$[\alpha]^{23}_D$ +4.94° (neat), suggesting ee ≥99.6% for the borohydride.

Generation of Optically Active Monoalkylboranes from the Corresponding Borohydrides. The following procedure for the preparation of essentially optically pure monosiamylborane dimer is representative. A 50-mL centrifuge vial with a rubber septum and a magnetic stirring bar was charged with a 0.5 M EE solution of lithium (2*S*)-3-methyl-2-butylborohydride (20 mL, 10 mmol) and cooled to 0 °C. A 3.0 M solution of HCl in EE (3.3 mL, ~10 mmol) was added slowly with vigorous stirring. Hydrogen gas evolved with the concurrent precipitation of lithium chloride. The reaction mixture was then centrifuged, and the clear supernatant solution (21 mL) containing the free (2*S*)-3-methyl-2-butylborane was transferred to another vial and estimated by hydrolysis: 85% yield; ^{11}B NMR δ +23.8 (d, J_{BH} = 131 Hz).

The monosiamylborane (8 mmol) in EE was reacted with 4 mmol of TMED at 0 °C with stirring. The EE was evaporated and the bis-adduct was washed with cold (0 °C) *n*-pentane (2 × 3 mL) and dried at 25 °C under reduced pressure (12 mmHg): 1.07 g (94% yield); mp 46-48 °C; ^{11}B NMR δ -0.5 (t, J_{BH} = 90 Hz); $[\alpha]^{23}_D$ +26.87 ± 0.05° (*c* 4, THF). Oxidation of the TMED adduct gave (2*S*)-(+)-3-methyl-2-butanol, which exhibited $[\alpha]^{23}_D$ +4.94° (neat), suggesting ee ≥99.6% for the TMED adduct.

Application of Lithium Monoisopinocampheylborohydride. Asymmetric Hydroboration of 1-Methylcyclopentene. Free monoisopinocampheylborane (25 mmol) was generated from lithium monoisopinocampheylborohydride (25 mmol) by treating it with HCl (25 mmol) in EE at 0 °C. Hydroboration of 1-methylcyclopentene (25 mmol) was carried out at -35 °C, using this reagent, as recommended in the literature.[8] Optically pure isopinocampheyl-(1*S*,2*S*)-*trans*-(2-methylcyclopentyl)borane was isolated in 60% yield. This dialkylborane was reacted with acetaldehyde to remove the isopinocampheyl group. The (1*S*,2*S*)-(+)-*trans*-(2-methylcyclopentyl)boronic acid, thus obtained on oxidation, afforded (1*S*,2*S*)-(+)-*trans*-2-methylcyclopentanol, which exhibited $[\alpha]^{23}_D$ +46.8° (*c* 1, MeOH), ee >99.9%.

Application of Lithium Diisopinocampheylborohydride. Asymmetric Hydroboration of *cis*-2-Butene. Lithium diisopinocampheylborohydride (30 mmol) and (+)-α-pinene (ee 92%, 9 mmol) in THF was cooled to 0 °C. Free diisopinocampheylborane was generated by adding methyl iodide (40 mmol) with stirring. The resulting slurry was cooled to -25 °C and utilized for the hydroboration of *cis*-2-butene (30 mmol) according to the literature procedure.[18] The reaction mixture was warmed to 25 °C, washed with water (2 × 10 mL) to remove lithium iodide, and then oxidized. Distillation provided (2*R*)-(-)-2-butanol in 65% yield, which exhibited α^{23}_D -10.368° (neat, *l* 1.0), ee ≥97%.

Acknowledgment. We thank the National Science Foundation for support provided by Grant CHE 79-18881.

Enantiospecific and Stereospecific Synthesis of Lipoxin A. Stereochemical Assignment of the Natural Lipoxin A and Its Possible Biosynthesis

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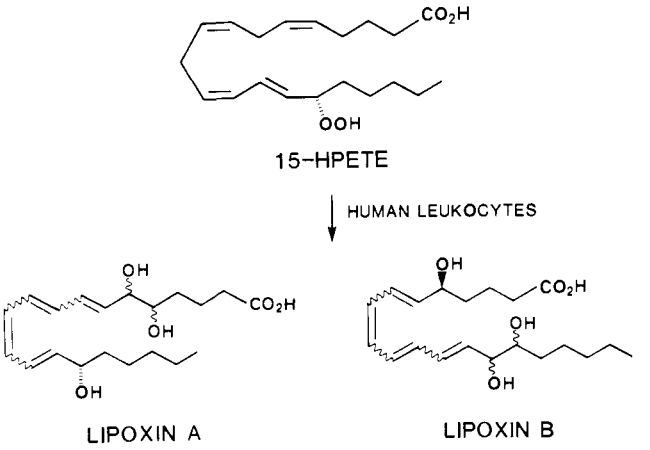
Abstract: Both chemical and enzymatic steps were employed to convert leukotriene A_4 and its unnatural epoxide isomers into four diastereomeric 5(*S*),6(*S*),15(*S*)-trihydroxy-7,9,13-*trans*-11-*cis*-eicosatetraenoic acids, possible structures for lipoxin A. These compounds were correlated with trihydroxy tetraene eicosatetraenoic acids derived from tetraene epoxide **3**, and the relative stereochemistries of the 5 and 6 positions were assigned. These assignments were confirmed by total synthesis of two diastereomers of lipoxin A. One of these isomers, 5(*S*),6(*S*),15(*S*)-trihydroxy-7-9,13-*trans*-11-*cis*-eicosatetraenoic acid (**1b**), corresponded to lipoxin A derived from natural sources. The structure and possible biosyntheses of lipoxin A are proposed.

In the spring of 1984, Samuelsson announced the isolation of a new class of metabolites of arachidonic acid and coined the names Lipoxin A and Lipoxin B.[1] The lipoxins represent the first natural products containing a fully conjugated tetraene derived from arachidonic acid via 15-HPETE (HP = hydroperoxy) (Scheme I). These novel trihydroxy tetraene eicosanoids possess intriguing biological properties. Samuelsson has proposed a gross chemical structure for the lipoxins, but the relative stereochemistry of the hydroxyl groups and double bond geometry remain unknown.

