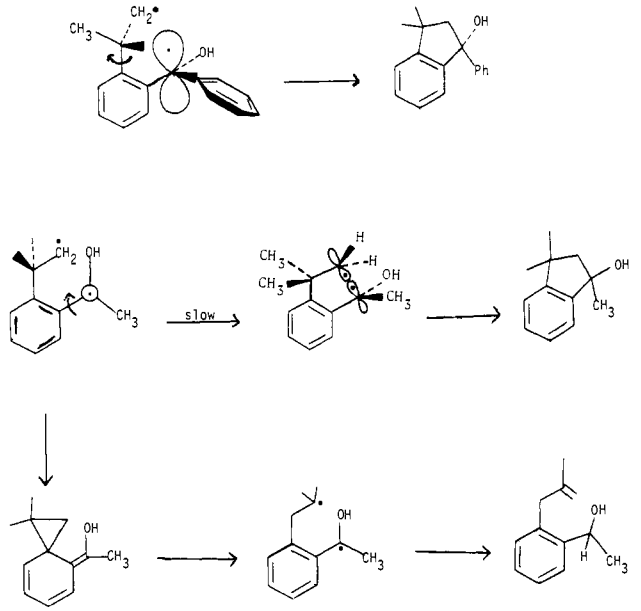
group strongly hindering approach to the carbonyl n-orbital.

The internal redox photochemistry of **1** also can be explained by a nearly coplanar π-system in the triplet. δ-Hydrogen abstraction gives a 1,5-biradical that must rotate so as to destroy benzylic conjugation in order for cyclization to an indanol to occur. This retarded rotation allows the biradical to undergo an otherwise less favorable reaction, namely a rearrangement to the unsaturated alcohol. In the benzophenone derivatives, the benzylic radical center of the biradical can remain conjugated with the unsubstituted benzene ring while the butylphenyl ring rotates.[1] In the *o-tert*-butylbenzophenones, hydrogen abstraction can take place even with a 70° twist so that the 1,5-biradical is formed almost in the correct geometry for cyclization.[3] We have corroborated Neckers' report that 2,4,6-tri-*tert*-butylacetophenone undergoes photocyclization to the indanol *tert*-butyl **6**.[13] The extra *tert*-butyl group apparently prevents even the triplet from attaining coplanarity such that it behaves like **2** instead of **1**.



We cannot yet assign a mechanism for the redox rearrangement; two major possibilities are disproportionation of a rearranged 1,5-biradical and a 1,5-sigmatropic hydrogen shift in a spiroenol. An unsaturated alcohol is a major photoproduct from *o*-isopropoxybenzophenone, so ditertiary 1,5-biradicals certainly can disproportionate appropriately.[14] A 1,2-aryl shift in the original 1,5-biradical, in competition with closure to indanol, would generate the biradical precursor to the major product. Such shifts have rate constants of only 10^2–10^3 s^{-1} in monoradicals,[15] so a more complicated process is required for the much shorter lived 1,5-biradical. As with the *o*-alkoxy ketones,[1] cyclization to a spiroenol is geometrically allowed in the original 1,5-biradical from **1**; and **3** gave evidence for ~1% of such a product.[3] We have not been able to trap such an intermediate from **1** with acetylene dicarboxylate. However, it would be expected to have a short lifetime because of a sigmatropic rearrangement to product or equilibration with the more stable of the two possible 1,5-biradicals. It is even possible that the biradical interconversion could proceed via a triplet spiroenol, just as the biradical formed by γ-hydrogen abstraction in *o*-alkyl ketones is a triplet enol.[16]

In summary, both the slow quenching of and the unusual products from an *o-tert*-butylacetophenone indicate that its triplet is much more coplanar than in the case of o-*tert*-butylbenzophenones. Therefore the 1,5-biradical formed by δ-hydrogen abstraction undergoes reactions dictated by a conjugatively restricted rotation.

