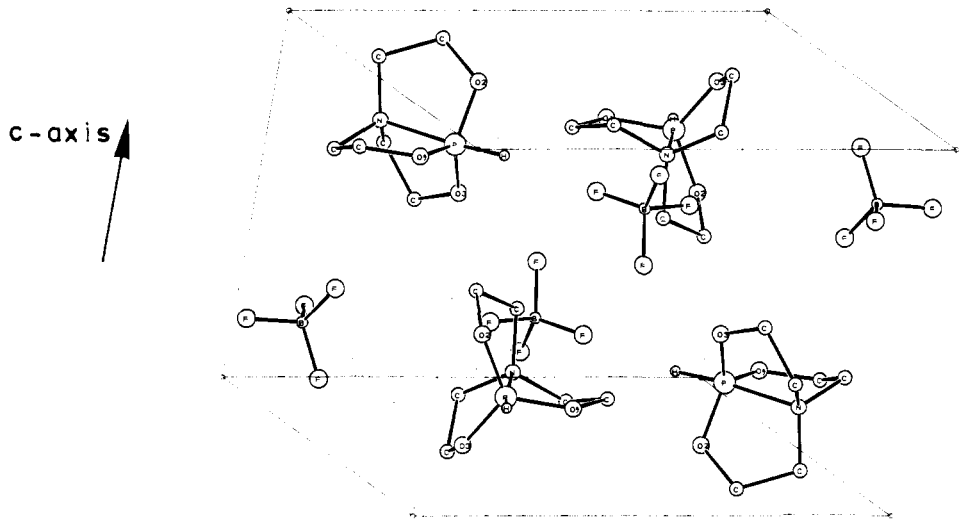


Figure 1.

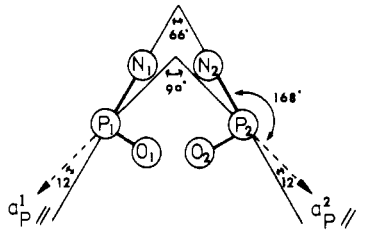


Figure 2.

hydrogen and nitrogen atoms in the apical positions as revealed by X-ray crystallography.[4] The ESR spectra of an X-irradiated single crystal[5] of **1** show that two identical radicals with an angle between their $a_{P\parallel}$ components of 90 ± 2° are present on rotation about the crystallographic *c* axis. The occurrence of differently oriented radicals is consistent with the X-ray analysis of precursor **1**, which also shows two orientations in the unit cell (Figure 1).[6] However, in the latter case, the angles between the P–N linkages are 66°. Taking into account that two such molecules are mirror images (Figure 1), we may indicate the direction of the $a_{P\parallel}$ components as shown in Figure 2. Thus, the structure of **2** can be decribed as a slightly deformed TBP configuration in which the unpaired electron and the nitrogen atom occupy the apical sites.

From the anisotropic contributions of the phosphorus hyperfine splittings, $a_{P\parallel}$ = 888 G and $a_{P\perp}$ = 753 G, one calculates[7] $a_{P,iso}$ = 798 G. These values indicate a phosphorus 3s spin density of 0.21 and a 3p spin density of 0.43, which gives a total spin density of 0.64 on phosphorus. The nearly isotropic ^{14}N splitting of 22 G indicates a spin density of 0.05 in its 2s orbital, a value which probably has a negative sign since it is the result of spin polarization in the P–N linkage. Apparently, the remaining spin density is distributed over the equatorial oxygen ligands.

The value of the ^{31}P isotropic coupling constant and the spin-density distribution in **2** are very similar to those observed for nonrigid phosphoranyl radicals.[8] Invariably, in the latter cases, a TBP structure is assigned in which the unpaired electron occupies an equatorial position. This structure seems to be supported by the p/s ratio, ~2, which is frequently observed. However, in spite of similar spectral data for **2**, this compound shows a quite different geometry, probably as a result of the molecular and crystal constraints.

The C_{3v} structure observed for **2** has also been found by Lucken et al.[1] for $Ph_3\dot{P}Br$ and $Ph_3\dot{P}Cl$. However, in these cases, the electron density is assumed to reside in the P–halogen σ^* orbital as inferred from the observed high spin density on the halogen. It is not clear whether the difference between these σ^*-C_{3v} structures and the present C_{3v} structure with the unpaired electron as the fifth apical ligand is the result of the electron-withdrawing character of the halogen in the former structures or the molecular constraints of the latter.

