 1.

Table I. Comparisons of Conformational Effects in Organocobaloximes

	$(C_6H_5)_3PCo(DH)_2CH_3$[a]	$pyCo(DH)_2CH_3$[b]	$(C_6H_5)_3PCo(DH)_2(i\text{-}C_3H_7)$[c]	$pyCo(DH)_2(i\text{-}C_3H_7)$[d]
Co-C, Å	2.026 (6)	1.998 (7)	2.22 (2)	2.085 (3)
Co-P(N), Å	2.418 (1)	2.068 (3)	2.412 (4)	2.099 (2)
C-Co-P(N), deg	175.4 (2)	178.0 (2)	170.3 (6)	175.4 (1)
d, Å[e]	0.11	0.04	0.17	0.02
α, deg[f]	14	4	14	4

[a] Reference 10. [b] Reference 12. [c] Present work. [d] Reference 8. [e] In all cases the displacement of Co is on the opposite side of the alkyl group. [f] The bending is always toward the alkyl group.

than the value of 2.085 Å found for $pyCo(DH)_2$-i-C_3H_7.[7] This difference appears statistically significant, being over six times the highest estimated standard deviation. Conversely the Co–P bond length of 2.412 (4) Å does not differ from that of 2.418 (1) Å found in $(C_6H_5)_3PCo(DH)_2CH_3$.[9] The apparently similar trans influence of CH_3 and i-C_3H_7 may be attributed to a secondary steric effect;[10] that is, steric hindrance prevents the i-C_3H_7 group from being a much better electron donor than CH_3.

The $Co(DH)_2$ unit exhibits steric strain, although bond lengths and angles within each DH unit are quite normal.[7,9,11] The cobalt atom is displaced by 0.17 Å out of the plane of the N donors (coplanar within ±0.01 Å) toward the phosphine ligand, whereas the two DH units, both coplanar with ±0.06 Å, make an interplanar angle of 14°. Finally, the C–Co–P angle of 170.3 (6)° is narrower than the analogous angle of 175.4 (2)° found in the methyl derivative. It is of interest to compare some structural data of the two pairs of complexes, $(C_6H_5)_3PCo(DH)_2R$ and $pyCo(DH)_2R$, in which R = CH_3, i-C_3H_7 (Table I). These results suggest that the increase in bulkiness from pyridine to $(C_6H_5)_3P$ provokes a lengthening of the Co–C bond, which appears mainly due to the increased distortion of the $Co(DH)_2$ moiety by the ligand trans to the alkyl group. This is shown by the larger values of C–Co–L angle, the out-of-plane distance of cobalt atom, d, and the interplanar angle, α, between the two DH units found in the $(C_6H_5)_3P$ complexes.

We believe that this lengthening is probably not a consequence of the effect of the conformational distortion on the electronic properties of the Co center, since in $LCo(DH)_2CH_3$ compounds with L = $(CH_3O)_3P$,[12] $(C_6H_5)_3P$,[9] and $(c\text{-}C_6H_{11})_3P$,[13] the Co–C bond lengths are very similar even though there are conformational changes in the $Co(DH)_2$ unit as the bulk of L is increased. This finding is in keeping with the known instability of cobaloximes containing secondary alkyl groups.[4,14]

Table II. Dependence of the Chemical Shift (^{1}H NMR) of the Isopropyl Methyl Groups in $LCo(DH)_2$-i-C_3H_7 on the Bulk of L[a]

N-donor L	shift	P-donor L	shift
1-ethyl-2-methylbenzimidazole	0.06	$(c\text{-}C_6H_{11})_3P$	0.16
2-methylpyridine	0.10	$(i\text{-}C_3H_7)_3P$	0.28
1,2-dimethylimidazole	0.32	$(C_6H_5)_3P$	0.41
pyridine	0.46	$(CNCH_2CH_2)_3P$	0.52
5,6-dimethylbenzimidazole	0.50	$(CH_3O)_3P$	0.54
1-methylimidazole	0.50	$(n\text{-}C_4H_9)_3P$	0.54

[a] In ppm downfield from $(CH_3)_4Si$, $CDCl_3$, JEOL MH-100.