We have initiated and completed a program to chemically and enzymatically synthesize various lipoxin A isomers with two goals in mind. Firstly, since only minute quantities of lipoxins are available from natural sources, it was our intent to prepare sufficient amounts to allow more extensive evaluation of their biological properties. Secondly, by comparing synthetic samples of unambiguous stereochemical origin to the natural product, we could assign the absolute configurations of the hydroxyl groups and the geometry of the double bonds. With this stereochemical information in hand, we could propose biosynthetic routes which account for the formation of lipoxins.

Scheme I. Formation of Lipoxins A and B

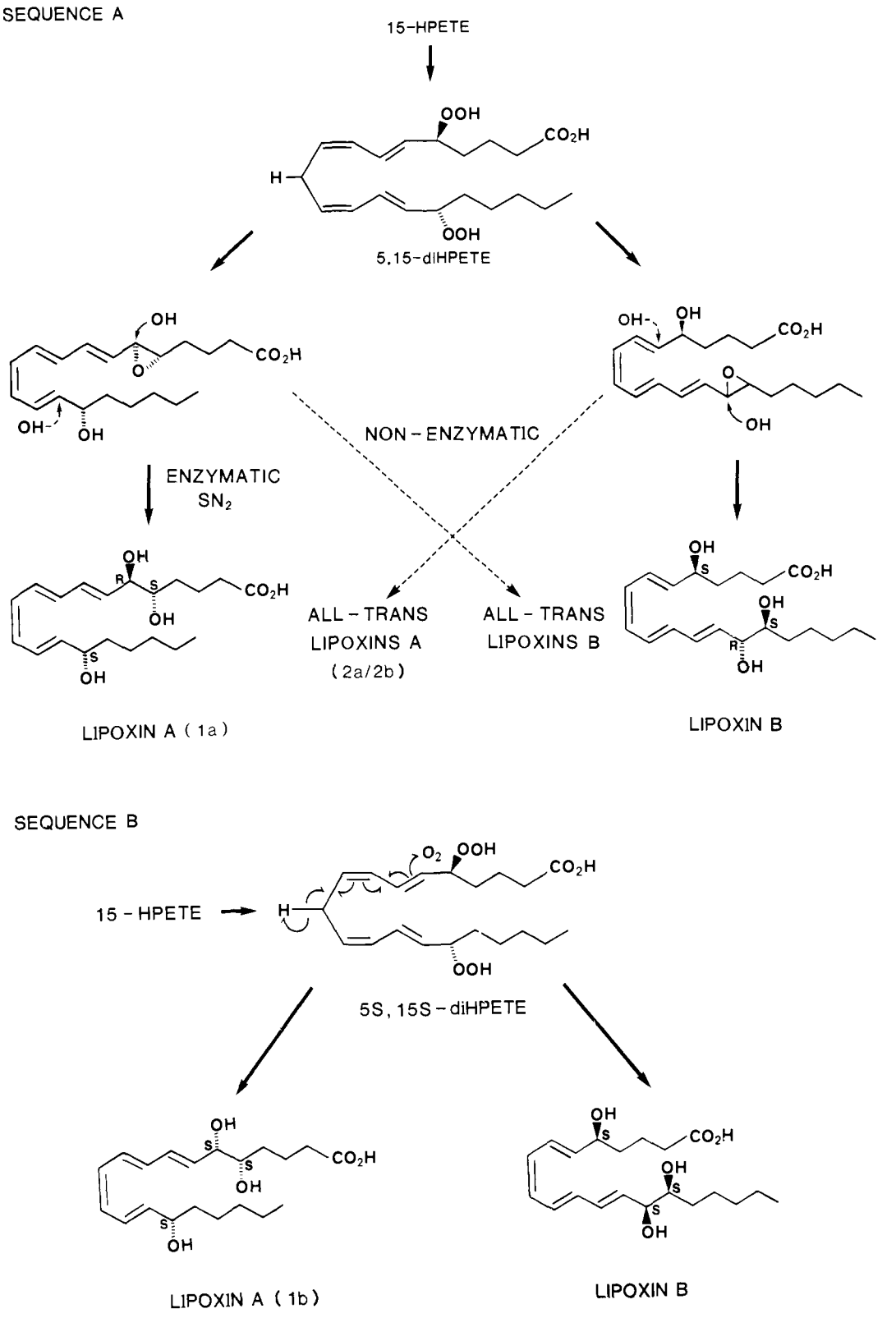


Upon analysis of the reported data and consideration of known polyoxygenated products of arachidonic acid, and in an effort to define the biochemical origins of lipoxins A and B, we considered several biosynthetic routes (Scheme II). Sequence A depicts the

(1) (a) Serhan, C. N.; Hamberg, M.; Samuelsson, B. *Biochem. Biophys. Res. Commun.* **1984**, *118*, 943. (b) Serhan, C. N., Prostaglandins and Leukotrienes '84, George Washington University, 1984, Abstr. No. 31.

0002-7863/85/1507-0464$01.50/0

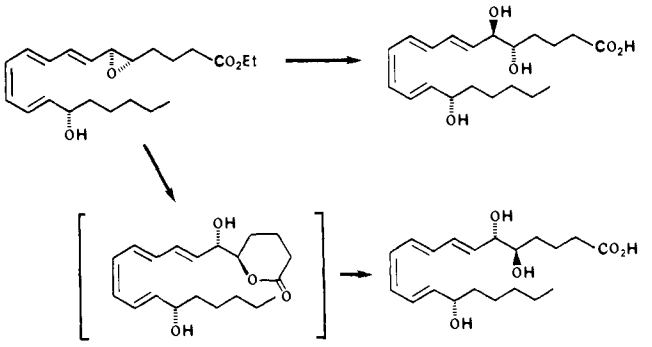
Scheme II. Possible Biosynthetic Routes to Lipoxins A and B