Recently, Roberts et al.[9] suggested that the relatively high rate of ligand exchange in $Me_2N\dot{P}(OEt)_2OBu$-*t* can be explained by assuming a C_{3v} intermediate with the unpaired electron in an antibonding P–N orbital. However, we show here that radical **2** is the cyclic analogue of the intermediate mentioned, which has to be described as trigonal bipyramidal with the unpaired electron and nitrogen in the apical positions.

Acknowledgments. This investigation has been supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO).

(4) Clardy, J. C.; Milbrath, D. S.; Springer, J. P.; Verkade, J. G. *J. Am. Chem. Soc.* **1976**, *98*, 623-624.
(5) The single crystal of **1** was a gift from Dr. D. van Aken, Department of Organic Chemistry, Eindhoven University of Technology, The Netherlands.
(6) The ORTEP drawing of the unit cell of **1** was kindly delivered by Dr. G. J. Visser, Computing Centre of the Eindhoven University of Technology, The Netherlands.
(7) Symons, M. C. R. "Chemical and Biological Aspects of Electron-Spin Resonance Spectroscopy", Van Nostrand-Reinhold: New York, 1978; pp 26-30.
(8) Dennis, R. W.; Roberts, B. P. *J. Organomet. Chem.* **1973**, *47*, C8.
(9) Hay, R. S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1978**, 770-778.
(10) For **2**, $g_\perp$ = 2.005 and $g_\parallel$ = 1.988.

J. H. H. Hamerlinck,* P. Schipper, H. M. Buck
Department of Organic Chemistry
Eindhoven University of Technology
Eindhoven, The Netherlands
Received March 3, 1980

A Three-Carbon Condensative Expansion. Application to Muscone

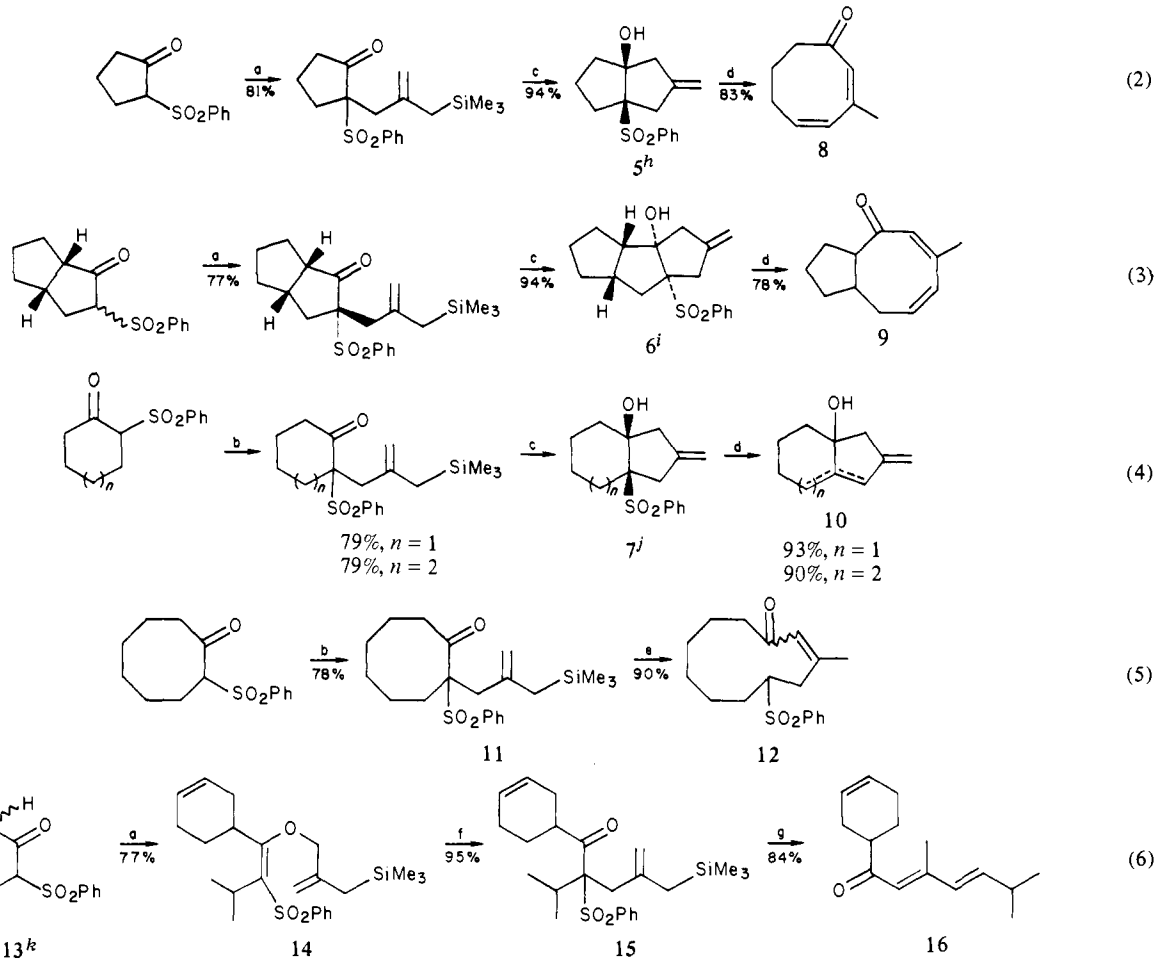
Sir:

Multicarbon ring expansions represent a relatively rare family of reactions. Recent emphasis on macrocyclic compounds heightens the interest in adjusting ring sizes by more than one carbon. We report (1) a simple approach to three-carbon ring expansions[1,2] involving a silyl-mediated fragmentation of β-keto

(1) Carlson, R. G.; Biersmith, E. L. *J. Chem. Soc. D* **1969**, 1049. Gutsche, C. D.; Redmore, D. "Carbocyclic Ring Expansion Reactions", Academic Press: New York, 1968; Chapter 10.

0002-7863/80/1502-5680$01.00/0 © 1980 American Chemical Society

Chart I. Three-Carbon Condensative Expansion[a,b]

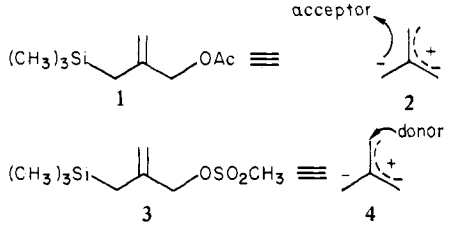


(2) (3) (4) (5) (6)

[a] See ref 5 and 6. [b] (a) 3, NaH, 1 equiv of NaI, DMF, 55 °C, 2–12 h. (b) 3, NaH, 0.2 equiv of NaI, DME, 65 °C, 36 h. (c) 0.2 equiv of $(C_4H_9)_4NF$, THF, 55 °C, 1 h. (d) KH, 1 equiv of 18-crown-6, DME, room temp, 2–5 h. (e) 0.2 equiv of $(C_4H_9)_4NF$, THF, 55 °C, 30 min. (f) $PhCH_3$, reflux, 48 h. (g) 0.4 equiv of $(C_4H_9)_4NF$, THF, 55 °C, 3 h then DBU, CH_2Cl_2, reflux, 1 h. (h) mp 115–116 °C. (i) mp 139–139.5 °C. (j) mp 114–115 °C, $n = 2$. (k) mp 55–60 °C and see ref 7.

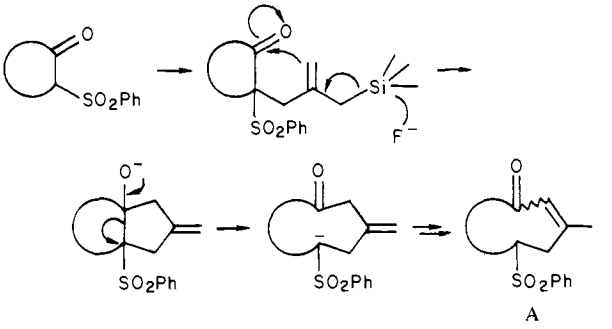
sulfones, (2) a short, high-yield synthesis of muscone,[3] an important ingredient of perfumes, (3) generalization of the concept to a three-carbon chain extension of an acylic system, and (4) a new methylenecyclopentane annulation.

