was eluted with 4 mL of methanol. After evaporation of the methanol, 0.9 mg ($2.68 \times 10^{-3}$ mmol) of $LTB_4$ was obtained (95%): $[\alpha]^{20}_J$ = +12.8° (c 0.0009; $CCl_4$) (Lit.[3g] $[\alpha]^{25}_D$ = +12.6°. The physicochemical characteristics (MS, IR, $^1H$ NMR, UV) were identical to literature values. The biological activity was comparable (see ref 18) to that of $LTB_4$ synthesized by Rokach.

**Registry No.** 1, 71160-24-2; 2, 111137-93-0; 3, 90108-28-4; 5, 140175-54-8; 6, 115418-90-1; 7, 140175-56-0; 8, 137725-13-4; 9, 137725-14-5; 10, 91842-15-8; 11, 140175-57-1; 12, 136693-12-4; 13, 83058-42-8; 14, 10340-23-5; 15, 31823-43-5; 16, 129030-85-9; 17, 128962-09-4; 18, 129030-91-7; tMSiC≡CSiMt, 14630-40-1; 19, 1501-26-4; 20, 90132-06-2; 21, 140175-55-9; tMSiC≡CH, 1066-54-2.

# Analogues of Tri-*o*-thymotide (TOT) and Tri-*o*-carvacrotide (TOC) by Direct Bromination of TOT and TOC[1]

Lulu Xu and Philip M. Keehn*

*Department of Chemistry, Brandeis University, Waltham, Massachusetts 02254-9110*

Jallal M. Gnaim and Bernard S. Green

*Department of Pharmaceutical Chemistry, The School of Pharmacy, The Hebrew University, P.O. Box 12065, Jerusalem, 91120, Israel*

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Mono-, di-, tri-, tetra-, and pentabrominated tri-*o*-thymotide (TOT) analogues (3–7) and mono-, di-, tri-, and tetrabrominated tri-*o*-carvacrotide (TOC) analogues (9–12) were synthesized by direct bromination of TOT and TOC. Total yields of about 60% were realized from TOT or TOC. The degree of bromination of the methyl group depended upon the reaction temperature and ratio of TOT (TOC):NBS. Tribromo-TOT (5) was generated in the greatest yield using a 1:18 ratio of TOT:NBS. No bromination occured in the isopropyl group. Structure assignments were made for all new analogues. The conformational mobility of some of these analogues as well as the effect of solvents on the proton chemical shifts were studied by NMR techniques.

## Introduction

The recent commercial availability of *o*-thymotic acid[2] allows TOT to be prepared more readily and makes feasible its direct conversion into other analogues by functional group transformation. The placement of one or more halogen atoms onto the TOT framework (specifically into the isopropyl or methyl groups appended to the aromatic rings) would not only provide new halogenated TOT analogues, but would afford an opportunity to further prepare a large number of substituted analogues by nucleophilic displacement reactions. A study of the bromination of TOT (1) and TOC (2) is described in this paper.

## Results and Discussion

**Bromination Studies.** In refluxing $CCl_4$ (77 °C), using 1–45 equiv of NBS, TOT affords a complex mixture of polybrominated and dehydrobrominated products. The components of this mixture were extremely difficult to separate. Integration of various NMR spectra of these reaction mixtures showed that the absorptions of the primary and tertiary isopropyl group hydrogen atoms in the products decreased relative to those in TOT. In addition the intensity of the Me group absorption decreased with the appearance of an AB quartet at δ 4.5–4.8. This indicated that bromination of TOT at elevated temperature took place both in the isopropyl and methyl groups. Dehydrohalogenation of some of these brominated compounds also occurred as demonstrated by the appearance of absorptions in the olefin region of the NMR spectra (δ 5–5.2). Lowering the temperature to 0 °C, under otherwise identical conditions, caused solubility problems with NBS and suggested further study.