Acknowledgment. This work was supported by National Science Foundation Grant no. 85-06703. We also thank Dr. Tito Scaiano at the NRC of Canada for his hospitality and cooperation in the measurement of triplet lifetimes by flash kinetics.

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(16) Haag, R.; Wirz, J.; Wagner, P. J. *Helv. Chim. Acta* **1977**, *60*, 2595. Das, P. K.; Encinas, M. V.; Small, R. D.; Scaiano, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 6965.

A Designed, Enantiomerically Pure, Fused Cyclopentadienyl Ligand with C_2 Symmetry: Synthesis and Use in Enantioselective Titanocene-Catalyzed Hydrogenations of Alkenes

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Received August 21, 1987

We report the synthesis of an enantiomerically pure, chiral cyclopentadienyl ligand[1,2] designed to possess C_2 symmetry and a rigid structural arrangement which effectively shields one face of an attached metal. Three X-ray structural analyses have served to establish relative and absolute configurations as well as structural features relevant to the interpretation of preliminary chemical data that strongly indicate synthetic utility.

The preparation of the key target **1** (generalizable for substituents other than phenyl)[3] is described in Scheme I.[4] It begins with *trans*-2-phenyl-4-cyclohexenol,[5] its stereoselective oxacyclopropanation,[6] and subsequent phenylcuprate ring-opening.[7] The resulting diol regiochemistry was established by ^{13}C NMR (7 lines, as expected for C_2 symmetry).

(1) (a) Halterman, R. L.; Vollhardt, K. P. C. *Tetrahedron Lett.* **1986**, *27*, 1461. (b) Paquette, L. A.; McKinney, J. A.; McLaughlin, M. L.; Rheingold, A. L. *Ibid.* **1986**, *27*, 5599 and the references therein.
(2) Gallucci, J. C.; Gautheron, B.; Gugelchuk, M.; Meunier, P.; Paquette, L. A. *Organometallics* **1987**, *6*, 15. Paquette, L. A.; Hathaway, S. J.; Schirch, P. F. T.; Gallucci, J. C. *Ibid.* **1986**, *5*, 500. Paquette, L. A.; Schirch, P. F. T.; Hathaway, S. J.; Hsu, L.-Y.; Gallucci, J. C. *Ibid.* **1986**, *5*, 490.
(3) DiMagno, T. J.; Halterman, R. L.; Vollhardt, K. P. C.; Welker, M. E., unpublished.
(4) All new compounds gave satisfactory analytical and spectral data. For example, (+)-**1**: off-white crystals, mp (ethoxyethane) 188-189 °C; MS, *m/z* (rel intensity) 298.1720 (M^+, **2**, calcd for $C_{23}H_{22}$ 298.1723), 230 (100); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.76 (ddd, J = 15.4, 7.5, 3.0 Hz, 2 H), 2.49 (ddd, J = 15.4, 12.3, 3.6 Hz, 2 H), 2.88 (br s, 2 H), 3.04 (s, 2 H), 3.29 (ddd, J = 12.4, 7.5, 2.5 Hz, 2 H), 5.87 (s, 2 H), 7.17–7.35 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.3, 38.1, 41.2, 43.1, 121.5, 125.8, 127.8, 127.9, 146.9, 147.7; IR (KBr) 2974, 1509, 1465, 1410, 1266, 1044 cm^{-1}; $[\alpha]^{25}_D$ = +21.8° (*c* 1, methylbenzene). (+)-Cp_2*$TiCl_2$: yellow-brown crystals, mp (petroleum ether–CH_2Cl_2) 220–222 °C; MS, *m/z* (rel intensity) 679, 677 (M^+–Cl, 90 for ^{35}Cl isotope fragment), 642 (100); HRMS 677.2468, calcd for $C_{46}H_{42}ClTi$ 677.2454; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (dd, J = 11, 8 Hz, 2 H), 2.15 (ddd, J = 20, 11, 3 Hz, 2 H), 2.36 (dd, J = 20, 8 Hz, 2 H), 2.49 (ddd, J = 11, 8, 3 Hz, 2 H), 3.23 (apparent t, "J" = 11 Hz, 4 H), 3.30 (apparent t, J = 8 Hz, 2 H), 3.90 2 H), 6.08 (dd, J = 4, 3 Hz, 2 H), 6.53 (m, 4 H), 7.05 (m, 16 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.3, 39.2, 39.4, 39.9, 41.8, 43.9, 107.8, 119.4, 123.7, 126.2, 126.6, 126.9, 127.5, 127.9, 128.6, 133.2, 142.8, 143.8, 153.2; IR (CH_2Cl_2) 3015, 2938, 2858, 1592, 1487, 1442, 1161, 1128, 1070, 1029, 969, 900 cm^{-1}; $[\alpha]^{25}_D$ = +381° (*c* 0.04, 1,2-dichloroethane).
(5) Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1503.
(6) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.
(7) Herr, R. W.; Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 3813. Wieland, D. M.; Johnson, C. R. *Ibid.* **1971**, *93*, 3047.