Previously, we noted the application of the conjunctive reagent **1** in a palladium-mediated cyclopentane annulation in which the reagent can be considered the equivalent of the zwitterion **2**.[4] It



behaved as a nucleophile and required an electron acceptor as a reaction partner. On the other hand, conjunctive reagent **3**, derived from its corresponding alcohol under typical mesylation conditions [CH_3SO_2Cl, $(C_2H_5)_3N$, CH_2Cl_2, 0 °C, 84%], behaves as the equivalent of an electrophilic version of the zwitterion and requires an electron donor as a reaction partner, as represented in **4**.

Equation 1 and Chart I outline the process. Reaction of **3** with the sodium enolate of a β-keto sulfone in the presence of sodium iodide in DME or DMF (only for cyclopentanones) afforded the desired C-alkylated product. For eq 2–4 (Chart I), treatment



(1)

(2) For three-carbon ring expansion of heterocycles, see: Vedejs, E.; Arco, M. J.; Powell, D. W.; Renga, J. M.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4831. Petrzilka, M. *Helv. Chim. Acta* **1979**, *62*, 1319. Schmid, R.; Schmid, H. *Ibid.* **1977**, *60*, 1361. Cere V.; Pollicino, S.; Sandri, E.; Fava, A. *J. Am. Chem. Soc.* **1978**, *100*, 1516.

(3) (a) Fehr, C.; Ohloff, G.; Büchi, G. *Helv. Chim. Acta* **1979**, *62*, 2655, and earlier references cited therein. (b) Büchi, G.; Wüest, H. *Ibid.* **1979**, *62*, 2661. (c) Branca, Q.; Fischli, A. *Ibid.* **1977**, *60*, 925. (d) Stork, G.; MacDonald, T. L. *J. Am. Chem. Soc.* **1975**, *97*, 1264.

(4) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429, 6432.

(5) All compounds have been characterized by spectral means. Satisfactory elemental composition has been determined for new compounds.

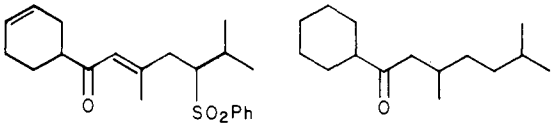
(6) In all cases except **13**, the β-keto sulfones were prepared in 70–80% yield by (1) sulfenylation (LDA, PhSSPh, THF, −78 °C → room temp) and (2) oxidation (MCPBA, CH_2Cl_2, 0 °C → room temp). Cf.: Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

(7) Prepared by acylation of the anion of isobutylphenyl sulfone with 3-cyclohexenylcarbonyl chloride.

of the allylsilanes with tetrabutylammonium fluoride[8-10] (0.2 equiv) in THF at 55 °C led to the fused methylenecyclopentanes **5–7**: IR 3500 (OH), 1300, 1150 (SO_2) cm^{-1}; NMR δ ~3.5 (OH), 5.8 ($=CH_2$). Further treatment of **5**[5] or **6**[5] with KH in the presence of 18-crown-6 led to smooth fragmentation and concurrent elimination of the elements of benzenesulfinic acid from the presumed intermediates related to A (eq 1) to give the three-carbon ring-expansion products **8**[5] [IR 1655, 1605 cm^{-1}; NMR δ 2.00 (s, 3 H), 5.85 (s, 1 H), 6.12–6.24 (m, 2 H)] and **9**[5] [IR 1650, 1603 cm^{-1}; NMR δ 1.92 (s, 3 H), 5.87 (s, 1 H), 5.95–6.35 (m, 2 H)]. Exposure of **7**[5] (n = 1 or 2) to these conditions led only to the elimination products **10**[5] without any evidence of ring-expansion products.

Remarkably, exposure of **11**[5] to a catalytic amount of tetra-*n*-butylammonium fluoride in warm THF led directly to the three-carbon ring-expanded product **12**:[5] 2:1 *Z*/*E*; IR 1682, 1628, 1304, 1149 cm^{-1}; NMR *Z* isomer δ 1.81 (s, CH_3), 6.09 (br s, =CH), *E* isomer 1.89 (s, CH_3), 6.28 (br s, =CH). No trace of the intermediate methylenecyclopentane could be detected.