successive enzymatic oxidations at C15 and C5 of arachidonic acid to yield the known[2] 5(*S*),15(*S*)-(diHPETE) which, by analogy to the formation of leukotriene A_4 (LTA_4), could undergo a stereospecific enzymatic dehydration to produce a 5(*S*),6(*S*) epoxide with concomitant formation of a tetraene of 7-*trans*,9-*trans*,11-*cis*,13-*trans* geometry. This epoxide could be expected to undergo further transformations to produce lipoxins. An enzymatic hydrolysis of the epoxide at C6 would lead to lipoxin A, **1a**, while nonenzymatic homoconjugate addition of water at C14 would produce lipoxin B. Formation of lipoxin A (solid arrows), as shown, would leave the tetraene geometry intact, and the stereochemistry at C6 would be *R*, assuming an S_N2 opening of the epoxide at the more electrophilic C6. Nonenzymatic hydrolysis of the tetraene epoxide (broken arrows) would form the all-trans tetraene and a diastereomeric mixture of lipoxins B epimeric at

(2) Maas, R. L.; Turk, J.; Oates, J. A.; Brash, A. *J. Biol. Chem.* **1982**, *257*, 7056–7067.

Scheme III. Hydroxide Opening of Tetraene Epoxide 3



C14 by analogy to the nonenzymatic hydrolysis of LTA_4. The same cascade would occur to form the 14(*S*),15(*S*) tetraene epoxide, and similar metabolism would ensue. The nonenzymatic homoconjugate addition of water in this case would yield two all-trans isomers of lipoxin A (**2a** and **2b**).

An alternative biosynthetic route is postulated in sequence B (Scheme II) in which 5(*S*),15(*S*)-(diHPETE) is also formed as a common intermediate. However, a third lipoxygenation was then envisaged. This would entail the formation of a carbon-centered radical at C10 (as in the formation of 8- or 12-HPETE),[3] followed by vinylogous trapping of molecular oxygen at C6 to give, after reduction of the hydroperoxide(s), lipoxin A or, at C14, to give lipoxin B. The stereochemistry at C6 in lipoxin A or C14 in lipoxin B could be of the *R* or *S* configuration. The tetraene geometry would be as shown 7-*trans*,9-trans, 11-*cis*,13-*trans* for lipoxin A.

Three separate synthetic approaches to the synthesis of lipoxin A were realized. The first synthesis involved the ring opening of tetraene epoxide **3** (Scheme III) to give lipoxin A isomers.[4] A second approach made use of LTA_4 as a starting material, and this was converted in three steps (two chemical, one enzymatic) to lipoxin A isomers. Finally, total syntheses of two lipoxin A isomers were designed whereby the absolute stereochemistry of hydroxyl groups was rigorously derived from 2-deoxy-D-ribose and L-xylose.

Treatment of epoxide **3** with KOH (0.8 N) in Me_2SO (15/85) at 70 °C for 1 h afforded two diastereomeric triols.[4] The 5-(*S*),6(*R*),15(*S*) triol **1a** results from the S_N2 opening at C6, and the 5(*R*),6(*S*),15(*S*) triol **4** is produced by an internal displacement at C5 by carboxylate, forming an intermediate δ-lactone followed by saponification. Structural assignment to distinguish the two products was not possible at this stage.

The lack of regiochemical control in the epoxide opening of **3** prompted us to seek a method to achieve epoxide cleavage at C6 exclusively (the more electrophilic carbon) with the carboxylic acid blocked as its ester. The chemical literature documents the difficulty in the epoxide opening using oxygen nucleophiles.[5] In general, polar solvents and high temperatures are required. Heating **3** in the presence of excess sodium benzoate in anhydrous dimethyl sulfoxide at 100 °C gave no reaction. However, heating **5** in dimethylsulfoxide in the presence of 1.2 equiv of benzoic acid at 60 °C for 1 h produced two benzoates, **6a** and **6b**, epimeric at C6 in over 80% yield (Scheme IV).[6] Removal of the silyl protecting group and base hydrolysis produced trihydroxy acids **1a** and **1b** epimeric only at C6 (ratio ~3:1).

Although the epoxide opening occurs exclusively at C6, it is evident that two mechanisms are operative. One epimer is formed with retention (5(*S*),6(*S*)) at C6 and the second epimer is formed by inversion (5(*S*),6(*R*)) of that center. Again, assignment of which compound corresponds to which relative stereochemistry was not yet possible at this point.

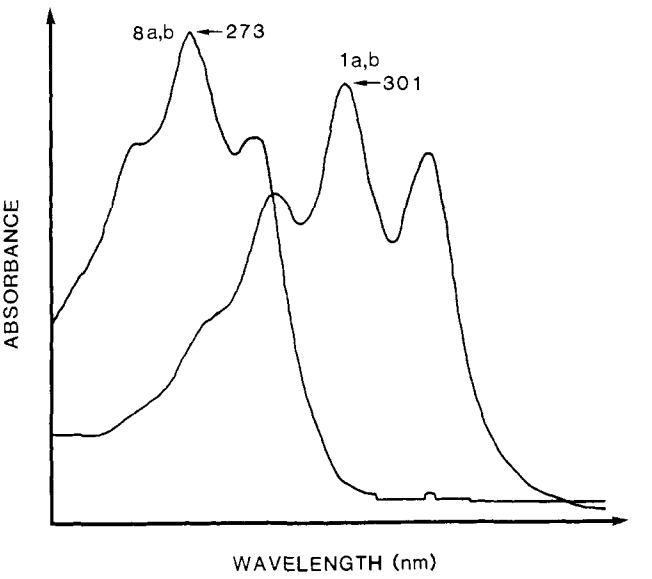
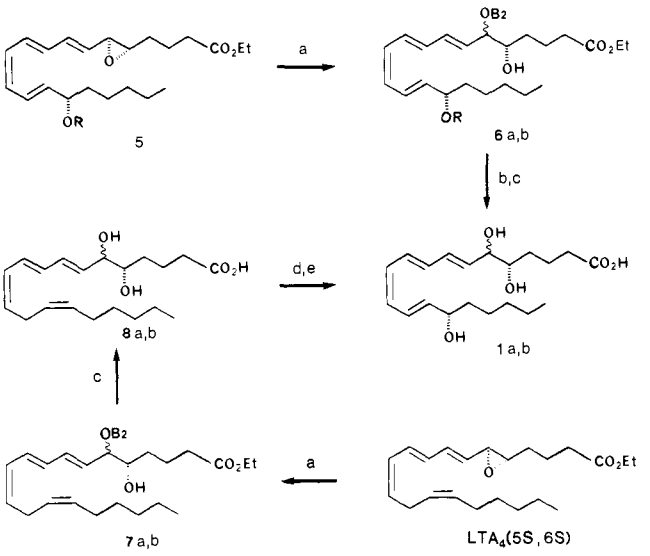


Figure 1. Enzymatic conversion of trienes **8a,b** to tetraenes **1a,b** (lipoxin A isomers).