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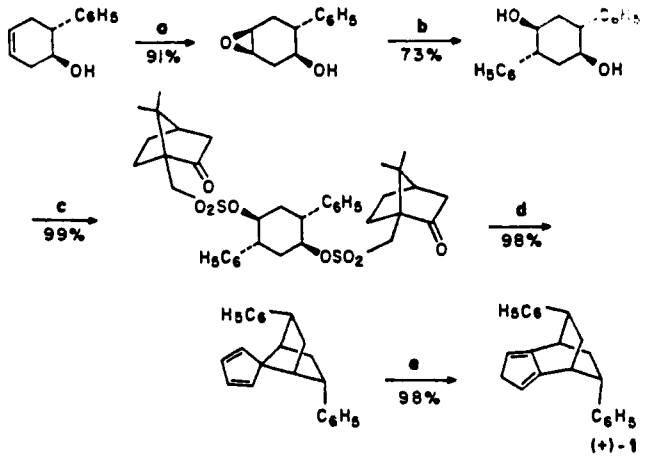
Scheme I[a]



[a] (a) $(CH_3)_3COOH$, $Mo(CO)_6$, methylbenzene, 60 °C, 2.5 h; (b) $(C_6H_5)_2CuLi$, ethoxyethane–oxacyclopentane (10:1), −45 °C to 25 °C, 12 h; (c) (+)-camphorsulfonyl chloride, pyridine, 0 °C, 2 h; (d) cyclopentadienylsodium–dimethoxyethane, NaH, oxacyclopentane, 0 °C, 2.5 h, Δ, 4 h; (e) methylbenzene, 220 °C (sealed tube), 21 h.

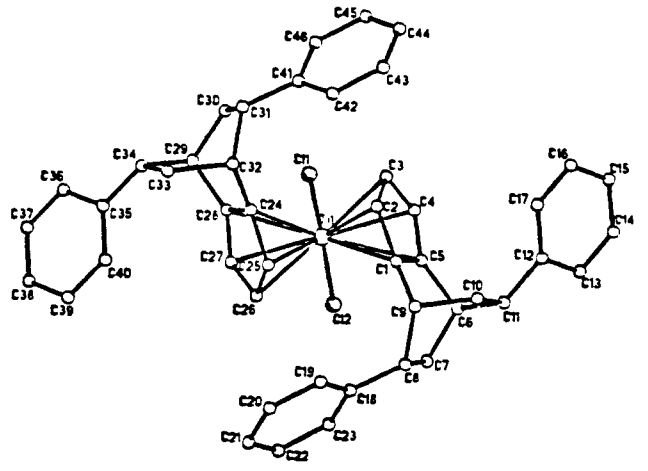


Figure 1. SHELXTL drawing of (+)-**2**.