The ^{1}H NMR spectra of nonalkylcobaloximes are sensitive to conformational distortions induced by bulky ligands.[15] A useful measure of such distortions is the length of the Co–P bond when the bulky ligand is a phosphine.[16] We now find that organocobaloximes exhibit similar effects, as illustrated for $LCo(DH)_2$-i-C_3H_7 compounds in Table II. The data in Table II clearly reflect primarily the bulk of the ligand L and suggest that some ligands such as $(c\text{-}C_6H_{11})_3P$ and 1-ethyl-2-methylbenzimidazole induce greater conformational distortions than does $(C_6H_5)_3P$. Thus, it is very likely that, since we have demonstrated here a relationship between steric distortion and Co–C bond length, even longer Co–C bond lengths would be observed if crystals of sufficient stability could be prepared.

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Supplementary Material Available: A listing of structure factors, atomic parameters, hydrogen atom coordinates, and bond lengths and angles of $(C_6H_5)_3PCo(DH)_2$-i-C_3H_7 (8 pages). Ordering information is given on any current masthead page.

(9) Bresciani-Pahor, N.; Calligaris, M.; Randaccio, L.; Marzilli, L. G. *Inorg. Chim. Acta* **1979**, *32*, 181.
(10) Toscano, P. J.; Marzilli, L. G. *Inorg. Chem.* **1979**, *18*, 421.
(11) Bigotto, A.; Zangrando, E.; Randaccio, L. *J. Chem. Soc., Dalton Trans.* **1976**, 96 and references therein.
(12) Stucky, G. D.; Swanson, J. S., private communication.
(13) Unpublished results.
(14) Schrauzer, G. N.; Windgassen, R. J. *J. Am. Chem. Soc.* **1966**, *88*, 3538.
(15) Trogler, W. C.; Marzilli, L. G. *Inorg. Chem.* **1975**, *14*, 2942; *J. Am. Chem. Soc.* **1974**, *96*, 7589.
(16) Bresciani-Pahor, N.; Calligaris, M.; Randaccio, L. *Inorg. Chim. Acta* **1980**, *39*, 173.
(17) Current address: Department of Chemistry, Emory University, Atlanta, GA 30322.

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Occurrence of a 1,2 Shift during Enzymatic and Chemical Oxidation of a Terminal Acetylene

Sir:

Evidence that acetylenic moieties can be oxidatively metabolized has remained sufficiently oblique for the very existence of this transformation to remain in doubt.[1] Scattered reports of acetylene group metabolism, generally based on in vivo studies, are am-

(1) Shirota, F. N.; DeMaster, E. G.; Nagasawa, H. T. *J. Med. Chem.* **1979**, *22*, 463.