The acyclic case **15**[6] behaved similarly to **11**. Treatment with fluoride ion led directly to the three-carbon ring-expansion product as a 1:2 mixture of **16**[5] (IR 1675, 1630, 1585 cm^{-1}) and **17** (IR 1685, 1619, 1305, 1152 cm^{-1}). The latter was converted quantitatively into the former upon exposure to DBU in refluxing methylene chloride. The complexity of the NMR spectrum of **16** indicated that it was a mixture of geometric olefin isomers. Subjection of this mixture to catalytic hydrogenation (1 atm of H_2, 5% $Pd/BaSO_4$, C_2H_5OH) gave a quantitative yield of a single compound (**18**:[5] IR 1708 cm^{-1}, NMR δ 0.80 (9 H, d, J = 5.5 Hz)), which was thus obtained in 84% overall yield from **15**. Only in this case could we not overcome the problem of O vs. C alkylation of the β-keto sulfone. However, this was no problem since the O-alkylation product **14** smoothly underwent a Claisen rearrangement in refluxing toluene to the desired C-alkylation product **15**.



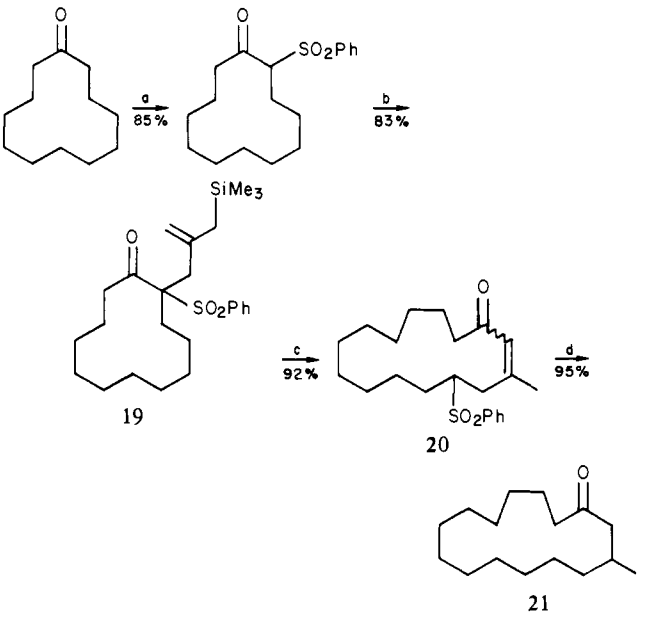
17

18

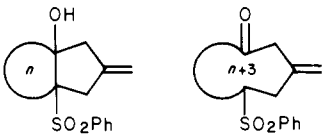
Scheme I outlines the application of this new ring expansion to a short synthesis of muscone (**21**).[3] The requisite β-keto sulfone, mp 110–112 °C, was available from cyclododecanone by oxidation of 2-phenylthiocyclododecanone or, preferably, by direct displacement of 2-bromocyclododecanone with sodium benzenesulfinate.[11] Treatment of **19**[5] with a catalytic quantity of fluoride ion led directly to the ring-expansion product **20**[5] [IR 1686, 1618, 1306, 1150 cm^{-1}; NMR δ 2.07 (s, 3 H), 6.16 (br s, 1 H)] with no detectable intermediates. Catalytic hydrogenation and desulfonylation led to *dl*-muscone, identical with an authentic sample by TLC and NMR and IR spectroscopy. The overall yield of muscone from cyclododecanone was 62%.