Complete resolution of this intermediate was achieved by (+)-camphorsulfonylation (lower R_f diastereomer: $[\alpha]^{25}_D$ = +31.5°, *c* 1, methylbenzene; the relative *and* absolute configuration established by x-ray analysis, see Supplementary Material; higher R_f diastereomer: $[\alpha]^{25}_D$ = +38.7°, *c* 1, methylbenzene; flash chromatography, silica gel, ethoxyethane–CH_2Cl_2, 2:98) eventually leading to the pure enantiomers of **1**. Attempted direct cyclopentadiene annelation[1a] furnished the spirodiene[8] initially ($[\alpha]^{25}_D$ = +200.1°, *c* 1, methylbenzene) which could, however, be smoothly thermolyzed[9] to (+)-**1**. The integrity of enantiomeric purity in these two steps was confirmed by ^1H NMR by using chiral lanthanide–silver(I) shift reagents, a technique not previously applied to chiral dienes.[10]

The crowded nature of the ligand is not detrimental to metal complexation as shown by the preparation[4] of (±)-Cp*Co(CO)$_2$[11,12] [(±)-**1**, $Co_2(CO)_8$, cyclohexene–1,2-dichloroethane, 1:1, Δ, 18 h, 87%], (−)-Cp*CpTiCl$_2$ (1. (+)-**1**, $CH_3CH_2CH_2CH_2Li$, oxacyclopentane, −45 °C, 0.5 h; 2. $CpTiCl_3$, 5 °C, 50 min, 73%), (+)-Cp$_2$*TiCl$_2$, **2**, (1. (+)-**1**, $CH_3CH_2CH_2CH_2Li$, oxacyclopentane, −45 °C, 0.5 h; 2. $TiCl_3$, −45 °C to 25 °C, 40 min, 53%), and (±)-Cp$_2$*ZrCl$_2$ (1. (±)-**1**, $CH_3CH_2CH_2CH_2Li$, oxacyclopentane, −45 °C, 0.5 h; 2. $ZrCl_4$, −45 °C to 67 °C, 4.5 h, 95%, two diastereomers, 1:1).

Table I

complex	temp (°C)	turnovers (6 h, 80% compltn)	alkene	% optcl purity (abslte confn)
(+)-**2**	25	100	**3**	68 (*S*)
	−40	60		83 (*S*)
	−75	25		95 (*S*)
(−)-**2**	25	60		64 (*R*)
	0	70		75 (*R*)
	−40	20		87 (*R*)
	−75	10		96 (*R*)
	25	50	**4**	41 (*R*)

[a] Conditions: **2** (~0.04 mmol) and the substrate (~3–4 mmol) in methylbenzene (10 mL) were stirred at 25 °C under H_2 (1 atm) for 10 min, cooled to 0 °C, and mixed with butyllithium (~0.04 mmol). H_2 uptake began within 10 min. The optical purity of the products (isolated by PGLC) was based on literature data: Craig, J. C.; Pereira, W. E., Jr.; Halpern, B.; Westley, J. W. *Tetrahedron* **1971**, *27*, 1173. Kenyon, J.; Platt, B. C. *J. Chem. Soc.* **1939**, 633.

The expected asymmetric steric encumbrance around the metal was revealed by an X-ray structural investigation of (+)-**2** (Figure 1),[14] a study which also confirmed the clean S_N2 nature of the cyclopentadiene annelation step.

Consideration of this system as a catalyst precursor in stereoselective hydrogenations[1] of 2-phenyl-1-butene (**3**) or 2-ethyl-1-hexene (**4**) would suggest that π complexation of the substrate should favor an arrangement in which the larger substituent on the double bond points away from the nearby backbone of one of the cyclopentadienyl rings, saturation thus resulting in (*R*)-product with use of (+)-**2**, its enantiomer with use of (−)-**2**. Surprisingly, exactly the opposite is observed (Table I), indicating the operation of a less straightforward mechanism. A binuclear pathway involving external hydrogen delivery is rendered unlikely by the observation of a linear dependence of the rate of hydrogenation on catalyst concentration.