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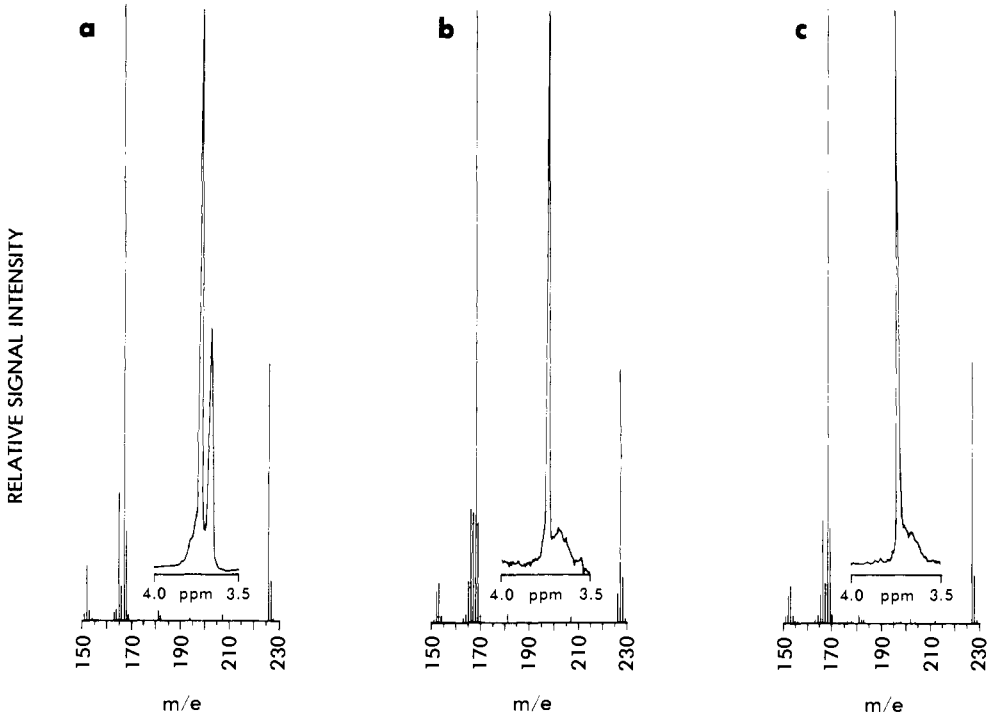
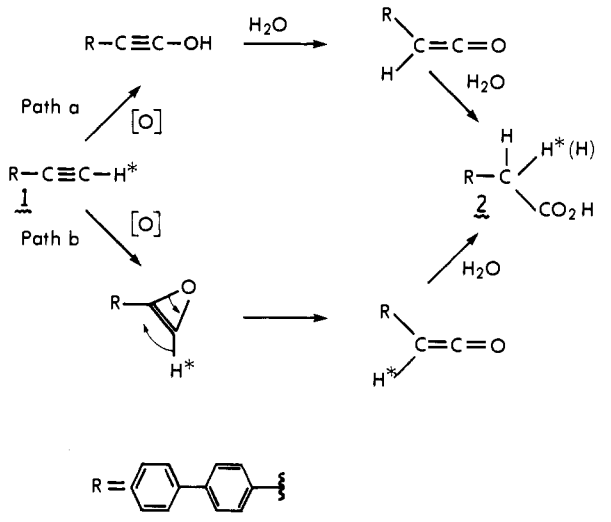


Figure 1. Partial mass and NMR (inset) spectra of (a) authentic unlabeled methyl 2-biphenylacetate, (b) the esterified metabolite from deuterated 1, and (c) the product from peracid oxidation of deuterated 1.

biguous due to uncertainties concerning the hydrolytic or oxidative origin of the observed transformations.[2] An early report that rabbits excrete phenylacetylene as phenylacetic acid,[2c] however, has recently been strengthened by observation of similar acetylene–acetic acid transformations in the metabolism of biphenylacetylene (**1**)[3a,c] and 4′-ethynyl-2-fluorobiphenyl.[3b] These four studies, but particularly the microsomal experiments with the two biphenyl substrates,[3b,c] clearly imply the intervention of an oxidative process. An ambiguity nevertheless arises in the case of terminal acetylenes, since their oxidation can be envisioned to occur by two distinct mechanisms, both of which have been invoked in rationalizing essentially identical experimental results.[3] Thus, either of the following sequences can, in principle, mediate conversion of the ethynyl group in **1** to the acetic acid substituent in **2** (Scheme I): (path a) oxygen insertion into the carbon–hydrogen bond, tautomerization of the hydroxyacetylene to a ketene, and addition of water or (path b) π-bond oxidation to an oxirene, concerted ring opening and hydride shift (oxidation and hydride shift may occur synchronously without the oxirene intermediate), and addition of water to the resulting ketene. One traceable difference in these two pathways is the fate of the acetylenic hydrogen atom. In path a, the hydrogen becomes an exchangeable hydroxyl proton barred by steric and orbital symmetry considerations from intramolecular transfer during tautomerization to the ketene, whereas in path b it is channeled by just such an (allowed) intramolecular 1,2 shift into a relatively stable linkage.[4] We report here the fate of the acetylenic hydrogen atom during both the enzymatic and chemical oxidation of biphenylacetylene which incisively defines the mechanism of metabolic acetylene oxidation.