Except for simple six- and seven-membered rings, this approach to ring expansion and chain extension appears general. A rationalization for the scope of the reaction considers the relationship of **22** to **23** The bond-energy changes associated with this transformation are approximately zero. The critical feature appears to be the change in strain energy. Approximating the strain of **22** as the sum of the strain energies of the cyclopentane and a cycloalkane of n members and that of **23** as the strain energy of a cycloalkane of n + 3 members[12] reveals that ring expansion from a simple cyclohexanone is 6-kcal endothermic and that of a cycloheptanone almost thermoneutral. These two cases failed (Chart I, eq 4). Ring expansion from a cyclopentanone is about 3-kcal exothermic. This reaction succeeds, but the intermediate bi (or tri) cycle is easily isolated (Chart I, eq 2 and 3). The acyclic case (Chart I, eq 6) and those of the 8- (Chart I, eq 5) and 12-membered rings are exothermic by about 5–9 kcal. In these cases, the chain-extended or ring-expanded product is obtained directly, with no detectable trace of any intermediates. It would appear that, within the context of the above strain considerations, a family of ring- and chain-growing reactions involving different substitution patterns and numbers of atoms may be possible, based on bifunctional conjunctive reagents related to **3**. In the case of five-, six-, and seven-membered cycloalkanones, this methodology also becomes an electrophilic version of methylenecyclopentane annulation.[4] For example, compounds of type **6** are of current interest with respect to coriolins[13] and hirsutanes.[14]

Scheme I. A Muscone Synthesis[a]



[a] (a) i, Br_2, $CHCl_3$, room temp, 1.5 h; ii, $PhSO_2Na$, catalytic $(C_6H_{13})_4NBr$, DMF, 120 °C, 1.5 h. (b) NaH, 0.2 equiv of NaI, DME, 65 °C, 36 h. (c) 0.2 equiv of $(C_4H_9)_4NF$, THF, 55 °C, 0.5 h. (d) i, 1 atm of H_2, 5% $Pd/BaSO_4$, C_2H_5OH; ii, 6% Na(Hg), Na_2HPO_4, CH_3OH.



22 23

(8) Sarkar, T. K.; Andersen, N. H. *Tetrahedron Lett.* **1978**, 3513. Hosomi, A.; Shirahata, A.; Sakurai, J. *Ibid.* **1978**, 3043. Wetter, H. *Helv. Chim. Acta* **1978**, *61*, 3072.

(9) Use of Lewis acids failed. Cf.: Deleris, G.; Dunogues, J.; Calas, R. *J. Organomet. Chem.* **1975**, *93*, 43; *Tetrahedron Lett.* **1976**, 2449. Hosomi, A.; Sakurai, H. *Ibid.* **1976**, 1295. Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941. Ojima, I.; Muyazawa, Y.; Kumagai, M. *J. Chem. Soc., Chem. Commun.* **1976**, 927. Itoh, K.; Fukui, M.; Kurachi, Y. *Ibid.* **1977**, 500. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, 71.

(10) Use of potassium fluoride and 18-crown-6 or cesium fluoride gave less satisfactory results.

(11) We have found the conditions specified in footnote (a) ii of Scheme I to be general. Cf.: Venrista, G. E.; Zwanenburg, B. *Synthesis* **1975**, 519. Suter, C. M. "The Organic Chemistry of Sulfur"; Wiley: New York, 1944; pp 721–724.

(12) Chang, S.; McNally, D.; Shary-Tehrary, S.; Hickey, S. M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109. Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *Ibid.* **1970**, *92*, 2377. Eliel, E. L.; Allinger, N. L.; Angyal, Morrison, G. A. "Conformational Analysis"; Wiley: New York, 1965; p 193.

(13) Nakamura, H.; Takita, T.; Umezawa, H.; Kunishima, M.; Nakayama, Y.; Sitaka, Y. *J. Antibiot.* **1974**, *27*, 301. Tatsuta, K.; Akimoto, K.; Kinoshita, M. *Ibid.* **1980**, *33*, 100. Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 2097.

Acknowledgments. We express our thanks to the National Science Foundation and the National Institutes of Health for their generous support of our programs. We are grateful to Dr. G. Ohloff, Firmenich SA., for an authentic sample of muscone.

(14) Comer, F. W.; McCapra, F.; Qureshi, I. H.; Scott, A. I. *Tetrahedron* **1967**, *23*, 4761. Comer, F. W.; Trotter, J. *J. Chem. Soc. B.* **1966**, 11. Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Tetrahedron Lett.* **1972**, 2053. Hashimoto, H.; Tsuzuki, K.; Sakan, F.; Shirahama, H.; Matsumoto, T. *Ibid.* **1974**, 3745. Trost, B. M.; Shuey, C. D.; DiNinno, F., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 1284. Little, R. D.; Muller, G. W. *Ibid.* **1979**, *101*, 7129.
(15) NIH Postdoctoral Fellow, 1979–1980.