The bromination of TOT could be controlled and made to take place in the methyl group(s) only by using acetone/$H_2O$ as the solvent and by carrying out the reaction at 50 °C to minimize dehydrohalogenation. Using a variety of conditions (as indicated in Table I), mono- (3), di- (4), tri- (5), tetra- (6), and even pentabrominated TOT (7) analogues were isolated. The total yield of brominated products, and the ratios between each of the brominated products, depended mainly on the temperature and the number of equivalents of NBS used.

The best conditions for the bromination of the Me groups in TOT is shown in runs 5–7 (Table I). These conditions afford the largest yield of tribrominated TOT (5) and the smallest amount of unreacted TOT. Under similar conditions TOC (2) also underwent bromination, affording 9–12 (Table I, runs 10 and 11).

Generally, the benzylic methine hydrogen atom (tertiary) of an isopropyl group is more easily brominated than a primary hydrogen atom of a benzylic methyl group.[4] However, in TOT, using the above conditions, the methyl group is brominated exclusively. Even when the three methyl groups in TOT are already brominated (as in 5), continued bromination occurs at the bromomethyl group ($CH_2Br$) and not at the formally more active isopropyl group, giving the tetra- and pentabrominated TOT analogues 6 and 7. We believe that steric inhibition of reso-

(1) This is the second paper in a series dealing with the effects of substituent modification on the host properties of TOT. See: Harris, T. D.; Oruganti, S. R.; Davis, L. D.; Keehn, P. M.; Green, B. S. *Tetrahedron* 1987, *43*, 1519–1540.

(2) (a) Aldrich Chemical Co. (b) Gnaim, J. M.; Green, B. S.; Arad-Yellin, R.; Keehn, P. M. *J. Org. Chem.* 1991, *56*, 4525.

(3) Each of the reaction products of the bromination of TOT is believed to be a mixture of the two propeller shaped chiral enantiomers. This was substantiated by using Pirkle's reagent. The AB q of the hydrogen atoms in the bromomethyl group in tribromo-TOT (5) was split in two when the ratio of Pirkle's reagent to solute was 1.14:1 (300 MHz, room temperature). Resolution of 5 has not yet been attempted.

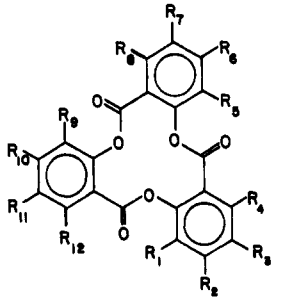
(4) (a) Pizey, J. S. *Synthetic Reagents*; John Wiley & Sons Inc.: New York, 1974; Vol. 2, pp 5–6. (b) Barnes, R. A.; Buckwalter, G. R. *J. Am. Chem. Soc.* 1951, *73*, 3858. (c) Offermann, W.; Vogtle, F. *Angew. Chem., Int. Ed. Engl.* 1980, *19*, 464. (d) Cram, D. J.; Helgeson, R. C. *J. Am. Chem. Soc.* 1966, *88*, 3515.

0022-3263/92/1957-3208$03.00/0 

**Table I. Yields of Brominated TOT and TOC analogues under Various Conditions[a]**

| runs | TOT:NBS (TOC:NBS) | temp (°C) | scale (g) | yields[b] (%) mono | di | tri | tetra | penta | total | TOT (TOC)[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1:3 | 0 | 0.16 | 10.9 | trace | trace | 0 | 0 | 10.9 | |
| 2 | 1:18 | 0 | 0.22 | 11.9 | 17.5 | 6.3 | 0 | 0 | 35.7 | 36.4 |
| 3 | 1:4 | 45–50 | 0.22 | 34.5 | 20.3 | 10.7 | 0 | 0 | 65.2 | 9.4 |
| 4 | 1:10 | 45–50 | 0.53 | 11.5 | 27.7 | 30.1 | 0 | 0 | 69.3 | 5.7 |
| 5 | 1:18 | 47–50 | 0.22 | 0 | 3.5 | 53.5 | 2.8 | trace | 59.8 | 0 |
| 6 | 1:18 | 47–50 | 0.22 | 0 | 6.0 | 50.0 | 8.0 | trace | 64.0 | 0 |
| 7 | 1:18 | 47–50 | 0.22 | 7.9 | 14.0 | 48.0 | 5.7 | trace | 75.6 | 0 |
| 8 | 1:18 | 47–50 | 1.06 | 10.7 | 10.9 | 42.5 | 3.0 | 2.2 | 69.3 | 0 |
| 9 | 1:18 | 47–50 | 0.53 | 6.6 | 9.5 | 39.2 | 3.6 | 2.2 | 61.1 | 0 |
| 10 | (1:18) | 47–50 | 0.22 | 7.9 | 38.5 | 21.0 | 8.4[e] | 0 | 75.8 | (0) |
| 11[d] | (1:18) | 47–50 | 0.22 | 15.8 | 21 | 22 | 0 | 0 | 58.5 | (0) |