Scheme IV. Conversion of Epoxy Tetraene and LTA_4 to Lipoxin A Isomers



R = t-BDPSi

a) HOBz / DMSO, 60°C 1 hr; b) nBu_4NF / THF;
c) 9:1 MeOH / 10 N NaOH, RT; d) 15-lipoxidase pH 9 borate buffer
e) $NaBH_4$

Conversion of LTA_4 to Lipoxin A Isomers. Relying on the availability at Merck of the Leukotriene A_4 (LTA_4) ethyl ester and its unnatural isomers,[7] a three-step synthesis of four lipoxin A isomers from the LTA_4 ethyl ester was achieved by (1) opening the epoxide using benzoic acid (Scheme IV), (2) hydrolysis of the benzoate esters to form diol acids **8a** and **8b** (epimeric at C6), and (3) enzymatic conversion of the diols **8a** and **8b** into lipoxin A hydroperoxides using commerically available lipoxidase,[8] and subsequent reduction afforded lipoxin A isomers **1a** and **1b**. This

(3) (a) Borgeat, P.; Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1976**, *251*, 7816–7820. (b) Shimizu, T.; Radmark, O.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 689.

(4) Adams, J.; Fitzsimmons, B. J.; Rokach, *J. Tetrahedron Lett.* **1984**, 4713.

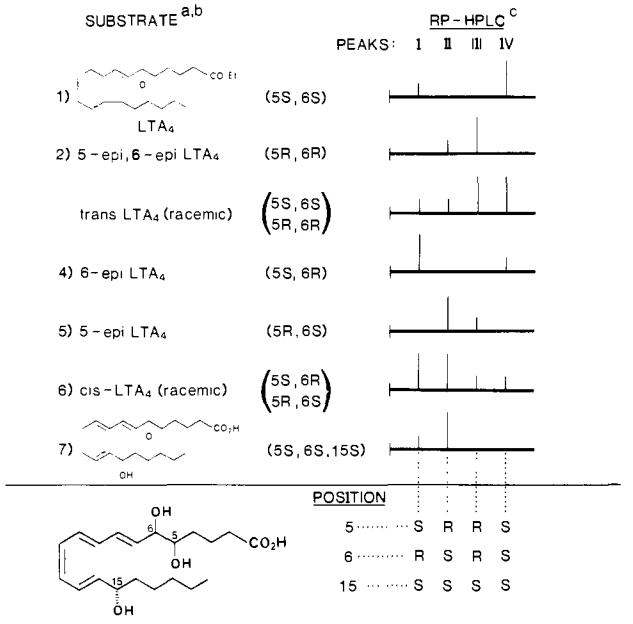
(5) For example, see: (a) Flaherty, B.; Overend, W. G.; Williams, N. R. *Chem. Commun.* **1966**, 434. (b) Berti, G.; Macchia, B.; Macchia, F. *Tetrahedron Lett.* **1965**, 3421.

(6) This reaction proceeds well in other solvents, i.e., acetonitrile, toluene, and 1,1 dichloroethane. The isomer ratio is 7:1 in toluene.

(7) (a) Rokach, J.; Zamboni, R.; Lau, C. K.; Guindon, Y. *Tetrahedron Lett.* **1981**, 2759. (b) Rokach, J.; Zamboni, R.; Lau, C. K.; Guindon, Y. *Tetrahedron Lett.* **1981**, 2763.

(8) Purchased from Sigma Chemical Co.

Table I. Stereochemical Correlation of Vicinal Diols at C_5 and C_6



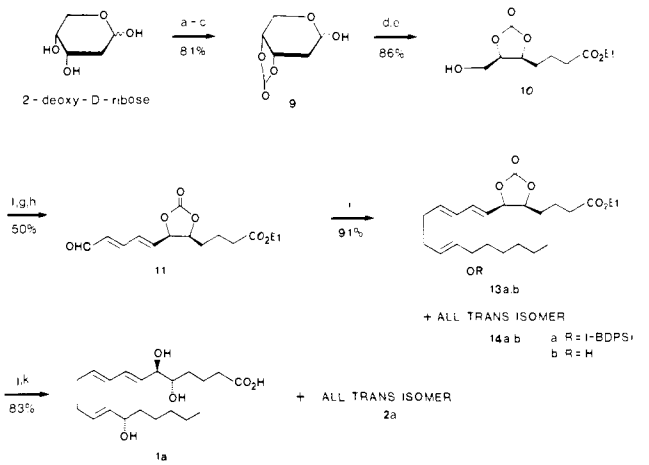
a) Substrates 1-6 are converted to Lipoxin A isomers according to Scheme IV
b) Substrate 7 is converted to Lipoxin A isomer according to Scheme III
c) Retention time shown is in arbitrary units: Solvent - 60/40 MeOH-H_2O, 0.1% HOAc. Waters μbondapak C_{18} column.

approach led to the same lipoxin A isomers **1a** and **1b** (5(*S*),6(*R*) and 5(*S*),6(*S*)) as were obtained from the opening of epoxide **5** (Scheme IV, 70% overall yield from LTA_4, Figure 1).