Several additional remarks are in order concerning our results: 1. the catalyst gives by far the best optical yields hitherto observed for titanocene-catalyzed hydrogenations;[1,2] 2. although reaction rates decrease, it is active even at very low temperatures providing synthetic flexibility; 3. the presence of a polarizable and potentially π complexing phenyl group in the substrate is not necessary for stereoselectivity; 4. the generality of Scheme I offers the opportunity for extensive fine-tuning; 5. employment of (−)-Cp*CpTiCl$_2$ as a precatalyst gave poor enantioselectivity suggesting the necessity for the presence of two chiral cyclopentadienyl ligands for satisfactory results.[16]

(8) Hallam, B. F.; Pauson, P. L. *J. Chem. Soc.* **1958**, 646. Antczak, K.; Kingston, J. F.; Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 2451.

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(10) Wenzel, T. J.; Sievers, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 382. Offermann, W.; Mannschreck, A. *Tetrahedron Lett.* **1981**, *22*, 3227. Alkenylhydrogen chemical shifts of **1** with added Eu(tfc)$_3$ (0.33 equiv), Ag(fod) (0.75 equiv) δ = 5.96 [(+)-**1**], 5.98 [(−)-**1**] ppm; with added Yb(tfc)$_3$ (0.33 equiv), Ag(fod) (0.75 equiv) δ = 5.96 [(+)-**1**], 6.06 [(−)-**1**] ppm.

(11) We suggest the use of Cp* as a short notation for *chiral* cyclopentadienyl, in accord with a well-established practice in organic chemistry. The description of pentamethylcyclopentadienyl by this abbreviation would have to be replaced by another, perhaps Cp′: see Schock, L. E.; Brock, C. P.; Marks, T. J. *Organometallics* **1987**, *6*, 232.

(12) The potential of this complex in enantioselective cobalt-mediated [2 + 2 +2]cycloadditions[13] is under investigation.

(13) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539.

(14) Crystal size 0.12 × 0.1 × 0.08 mm, monoclinic Laue symmetry, 2θ scan range 3–23°, *a* = 13.630 (6) Å, *b* = 14.593 (3) Å, *c* = 20.985 (9) Å, α = γ = 90°, β = 105.35 (3)°, *V* = 4024.1 Å^3, space group $P2_1$, *Z* = 4, D_{calcd} = 1.207 g cm^{-3}, μ = 4.13 cm^{-1}, reflections collected at room temperature, 6804, of which 5059 were taken as observed [$F_0 \geq 4.5\sigma(F)$], with no absorption correction. One phenyl ring of one independent molecule appeared disordered (C68 to C73 and C62′ to C73′); these atoms were included with site occupation factors (0.75 and 0.25, respectively). All phenyl rings were treated as rigid groups (C–C distance 1.396 Å, C–C–C angle 120°, C–H distance 0.96 Å, C–C–H angle 120°) as were the hydrogen atoms attached to carbon (C–H distance 0.96 Å, H–C–H and C–C–H angle 109.5°). All hydrogen atoms were given the 1.2-fold isotope U of the corresponding C atom. With anisotropic temperature factors given only to titanium and chlorine, the last model converged with 398 parameters at R = 0.099, R_w = 0.097, $w^{-1} = \sigma^2(F) + 5.10^{-4}F^2$.

The ready availability of enantiomerically pure **1** and its analogues should open up the exploration of other cyclopentadienylmetal-catalyzed enantioselective transformations.

Acknowledgment. This work was supported by NIH-GM 22479. R.L.H. was the recipient of a University of California Reagents' Fellowship (1982-1984). M.E.W. was an Exxon Research and Engineering Company and NIH postdoctoral fellow (NRSA GM 11105; 10.1.-12.11.1986). K.P.C.V. was a Miller Research Professor in residence (1985-1986). We thank Dr. A. Mori for carrying out the kinetic experiments.