[a] Reactions carried out in acetone/$H_2O$. [b] The yield is based on total starting material used. [c] Recovered TOT or TOC. [d] In this reaction one other unidentified product was present. [e] This compound was difficult to work with.



| | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | $R_8$ | $R_9$ | $R_{10}$ | $R_{11}$ | $R_{12}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TOT (1) | i-Pr | H | H | Me | i-Pr | H | H | Me | i-Pr | H | H | Me |
| TOC (2) | Me | H | H | i-Pr | Me | H | H | i-Pr | Me | H | H | i-Pr |
| monobromo-TOT (3) | i-Pr | H | H | $CH_2Br$ | i-Pr | H | H | Me | i-Pr | H | H | Me |
| dibromo-TOT (4) | i-Pr | H | H | $CH_2Br$ | i-Pr | H | H | $CH_2Br$ | i-Pr | H | H | Me |
| tribromo-TOT (5) | i-Pr | H | H | $CH_2Br$ | i-Pr | H | H | $CH_2Br$ | i-Pr | H | H | $CH_2Br$ |
| tetrabromo-TOT (6) | i-Pr | H | H | $CHBr_2$ | i-Pr | H | H | $CH_2Br$ | i-Pr | H | H | $CH_2Br$ |
| pentabromo-TOT (7) | i-Pr | H | H | $CHBr_2$ | i-Pr | H | H | $CHBr_2$ | i-Pr | H | H | $CH_2Br$ |
| hexabromo-TOT (8) | i-Pr | H | H | $CHBr_2$ | i-Pr | H | H | $CHBr_2$ | i-Pr | H | H | $CHBr_2$ |
| monobromo-TOC (9) | $CH_2Br$ | H | H | i-Pr | Me | H | H | i-Pr | Me | H | H | i-Pr |
| dibromo-TOC (10) | $CH_2Br$ | H | H | i-Pr | $CH_2Br$ | H | H | i-Pr | Me | H | H | i-Pr |
| tribromo-TOC (11) | $CH_2Br$ | H | H | i-Pr | $CH_2Br$ | H | H | i-Pr | $CH_2Br$ | H | H | i-Pr |
| tetrabromo-TOC (12) | $CHBr_2$ | H | H | i-Pr | $CH_2Br$ | H | H | i-Pr | $CH_2Br$ | H | H | i-Pr |

**Figure 1.**

nance destabilizes the tertiary benzylic radical intermediate in TOT and thus lowers the reactivity of this site toward bromination. The usual coplanar orientation of the tertiary isopropyl center with the benzene ring in the intermediate is somewhat restricted in the TOT structure. This allows the primary benzylic position (Me group) to be more competitive during the bromination reaction.

This phenomenon was also observed in the bromination of TOC (2), an isomer of TOT (1) in which the three isopropyl and methyl groups are at interchanged positions on the benzene rings (see Figure 1). Besides showing the generality of the bromination reaction in these cyclic triesters, it was of some interest to observe that the isopropyl group was equally unreactive in TOC despite the greater accessibility of the isopropyl group in TOC. Once again, bromination occurred only in the methyl groups giving mono- (9), di- (10), and tribromo-TOC (11). Tetrabromination of TOC was also observed (see entries 10 and 11, Table I).