The assignment of stereochemistry remained a thorny problem until a correlation scheme was devised using various synthetic isomers of LTA_4. Conversion of these isomers into their respective trihydroxy tetraenes, by the method described above, and correlation of the RP-HPLC analysis of these products and those obtained from treatment of epoxide **3** with hydroxide were used to determine the relative and absolute stereochemistries of the vicinal diols at C5 and C6, as shown in Table I. Beginning with natural LTA_4 (5(*S*),6(*S*)), conversion to lipoxin A isomers **1a** and **1b** gave a 1:3 ratio of epimers at C6 with the C5 alcohol bearing the *S* configuration. The same operations performed on 5-epi,6-epi-LTA_4 (5(*R*),6(*R*)) gave rise to the same ratio of 5(*R*) diastereomers, and of course racemic LTA_4 gave all four diastereomers. Turning to the cis epoxide series, the only change noted was the inversion of the ratio of epimers at C6 (~3:1) for the corresponding pairs of diastereomers. At this point the stereochemistry is unabmiguously established for the C5 and C15 alcohols, derived from LTA_4's. When trihydroxy acids **1a** and **4** obtained from the hydroxide opening of **3** are coinjected, the minor isomer corresponds with peak 1 in the table and the major isomer coincides with peak II. Since the relative stereochemistry, but not the absolute one, is known (5(*S*),6(*R*) and 5(*R*),6(*S*) for **1a** and **4**, (respectively) to have come from inversion of only one center of the epoxide (vide supra), identities can be matched based on the established stereochemistry at C5 of compounds derived from LTA_4 isomers. The minor isomer from the hydroxide opening of **3** is also the minor isomer (the inversion product) derived from LTA_4 as shown in Scheme IV. Thus, the isomer corresponding to peak I has the 5(*S*),6(*R*),15(*S*) configuration. Conversely, the minor isomer derived from 5-epi,6-epi-LTA_4 with inversion at C6 is the same product as the major isomer derived from the hydroxide opening of 3 (inverting C5), yielding the 5(*R*),6(*S*),15(*S*) diastereomer. The identities of the compounds corresponding to peaks I and II are thus established. The remaining peaks (III and IV) were assigned by default since peaks I and IV and peaks II and III, respectively, are representative of epimers at C6.

Considering possible biosynthetic pathways that account for the formation of lipoxins, it is unlkely that a 5(*R*) isomer exists in nature, based on what is known about the lipoxygenase and other enzymes in arachidonic acid metabolism. It is, therefore, tempting to speculate that the hydroxyl groups in lipoxin A are of absolute stereochemistry, 5(*S*),6(*S*),15(*S*) or 5(*S*),6(*R*),15(*S*). Although we have not formally addressed the rationale for the tetraene geometry in this paper, the 7-*trans*,9-trans,11-*cis*,13-*trans* geometry is presumed by examining possible biosynthetic pathways.[4]

Scheme V. Synthesis of the 5(*S*),6(*R*),15(*S*) Isomers of Lipoxin A, 1a, and 2a



a) MeOH/HCl, b)  , acetone ⊿, c) aq. HCl/dioxane, ⊿,
d) $(C_6H_5)_3P$=CO_2Et, THF, RT, e) H_2/Pd·C/EtOH, f) $(COCl)_2$/DMSO/Et_3N/THF, -60°C, g) $(C_6H_5)_3P$=CHO; h) cat I_2/CH_2Cl_2 hv;
i) $(C_6H_5)_3P$=C_5H_{11}, THF, -100°C, 5 min then HMPA warm -40°C, 1 hr.
12 OR
j) excess nBu_4NF/THF/HOAc 1 eq.; k) 9:1 MeOH/10 N NaOH, RT

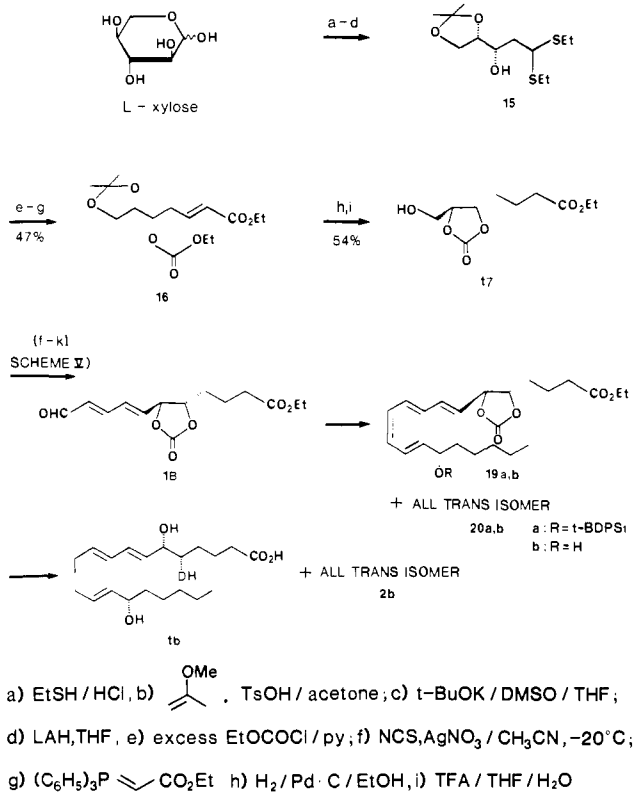
Total Synthesis of Lipoxin A Isomers. In order to obtain sufficient quantities of lipoxin A and its isomers for identification and biochemical evaluation, synthetic schemes were devised which would lead unambiguously to four possible structures of lipoxin A. Since these routes utilize carbohydrate precursors, the absolute and relative stereochemistries of the products are unambiguously predetermined. The totally synthetic compounds also serve to confirm our assignments of structures in our correlation of lipoxin A isomers (Table I).