Scheme I



[1-^{2}H]Biphenylacetylene[5] was incubated at 37 °C for 40 min with hepatic microsomes from phenobarbital-induced Sprague-Dawley male rats.[6] The residue obtained after acidification (0.1 N HCl) to pH 5, extraction with CH_2Cl_2, drying (anhydrous $MgSO_4$), methylation with CH_2N_2 (ether, 2 °C, 24 h), and solvent removal was analyzed by coupled gas chromatography–mass spectrometry (GCMS).[8] The esterified 2-biphenylacetic acid

(2) (a) Hoppe-Seyler, G. *Z. Physiol. Chem.* **1882**, *7*, 178. (b) Bohm, F. *Ibid.* **1939**, *261*, 35. (c) El Masry, A. M.; Smith, J. N.; Williams, R. T. *Biochem. J.* **1958**, *68*, 199. (d) Yih, R. Y.; Swithenbank, C. *J. Agric. Food Chem.* **1971**, *19*, 320. (e) Sisenwine, S. F.; Kimmel, H. B.; Liu, A. L.; Ruelius, H. W. *Drug Metab. Dispos.* **1979**, *7*, 1. (f) Abdel-Aziz, M. T.; Williams, K. I. H. *Steroids* **1969**, *13*, 809.

(3) (a) Wade, A.; Symons, A. M.; Martin, L.; Parke, D. V. *Biochem. J.* **1979**, *184*, 509. (b) Sullivan, H. R.; Roffey, P.; McMahon, R. E. *Drug Metab. Dispos.* **1979**, *7*, 76. (c) Wade, A.; Symons, A. M.; Martin, L.; Parke, D. V. *Biochem. J.* **1980**, *188*, 867.

(4) A hydrogen rather than biphenyl 1,2 shift is presently assumed. Further evidence defining the migrating group is being sought.

(5) Biphenylacetylene (178 mg, 1 mmol) in 10 mL of dry THF was treated with 1.1 equiv of *n*-BuLi at −78 °C. After the solution was warmed to 0 °C and stirred 1 h, deuterated water was added. Ether extraction and chromatographic purification gave 125 mg (70%) of >95% labeled (by MS and NMR) [1-^{2}H]biphenylacetylene.

(6) Microsomes were prepared as previously reported.[7] The incubation mixture (40 mL) contained 4 mg/mL microsomal protein, 1.5 mM EDTA, 150 mM KCl, 83 mg NADPH, and 10 mg of deuterated biphenylacetylene in 0.1 M Na/K phosphate buffer (pH 7.4).

(7) (a) Ortiz de Montellano, P. R.; Kunze, K. L. *J. Biol. Chem.* **1980**, *254*, 5578. (b) Ortiz de Montellano, P. R.; Kunze, K. L.; Yost, G. S.; Mico, B. A. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 746.

(8) A Kratos MS-25 electron-impact (at 70 eV) GCMS with an OV-1 column programmed to rise at 10 °C/min from 140 to 240 °C was used. NMR were obtained in $CDCl_3$ on a Varian FT-80 instrument.

metabolite (2-methyl ester) was then isolated from the extracted mixture by low-pressure silica gel chromatography (1:19 ethyl acetate–hexane) and was analyzed by NMR.[8] Essentially quantitative retention of deuterium in the metabolite was indicated by its mass spectrum (Figure 1b),[9] which exhibited both a base peak (due to decarbomethoxylation) and a molecular ion one mass unit higher than the corresponding peaks in the spectrum of a reference sample (Figure 1a). Deuterium retention and localization of the label on the methylene group of the acetic acid side chain were independently confirmed by the NMR analysis, the sharp two-proton singlet adjacent to the ester methyl in a reference sample (Figure 1a) being replaced by a broad (deuterium coupled) one-proton signal in the metabolite (Figure 1b).