Barry M. Trost,* John E. Vincent
McElvain Laboratories of Organic Chemistry
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

Received April 28, 1980

Kinetics of CO Binding to Manganese, Zinc, and Cobalt Hybrid Hemoglobins

Sir:

We present a comparison of ligand binding by mixed-metal hybrid hemoglobins in which the iron atoms of one pair of subunits have been replaced by divalent Mn, Zn, or Co.[1] The noniron subunits of a hybrid do not bind CO, and only with cobalt is O_2 bound even weakly. Thus, through appropriate choice of metal hybrid and ligand, one can study the sequential binding of the "first two" ligands by the ferrous-iron chains while the analogous chains remain unliganded. The measurements permit us to characterize the individual chains within the hemoglobin A tetramer, as well as the allosteric equilibrium between the low-affinity (T) and high-affinity (R) forms of partially ligated hemoglobin A intermediates. These characterizations are unavailable from studies with hemoglobin A because of the strongly cooperative ligation process.[2] The use of a series of hybrids, involving several metals for which the metalloporphyrin properties are documented, further allows us to directly examine the influence of well-defined stereochemical changes in the prosthetic group of one chain pair on the T–R equilibrium and on the ligation properties of the complementary chains.

Hybrids were prepared by adaptations[3] of the scheme of Yip et al[4] or of Lee,[5] and their purities were confirmed by isoelectric focusing. Samples for kinetic measurements were typically ~5 μM in heme in 0.01 M bis-Tris-HCl, pH 6.6, containing ~0.1% β-mercaptoethanol. The (Co, Fe) hybrids were studied in 0.1 M KP_i buffer, pH 7, and therefore the (Mn, Fe) and (Zn, Fe) hybrids were also examined in this buffer for comparison. The manganese hybrids as synthesized are in the $[(Mn_2(III), Fe_2(CO)_2]$ form. The Mn(II) form was prepared by addition of minimal dithionite following deaeration; methylene blue was used as a redox mediator. Descriptions are given elsewhere for the apparatus employed in flash photolysis at Northwestern[6] and at Cornell,[7] and for the stopped-flow measurements.[8]

Stopped-flow measurements reveal that the time course for CO binding to the Fe(II) chains of the unliganded (Mn, Fe) and (Zn, Fe) hybrids is homogeneous and pseudo first order in both the absence and the presence of inositol hexaphosphate (IHP). The low values for the rate constants (Table I) and the homogeneous time course indicate that each of these four unliganded hybrids is in the T state, confirming the earlier (Mn, Fe) observations.[9] In the absence of IHP, the Fe chains of the $(\alpha_2^{Fe},\beta_2^{M})$ and $(\alpha_2^{M},\beta_2^{Fe})$ hybrids have equal binding rates, indicating that in the T state the α and β chains have essentially equal reactivity toward carbon monoxide. Addition of IHP reduces the β chain binding rates by a factor of roughly two but does not influence the α rates; in conjunction with the flash photolysis results presented below, this demonstrates a tertiary structure influence on the reactivity within the T state.

The (Co, Fe) hybrids differ in that the time course for CO binding is not homogeneous. There is an initial rapid phase whose percentage decreases upon addition of IHP (Table I). In both cases, the rate constant for the slow component in a (Co, Fe)

Table I. CO Binding to Fe Chains of (Fe, M) Hybrid Hemoglobins[a]

hybrid	binding rates,[b] × 10^{-6} M^{-1} s^{-1} k_T −IHP	k_T +IHP	k_R	slow phase, %[c] −IHP	+IHP[d]	method
$\alpha^{Fe}\beta^{Mn}$	0.15	0.11	5.0	100	100	SF
				74	100	FP
$\alpha^{Mn}\beta^{Fe}$	0.14	0.05	6.0	100	100	SF
				70 (89[e])	100	FP
$\alpha^{Fe}\beta^{Zn}$	0.10	0.10	4.0	100	100	SF
				48	100	FP
$\alpha^{Zn}\beta^{Fe}$	0.10	0.05	4.5	100	100	SF
				58 (92[e])	100	FP
$\alpha^{Fe}\beta^{Co}$ [e]	0.09	0.09	6.0	85	~100	SF
				25	40	FP
$\alpha^{Co}\beta^{Fe}$	0.10	0.05	6.0	90	100	SF
				41	60	FP