The synthesis of the 5(*S*),6(*R*),15(*S*) isomers of lipoxin A utilized 2-deoxy-D-ribose as the starting material (Scheme V). Glycosidation of the sugar followed by formation of the 3,4 cyclic carbonate and then hydrolysis of the glycoside yielded the intermediate **9** in which the future 5,6-diol is protected with a single protecting group and the termini are distinguishable. Condensation of the hydroxyaldehyde **9** with ethyl (triphenylphosphoranylidene)acetate and hydrogenation of the olefin generated afforded the alcohol **10**. Oxidation of the alcohol **10**, condensation of the aldehyde produced with 4-(triphenylphosphoranylidene)but-2-enal,[9] and isomerization provided the diene aldehyde **11** required for the formation of the final carbon–carbon double bond. Condensation of the aldehyde **11** with the ylide **12** yielded the two 5(*S*),6(*R*),15(*S*) isomers **13a** and **14a** in a 1:1 ratio. Finally, removal of the silyl protecting group, separation of the 11-*cis* and the 11-*trans* isomers and basic hydrolysis afforded two 5(*S*),6(*R*) isomers of lipoxin A, **1a** and **2a**.

L-Xylose was chosen as the starting material for the synthesis of the 5(*S*),6(*S*),15(*S*) isomers of lipoxin A. Since it was necessary to excise the C2 hydroxyl group and to protect the C3 and C4 hydroxyl groups, a simple and efficient method to prepare the 5(*S*) diastereomer of the alcohol **10** was devised. Pivotal to this scheme was the formation of the cyclic carbonate from an acyclic car-

(9) Ernest, I.; Main, A. J.; Menasse, R. *Tetrahedron Lett.* **1982**, *23*, 167–170.

Scheme VI. Synthesis of the 5(S),6(S),15(S) Isomers of Lipoxin A, 1b, and 2b



bonate upon hydrolysis of an acetonide. Using the method Wong and Gray,[10] L-xylose was converted into the alcohol **15** in four steps (Scheme VI). Protection of the alcohol **15** as its ethyl carbonate derivative, hydrolysis of the thioacetal, and condensation of the resulting aldehyde with ethyl (triphenylphosphoranylidene)acetate gave the acyclic carbonate **16**. Hydrogenation gave the corresponding saturated compound. Hydrolysis of the acetonide occurred with concomitant formation of the cyclic carbonate as expected, yielding the alcohol **17**. The alcohol **17** is diastereomeric with the alcohol **10** and was converted to the 5(*S*),6(*S*),15(*S*) isomers of lipoxin A, **1b** and **2b**, using the same procedure as for the preparation of the 5(*S*),6(*R*) isomers of lipoxin A from the alcohol **10**.

The two 11-cis isomers of lipoxin A were identical by HPLC and 250-MHz ^{1}H NMR with those prepared from LTA_4 by the chemical/enzymatic route described previously. This confirmed the original assignment of the absolute stereochemistry of these compounds.

What remained at this point was to determine which of the isomers prepared was lipoxin A. To this end lipoxins A and B were prepared biologically from human leukocytes as described by Samuelsson.[1,11] The natural material thus obtained coeluted on reverse-phase liquid chromatography, both as its free acid (60/40 MeOH–H_2O, 0.1% HOAc) and as its methyl ester (70/30 MeOH–H_2O) with the 5(*S*),6(*S*),15(*S*)-11-*cis* isomer **1b** and its methyl ester, respectively. *None* of the other diastereomers[12] or geometric isomers prepared coeluted with lipoxin A as their free acids or methyl esters. Therefore, lipoxin A is proposed to possess the structure **1b**.

In summary, six isomers of lipoxin A were prepared in chemically and optically pure form. One of these isomers, **1b**, corresponded to biologically prepared lipoxin A. Therefore, lipoxin A is proposed to be 5(*S*),6(*S*),15(*S*)-trihydroxy-11-cis-7,9,13-trans-eicosatetraenoic acid, **1b**. Further studies to elucidate the biosynthetic pathway to the lipoxins are currently under way.

Experimental Section

3,4-*O*-Carbonyl-2-deoxy-D-*erythro*-pentopyranose (9). To methanol (200 mL) at 0 °C was added with stirring acetyl chloride (4 mL). The resulting solution was allowed to warm to room temperature and then 2-deoxy-D-ribose (20.01 g, 149 mmol) was added. The resulting mixture was stirred at room temperature for 18 h and then neutralized by the addition of silver(I) carbonate. The resulting suspension was filtered, and the solvent was removed at reduced pressure to yield the syrupy methyl pyranosides.

To a solution of the syrup from above in 2-butanone (200 mL) was added 1,1′-carbonyldiimidazole (29 g, 179 mmol), and the resulting mixture was heated at reflux for 12 h. Removal of the solvent at reduced pressure and chromatography of the residue (Waters, Prep 500, 50% ethyl acetate in hexane) gave 21.93 g (84%) of the carbonate pyranoside.

To a solution of the above pyranoside (21.9 g, 126 mmol) in dioxane (150 mL) and water (50 mL) was added 12 N hydrochloric acid (10 mL). The resulting solution was heated at reflux until TLC indicated complete consumption of the starting material (1–3 h). The mixture was then cooled to room temperature and neutralized by the addition of a small excess of silver(I) carbonate. The resulting suspension was filtered and the filtrate was concentrated at reduced pressure to approximately 50 mL. This solution was diluted with saturated aqueous sodium chloride (50 mL), and sufficient sodium chloride was added to saturate the resulting solution. The mixture was extracted with 3:1 ethyl acetate/THF (4 × 150 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed at reduced pressure to yield the pyranose **9** (17.40 g, 86%) as a white solid: mp 117–118 °C (acetone–hexane); IR ($CHCl_3$) 3600, 3350, 1795, 1375, 1175, 1040 cm^{-1}; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.86 (1 H, ddd, $J_{2,2'}$ = 15, $J_{1,2}$ = 7.5, $J_{2,3}$ = 3.3 Hz, H-2), 2.39 (1 H, ddd, $J_{2,2'}$ = 15, $J_{1,2'}$ = 6.8, $J_{2',3}$ = 3.75 Hz, H-2′), 3.69 (1 H, d, $J_{5,5'}$ = 15 Hz, H-5), 4.10 (1 H, dd, $J_{5,5'}$ = 15, $J_{4,5'}$ = 1.7 Hz, H-5′), 4.86 (1 H, brd, $J_{3,4}$ = 9.4 Hz, H-4), 5.11 (1 H, ddd, H-3), 5.24 (1 H, dd, H-1). Anal. Calcd for $C_6H_8O_5$: C, 45.01; H, 5.09. Found: C, 44.98; H, 4.95.