Supplementary Material Available: A listing of positional and thermal parameters, and tables of bond lengths and angles for (+)-**2**, the dicamphorsulfonate of (1*S*,2*S*,4*S*,5*S*)-2,5-diphenylcyclohexane-1,4-diol, and (±)-Cp*CpTiCl$_2$, including SHELXTL renditions of the structures of the latter two compounds (16 pages); tables of observed and calculated structure factors for the three previously listed compounds (34 pages). Ordering information is given on any current masthead page.

(15) This picture presupposes that the stereochemistry of hydrogenation is set at this stage, an assumption which may not be valid: Halpern, J. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, Fl, 1985; Vol. 5, p 41. Indeed, the mechanism of this process has not been established. See, also: Lehmkuhl, H.; Tsien, Y.-L.; Janssen, E.; Mynott, R. *Chem. Ber.* **1983**, *116*, 2426.

(16) An X-ray structural analysis of this compound (in the racemic series) reveals the openness of one of the metal faces to a nonstereodifferentiating substrate approach (see Supplementary Material).

Evidence in Favor of an Organoiron-Mediated Pathway for Lipoxygenation of Fatty Acids by Soybean Lipoxygenase

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Received May 26, 1987

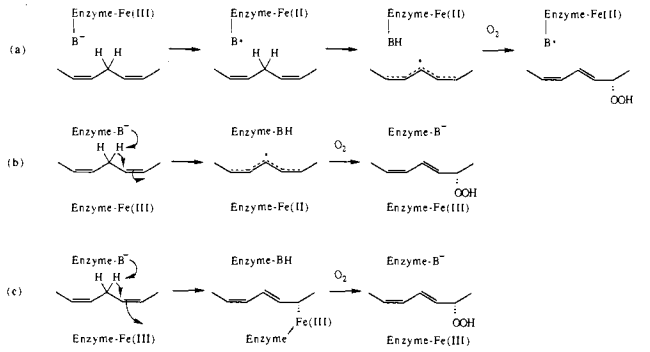
The enzymatic lipoxygenation of polyunsaturated fatty acids is of interest both mechanistically and because of its fundamental role in the biosynthesis of physiologically important compounds such as prostaglandins and leukotrienes.[1] A still unresolved mechanistic question is whether lipoxygenation proceeds via free-radical or organoiron intermediates formed during rate-limiting C-H bond cleavage.[2] Free carbon radicals might reasonably arise by processes (**a**) or (**b**) in Scheme I. In the case of (**a**), the reactive high-spin Fe(III) form of the enzyme activates itself by electron transfer to form an H atom abstracting group, whereas in the case of (**b**) a proton acceptor and the enzyme-bound Fe(III) participate in a concerted proton-electron-transfer reaction with substrate. The alternative organoiron pathway involves concerted deprotonation and electrophilic addition of Fe(III) to carbon giving an organoiron intermediate (coordinated to enzyme) from which product can be formed by σ bond insertion of dioxygen as depicted in (**c**). Described herein are three lines of evidence favoring process (**c**) for soybean lipoxygenase (SBLO).

The first argument is based on the assessment of the self-inactivation of SBLO during fatty acid oxidation as a function of substrate structure and reaction conditions by using the total turnover number (TTN) for lipoxygenation, i.e., the maximum number of molecules of lipoxygenation product produced per molecule of enzyme, as a measure of the frequency of self-inactivation during lipoxygenation. The enzyme utilized in these and all other experiments described herein was Sigma Co. type I SBLO further purified by DEAE-Sephadex column chromatography.[3]

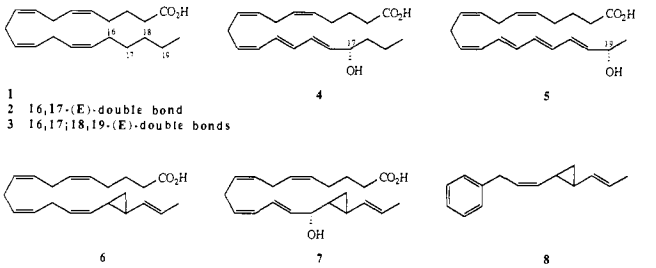
(1) For a recent review, see: Corey, E. J. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, K. B., Eds.; VCH Publishers: 1986; pp 1-12.