The chemical oxidation of acetylenes has been the focus of considerable experimental attention.[10] However, the intrinsic instability of the strained antiaromatic oxirene moiety has foiled all attempts to directly demonstrate its existence, although indirect evidence supports its transient formation.[10] Particularly relevant is the oxidative conversion of disubstituted acetylenes to disubstituted ketenes due to substituent migration.[8a,d] Surprisingly, however, no mechanistic studies have been carried out on the chemical oxidation of terminal acetylenes. The fate of the deuterium on oxidation of [1-^{2}H]-**1** with *m*-chloroperbenzoic acid in the presence of methanol (as a ketene trap) has therefore been examined.[11] The spectroscopic data on the methyl 2-biphenylacetate thus obtained (Figure 1c), virtually indistinguishable from that of the biological product (Figure 1b), places beyond question the occurrence of an intramolecular 1,2 shift in the chemical process. The observation of a 1,2-hydride shift in both the peracid oxidation and microsomal metabolism of a triple bond[12] establishes that acetylenic moieties are in fact oxidatively metabolized and lucidly demonstrates that this oxidative process involves reaction of the activated oxygen with the π bonds rather than with the terminal C–H bond of the acetylene.

This laboratory has recently demonstrated that the prosthetic heme moiety of cytochrome P-450 is alkylated during catalytic turnover of terminal acetylenes.[7,14] A mechanism involving an electron-deficient transient species generated by oxygen transfer to the acetylenic π bonds has been proposed for this suicidal interaction.[7] Both phenylacetylene[7a] and biphenylacetylene[14] mediate such cytochrome P-450 destruction, even though neither is a particularly effective agent. The present evidence for π-bond involvement in oxidative metabolism of acetylenes confirms a key aspect of the proposed destructive mechanism and suggests that enzyme destruction and metabolite formation are competitive outcomes of enzymatic triple bond oxidation.

Acknowledgment. Biphenylacetylene was kindly provided by Dr. R. E. McMahon (Eli Lily Co.). Support for the mass spectrometer facility is provided by NIH Grant RR 00719. This research was funded by NIH Grant GM 25515.

(9) The intensity of the peak at *m/e* 157 in Figure 1b suggests the presence of a trace of undeuterated **2**. This most likely reflects slow chemical exchange of the methylene protons in **2** subsequent to the metabolic reaction.

(10) (a) Stille, J. K.; Whitehurst, D. D. *J. Am. Chem. Soc.* **1964**, *86*, 4871. (b) McDonald, R. N.; Schwab, P. A. *Ibid.* **1964**, *86*, 4866. (c) Concannon, P. W.; Ciabattoni, J. *Ibid.* **1973**, *95*, 3284. (d) Ciabattoni, J.; Campbell, R. A.; Renner, C. A.; Concannon, P. W. *Ibid.* **1970**, *92*, 3826. (e) Timm, U.; Zeller, K. P.; Meier, H. *Chem. Ber.* **1978**, *111*, 1549.

(11) A mixture of deuterated biphenylacetylene (10 mg) and 12 mg of *m*-chloroperbenzoic acid was stirred for 24 h in CH_2Cl_2 containing 1% MeOH. The resulting reaction mixture was washed ($NaHCO_3$) and concentrated.

(12) By analogy with the oxidative NIH shift of aromatic hydrogens,[13] the present class of rearrangements could properly be termed the UC shift.

(13) Guroff, G.; Daly, J. W.; Jerina, D. M.; Renson, J.; Witkop, B.; Udenfriend, S. *Science* **1967**, *158*, 1524.

(14) Under conditions similar to those already published,[7a] a 10 mM concentration of biphenylacetylene brings about a 10% loss of cytochrome P-450 in 30 min.