Ethyl 4-(4(*S*)-(hydroxymethyl)-1,3-dioxolan-2-on-5(*S*)-yl)butanoate (17). To a solution of the acyclic carbonate, from hydrogenation of **16** (569 mg, 1.91 mmol), in THF (25 mL) at 0 °C were added water (2.5 mL) and trifluoroacetic acid (2.5 mL) sequentially. The resulting mixture was stirred at room temperature overnight. The mixture was then neutralized with aqueous sodium bicarbonate and diluted with water (50 mL), and the resulting mixture was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed at reduced pressure. Flash chromatography of the residue (80% ethyl acetate in hexane) gave the cyclic carbonate **17** (339 mg, 81%): $[\alpha]^{22}_D$ −55.0 (*c* 1.1, acetone); IR (neat) 3490, 1795, 1730, 1190, 1170, 775 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.24 (3 H, t, *J* = 8 Hz), 1.76 (4 H, m), 2.36 (2 H, brt), 3.67 (1 H, brd, *J* = 12.5 Hz), 3.91 (1 H, brd, *J* = 12.5 Hz), 4.11 (2 H, q, *J* = 8 Hz), 4.33 (1 H, m), 4.62 (1 H, brm); ^{13}C NMR (acetone-d_6) δ 14.65 ($CH_2CH_2CO_2$), 24.42 ($CH_2CH_2CH_2CO_2$), 34.02 ($CO_2CH_2CH_3$), 34.31 (CH_2CO_2), 60.75 (CO_2CH_2), 61.81 (−CH_2OH), 78.62 (−$CHCH_2OH$), 82.60 (−$CHCH_2OH$), 155.25 (−$OC(O)O$−), 174.21 (−CO_2CH_2). HRMS Calcd for $C_{10}H_{16}O_6$: 233.1025. Found: 233.1040.

Preparation of the Carbonate Derivative of 5(*S*),6(*S*)-Lipoxin A Ethyl Ester 19b. To a solution of the phosphonium salt (168 mg, 0.233 mmol) in dry THF (5 mL) at −100 °C under argon was added a 1.5 M solution of *n*-butyllithium in hexanes (108 μL, 0.162 mmol) in one portion with stirring to generate the ylide **12**. After 1 min a solution of the aldehyde **18** (59 mg, 0.218 mmol) in THF (1.5 mL) was added. After a further 5 min at −100 °C HMPA (0.35 mL) was added and the resulting mixture warmed to −40 °C. After 1 h the reaction mixture was quenched by addition of 25% aqueous ammonium acetate (10 mL). The resulting mixture was diluted with ether (50 mL), and the organic layer was washed with 25% ammonium acetate (2 × 25 mL) and brine (1 × 25 mL) and dried ($MgSO_4$). Removal of the solvent at reduced pressure and flash chromatography of the residue (35% ethyl acetate in hexane) gave a 1:1 mixture of the tetraenes **19a** and **20a** (98 mg, 94%). Desilylation of a portion of the above mixture (25 mg, 0.04 mmol) gave after HPLC separation of the isomers pure 11-*cis*-**19b** (6 mg, 39%) and 11-*trans*-**20b** (6 mg, 39%) (total yield 78%). The 5(*S*),6(*R*) diastereomers **13b** and **14b** were prepared in a similar manner and in similar yields from the aldehyde **11**.

Data for **19b**: IR ($CHCl_3$) 3450, 1790, 1730, 1185, 780 cm^{-1}; UV (MeOH) λ_{max} 291, 304, 319 nm; ^{1}H NMR (400 MHZ, acetone-d_6) δ 0.87 (3 H, brt, *J* = 8 Hz), 1.19 (3 H, t, *J* = 7.6 Hz), 2.37 (2 H, t, *J* = 7.4 Hz), 4.07 (2 H, q, *J* = 7.6 Hz), 4.14 (1 H, brm), 4.49 (1 H, m), 4.91 (1 H, dd, *J* = *J*′ = 7.5 Hz), 5.86 (2 H, m), 6.07 (2 H, 2t), 6.33 (1 H,

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(11) Beginning with 2 L of human blood less than 1 μg of purified lipoxin A was obtained.

(12) Including 5(*R*) diastereomers described in Table I.

dd, J = 10, J' = 15 Hz), 6.63 (1 H, dd, J = 10, J' = 15 Hz), 6.78 (1 H, dd, J = 10, J' = 15 Hz), 6.94 (1 H, dd, J = 10, J' = 15 Hz).

Data for **20b**: IR identical with that of **19b** UV (MeOH) λ_{max} 292, 304, 319 nm; ^{1}H NMR (400 mHz, acetone-d_6) (the 0-4 ppm range of the spectrum was identical with that of **19b**) δ 4.11 (1 H, m), 4.49 (1 H, m), 4.91 (1 H, dd, $J = J'$ = 7.5 Hz), 5.84 (2 H, m), 6.21-6.64 (6 H, m).

The spectral characteristics of **13b** and **14b** were similar to the corresponding 5(*S*),6(*S*) diastereomer.