[a] Conditions, except as noted: 0.01 M, bis-Tris-HCl, pH 6.6; T = 21 °C. The addition of IHP to 10–50 μM is indicated in "+IHP". [b] Estimated uncertainties: k_T, ±0.02 × 10^6 M^{-1} s^{-1}, k_R, ±0.5 × 10^6 M^{-1} s^{-1}. [c] Percentages are reproducible between samples to within ±5%. SF = stopped flow. FP = flash photolysis. [d] With some samples, small (≲5%) variable amounts of rapidly reacting materials are seen in the stopped-flow method, even with IHP present. This portion of the material is assumed to be partially denatured protein. [e] Conditions: 0.1 M KP, pH 7.0.

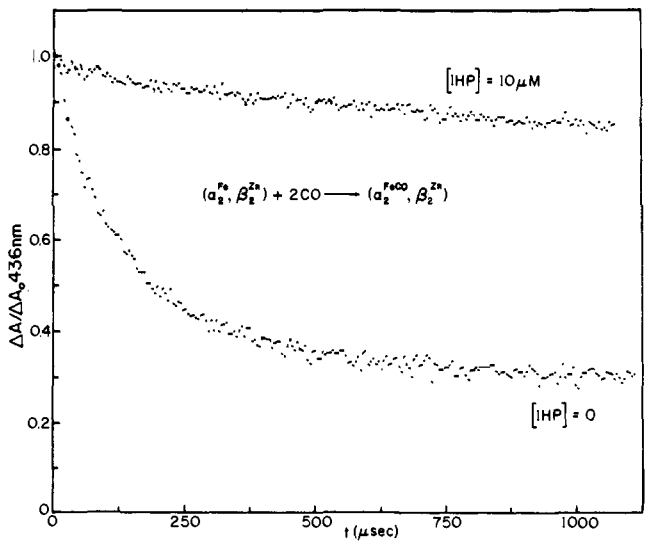


Figure 1. Recombination of CO with $(\alpha_2^{Fe}, \beta_2^{Zn})$ monitored at 436 nm after flash photolysis of $[\alpha_2^{Fe}(CO)_2,\beta_2^{Zn}]$. Lower trace; [IHP] = 0, [CO] = 1.03 mM. Fitting a two-exponential decay to this trace gives percentages and rates as given in Table I. Upper trace; same conditions, but with [IHP] = 10 μM. The slow phase now represents the totality of the progress curve.

(1) Hoffman, B. M. *Porphyrins* **1978–1979**, *7*, 1.
(2) (a) Shulman, R. G.; Hopfield, J. J.; Ogawa, S. *Q. Rev. Biophys.* **1975**, *8*, 325–410. (b) Edelstein, S. J. *Annu. Rev. Biochem.* **1975**, *44*, 209–232.
(3) To be published.
(4) Yip, Y. K.; Waks, M.; Beychok, S. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 64–68.
(5) Lee, T. C. K. *Anal. Biochem.* **1978**, *91*, 646–650.
(6) Stanford, M. A.; Swartz, J. C.; Phillips, T. E.; Hoffman, B. M. *J. Am. Chem. Soc.* **1980**, *102*, 4492–4499.
(7) Gibson, Q. H.; Hoffman, B. M. *J. Biol. Chem.* **1979**, *254*, 4691–4697.
(8) Gibson, Q. H.; Milnes, L. *Biochem. J.* **1964**, *91*, 161–171.
(9) Hoffman, B. M.; Gibson, Q. H.; Bull, C.; Crepeau, R. H.; Edelstein, S. J.; Fisher, R. G.; McDonald, M. J. *Ann. N.Y. Acad. Sci.* **1975**, *244*, 174–186.

0002-7863/80/1502-5683$01.00/0 © 1980 American Chemical Society