(15) Fellow of the Alfred P. Sloan Foundation.

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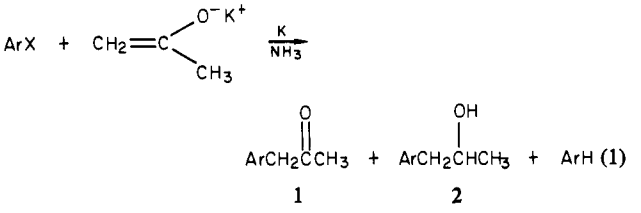
Product Ratios Dependent on and Independent of the Left Group in a Single Series: Potassium Metal Provoked Reactions of Aryl Halides with Amide and Acetone Enolate Ions That Occur during Mixing[1]

Sir:

The term "leaving group" has been variously used by physical organic chemists, for example, sometimes for a nucleofugal group in a molecule eligible to react with a nucleophile, sometimes for the nucleofuge detached as a consequence of reaction, often nonspecifically for both these meanings as well as for the group as it exists in the transition state. We use in the title the unusual term, "left group", because we refer to a system in which selection between alternative products is strongly influenced by leaving groups which have become detached from the substrate at the point of selection.

The system to which we refer is that of aryl halides (ArX) reacting with potassium acetone enolate and potassium metal in liquid ammonia.[2,3] Products are an arylacetone (**1**), the corresponding 1-aryl-2-propanol (**2**), and the dehalogenation product (ArH) (eq 1). Observed product distributions are strongly de-



pendent on the halogen. For example, with fluorobenzene the amount of benzene is high (~30%) and the ketone/alcohol (**1**/**2**) ratio is low (<0.3), while with iodobenzene the amount of benzene is low (~5%) and the **1**/**2** ratio is high (>5). Although these product distributions vary somewhat from experiment to experiment, the dominant factor in their determination is the identity of the halogen. Minor changes in the aromatic moiety do not have much effect on the product distribution.[3]

These reactions are understood in terms of the elaborated $S_{RN}1$ mechanism[4] sketched in Scheme I.[3] This is a radical chain mechanism, although the chain is sometimes forestalled by the incursion of termination steps. Step 1 is the initiation component, steps 2, 3, and 4 are the propagation cycle, and steps 6 and 8 effect termination. Steps 5, 7, and 9 are proton-transfer reactions, and step 10 involves electron transfer. According to this mechanism, product selection between substitution (**1** plus **2**) and dehalogenation (ArH) involves competition between steps 3 and 6 while selection between ketone (**1**) and alcohol (**2**) concerns whether step 4 or 8 is utilized.

A noteworthy feature of this mechanistic representation is that, despite the observed strong leaving group effects on product composition, *the leaving group is not present in the reacting species at the points where product selection occurs.* Actually this is not quite completely the case inasmuch as ArX is involved in step 4 which is competitive with step 8, but we have shown that the identity of the halogen at this point is not the dominant factor.[3] Insight into the origin of these effects is provided, within the $S_{RN}1$ framework, by the postulate that reaction occurs *during the mixing process* with the rate of fragmentation of $[ArX]^{-\cdot}$ (in step 2) being identified as the major factor that determines product distribution.

The general idea of this mechanistic model is that reaction occurs during mixing of a solvated electron-containing zone of solution (in ammonia) with a solvated electron-free zone that contains aryl halide molecules as well as enolate ions. When a small portion of solvated electron-containing solution swirls into the solvated electron-free zone, reaction with aryl halide molecules

(1) Research supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

(2) R. A. Rossi and J. F. Bunnett, *J. Am. Chem. Soc.*, **94**, 683 (1972).

(3) R. R. Bard, J. F. Bunnett, X. Creary, and M. J. Tremelling, *J. Am. Chem. Soc.*, **102**, 2852 (1980).

(4) J. F. Bunnett, *Acc. Chem. Res.*, **11**, 413 (1978).

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