(2) See, for example; Corey, E. J.; d'Alarcao, M.; Matsuda, S. P. T. *Tetrahedron Lett.* **1986**, *27*, 3585-3588.

Scheme I



Three substrates were selected to probe the issue of radical vs organoiron intermediates, arachidonic acid (**1**), 16,17-(*E*)-



dehydroarachidonic acid (**2**), and 16,17-(*E*);18,19-(*E*)-bisdehydroarachidonic acid (**3**). Dramatic effects of structure, O_2 pressure, and temperature on TTN values were observed. All enzymatic experiments were conducted in pH 9.2 0.2 M sodium borate buffer by using 0.04-10 nM purified SBLO with substrate at concentrations in the 4-20 μM range.

It was determined (at 23 °C in air) that substrate **2** was bound more tightly but oxidized more slowly (K_m 5.7 μM, V_{max} 2700 min^{-1}) than arachidonate (**1**, K_m 13.3 μM, V_{max} 11 000 min^{-1}).[4] This result runs counter to expectations based on a free-radical intermediate (paths (**a**) or (**b**)) that V_{max} for **2** should exceed that for **1** because of the considerably lower C_{13}-H bond dissociation energy (ca. 10-14 kcal/mol).[4] Values for TTN of **1** and **2**, which were found to be 50 000 and 2200 (air, 23 °C), respectively, also do not accord with the idea of a free-radical intermediate which occasionally causes enzymic inactivation by attack on the enzyme in competition with oxygenation.[5] Clearly the more stabilized radical formed by processes (**a**) or (**b**) operating on **2** as compared with **1** should produce less inactivation of SBLO rather than more. On the other hand, the organoiron intermediate from **2** should homolyze more readily than that from **1** and lead to more frequent deactivation of SBLO. Thus process (**c**) is consistent with these experimental observations. Further, as expected for process (**c**), in which capture of the organoiron intermediate ought to be favored by increasing O_2 pressure, the TTN for arachidonate can be increased to 185 000 at 10 atm of O_2 and further to 340 000 at 50 atm of O_2 (all at 23 °C). Similarly, TTN values for **2** increase from 500 at 0.02 atm of O_2 to 3500 at 1 atm of O_2 and further to 12 800 at 50 atm of O_2 (all at 23 °C).[6] Values of TTN

(3) Axelrod, B.; Cheesbrough, T. M.; Laakso, S. *Methods Enzymol.* **1981**, *71*, 441-451.

(4) Reaction rates were measured by ultraviolet absorption and values of K_m and V_{max} were determined by Lineweaver-Burk analysis.

(5) There is much evidence[1] that free radicals formed from substrate can effectively inactivate SBLO. The values of TTN measured in this work were generally unaffected by carrying out the lipoxygenation in the presence of sodium borohydride which serves to reduce immediately the product hydroperoxide to the corresponding alcohol. This fact argues against enzyme inactivation by alkoxy radicals derived from LO product.

(6) Incubation experiments performed at pressures of O_2 above 1 atm were carried out in a Teflon vessel within a Parr stainless steel autoclave. Reaction was initiated under pressure by magnetically lowering a small vial containing substrate into the oxygenated solution of SBLO. Maximum conversion of substrate to product generally occurred in less than 60 min. Concentrations of SBLO were 0.04-1.0 nM. Control experiments showed no measurable oxidation in the absence of enzyme. At low O_2 pressures (0.02 atm) reaction was initiated by adding a trace amount of 15-HPETE.

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