Conversion of LTA_4 to Lipoxin A Isomers 1a and 1b. The methyl ester of LTA_4 (20 mg, 0.06 mmol) was dissolved in 1,2-dichloroethane (or Me_2SO) (5 mL) containing benzoic acid (7.5 mg, 0.06 mmol). The reaction was heated for 30 min at 60 °C under an inert atmosphere. Removal of the solvent and silica gel chromatography (20% EtOAc/hexane) of the residue produced epimeric benzoates **7a,b** (23 mg, 86% yield). The benzoates **7a,b** were subjected to saponifying conditions (2.5 mL, 4:1 MeOH/2 N NaOH) for 30 min at room temperature to produce vicinal dioi acids **8a,b**. The reaction mixture was concentrated in vacuum to remove MeOH, and the remaining solution was diluted in pH 9 borate buffer (1 L). The lipoxidase enzyme (50 mg) was added, and the reaction occurred immediately as determined by monitoring an aliquot by UV spectroscopy (λ_{max} 273 nm → 301 nm). $NaBH_4$ (20 mg) was added to reduce the resulting hydroperoxides, and after stirring for 10 min at room temperature, the solution was acidified to pH 4-5 by addition of HCl. Extraction with Et_2O, drying (Na_2SO_4), addition of Et_3N, followed by evaporation to dryness produced lipoxin A isomers **1a,b** epimeric at C6 (19 mg, 84% yield). The two isomers were separated by reverse-phase HPLC (MeOH/H_2O/AcOH, 62:38:0.025) to afford 7.5 mg of the 5(*S*),6(*S*),15(*S*) isomer **1b** and 2.5 mg of the 5(*S*),6(*R*),15(*S*) isomer **1a**.

Data for lipoxin A (5(*S*),6(*S*),15(*S*) isomer **1b**) and 6-epi-lipoxin A (5(*S*),6(*R*),15(S) isomer **1a**): 5(*S*),6(*R*),15(*S*) isomer **1a**; ^{1}H NMR (250 MHz, 5% CD_3OD/D_2O) δ 0.8-0.9 (3 H, brt), 1.2-1.8 (14 H, complex m), 2.1-2.3 (2 H, brt, $J \approx$ 7.5 Hz), 3.6-3.7 (1 H, m), 4.05-4.15 (1 H, m), 4.15-4.25 (1 H, q, J = 6.7 Hz), 5.7-5.9 (2 H, six lines, 2 overlapping dd), 6.0-6.2 (2 H, five line m), 6.3-6.5 (2 H, complex m), 6.7-6.9 (2 H, complex m); 5(*S*),6(*S*),15(*S*) isomer **1b** (lipoxin A); ^{1}H NMR (250 MHz, 5% CD_3OD/D_2O) δ 0.8-0.9 (3 H, brt), 1.2-1.8 (14 H, complex m), 2.1-2.3 (2 H, complex m), 3.4-3.6 (1 H, m), 3.95-4.05 (1 H, t, J = 6.8 Hz), 4.1-4.2 (1 H,q, J = 7.1 Hz), 5.6-5.85 (2 H, seven line m), 5.9-6.1 (2 H, m), 6.2-6.45 (2 H, m), 6.6-6.8 (2 H, m); UV (MeOH) λ_{max} 287, 301, 316 nm; GC mass spectrum, *m/e* (tri-TMS methyl ester derivative) 582 M^+, 203, 100% peak cleavage of vicinal diol. The same result is obtained for 5(*S*),6(*R*),15(*S*) isomer **1a**.

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Supplementary Material Available: Experimental data of **10**, **11**, **15**, **16**, and **18** and ^{1}H NMR, mass, and RP-HPLC spectra of lipoxins A and B (7 pages). Ordering information given on any current masthead.

Unconventional Ionic Hydrogen Bonds. 1. $CH^{\delta+}\cdots X$. Complexes of Quaternary Ions with n- and π-Donors

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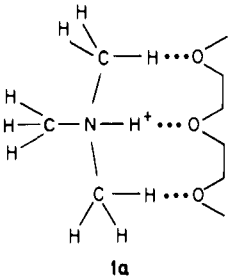
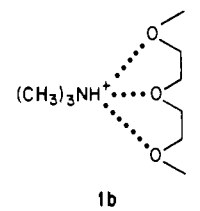
Abstract: $CH^{\delta+}\cdots X$ interaction energies are obtained from the clustering of quaternary onium ions with n-donor solvent molecules. The dissociation energies ($\Delta H°_D$) of Me_4N^+ clustered with the n-donors H_2O, MeOH, $MeNH_2$, and Me_3N and with the π-donors benzene and toluene range between 8 and 10 kcal mol^{-1}. With the weak, bulky n-donor MeCl the interaction is weaker (6.5 kcal mol^{-1}) while the more polar ligands Me_2CO and $MeCONMe_2$ attach strongly (14.6 and 18.0 kcal mol^{-1}, respectively) to Me_4N^+. Strong interactions, 20-23 kcal mol^{-1}, are also observed with polyethers and CH_3CO-gly-OCH_3, indicating polydentate complexing. The attachment energies of ligands to Et_4N^+ are smaller by 2 kcal mol^{-1} than those to Me_4N^+. Ab initio calculations show that in the $Me_4N^+\cdot H_2O$, MeOH, $MeNH_2$, and MeCl complexes the ligands attach electrostatically to a cavity created by protons of three CH_3 groups rather than hydrogen bonding to one proton or to one CH_3 group. Both experiment and theory indicate that a second solvent molecule (H_2O or CH_3OH) attaches preferentially to the first solvent molecule rather than to Me_4N^+.

Ionic hydrogen bonding between protonated and neutral n-donors has been investigated extensively by mass spectrometric methods.[1] These ionic hydrogen bonds range in strength up to 30 kcal mol^{-1} in $R_2OH^+\cdots OR_2$ and $R_2OH^+\cdots NR_3$ and 24 kcal mol^{-1} in $R_3NH^+\cdots NR_3$ type complexes.[2] In addition to such strong interactions, recent evidence[3] suggests that methyl hydrogens of alkylammonium ions may also interact significantly, through more weakly than conventional hydrogen bonds, with n-donors. Thus, the complexes of Me_3NH^+ with polyethers showed evidence for multiple ion-neutral interactions within the complex,[3] even though in Me_3NH^+ only one NH proton is available for hydrogen bonding. These results indicate that $-CH^{\delta+}\cdots O-$ interactions contribute ≈6 and 4 kcal mol^{-1} (for the first and the second such interaction) to the stability of **1**.



1a



1b

Other indirect evidence also suggests significant $CH^{\delta+}\cdots X$ interactions. For example, Grimsrud and Kebarle[4] have observed

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