**Structure Assignment.** Spectral data corroborated the assigned structures. Each brominated analogue exhibited C—Br and C=O absorptions around 570–600 and 1760–1765 $cm^{-1}$, respectively, in the infrared. Besides indicating correct molecular weight, the mass spectra showed correct bromine isotope patterns for each compound, and the fragmentation patterns were essentially the same as that for TOT.[5,6]

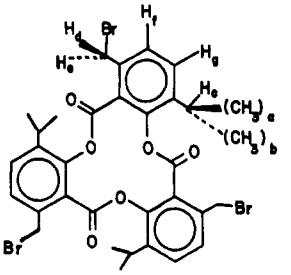


**Figure 2.** Prochiral protons in tribromo-TOT (5).

The $^1H$ NMR spectra of the brominated analogues (300 MHz, $CDCl_3$) are summarized in Table II (see Figure 2). Tribromo-TOT (5) is symmetric and gives the simplest spectrum of all the brominated products. Double doublet multiplicity for the prochiral methyl units ($(CH_3)_a$ and $(CH_3)_b$) of the i-Pr group is observed because the molecule has a nonplanar conformation.[3] However, one of these Me units appears almost 0.1ppm higher than in TOT. The methine hydrogen of the isopropyl group ($H_c$) is also ob-

(5) Gerdil, R. In *Topics in Current Chemistry. Molecular Inclusion and Molecular Recognition. Clathrates I*; Weber, E., Ed.; Springer-Verlag: New York, 1987; Vol. 140, pp 71–105.

(6) See ref 1 and Farias, C. M.; Hosangadi, B. D. *Indian J. Chem.* **1977**, *15 B*, 997.

Table II. The $^1$H NMR Chemical Shifts of TOT and TOC and Their Brominated Analogues[a]

| compd | $C(CH_3)_2$ | $CH_3$ | CH | $CH_2Br$ | $CHBr_2$ | aromatic H |
|---|---|---|---|---|---|---|
| 1 | 1.20, 1.26 dd | 2.46 s | 3.08 sept | | | 7.25, 7.42 AB q |
| 2 | 1.21 dd[b] | 2.14 s | 3.09 | | | 7.15–7.28 m |
| 3 | 1.00–1.45 m | 2.45 s | 3.10 m | 4.57, 4.84 AB q ($J$ = 10.9 Hz) | | 7.24, 7.44 AB q ($J$ = 8 Hz) |
| | | 2.46 s | 3.22 sept (1 H) | | | 7.25, 7.45 AB q ($J$ = 8 Hz) |
| | | | | | | 7.56 s (2 H) |
| 4 | 1.19–1.34 m | 2.45 s | 3.05–3.30 m | 4.56, 4.80 AB q ($J$ = 10.9 Hz) | | 7.26, 7.49 AB q ($J$ = 8 Hz) |
| | | | | 4.57, 4.84 AB q ($J$ = 10.9 Hz) | | 7.58 s (4 H) |
| 5 | 1.22, 1.33 dd ($J$ = 6.8 Hz) | | 3.22 sept ($J$ = 6.8 Hz) | 4.57, 4.77 AB q ($J$ = 10.9 Hz) | | 7.59 s |
| 6 | 1.21–1.39 m | | 3.02 sept ($J$ = 6.8 Hz) | 4.56, 4.77 AB q ($J$ = 10.9 Hz) | 6.95 s | 7.60 s (4 H) |
| | (12 lines) | | 3.21–3.27 (m 2 H) | 4.57, 4.79 AB q ($J$ = 10.9 Hz) | | 7.71, 8.12 AB q ($J$ = 8 Hz) |
| 7 | 1.21–1.55 m | | 3.22 sept (1 H), 2.90–3.15 m | 4.56, 4.79 AB q ($J$ = 10.9 Hz) | 6.91 s | 7.65, 8.11 AB q ($J$ = 8 Hz) |
| | | | | | 6.99 s | 7.65, 8.14 AB q ($J$ = 8 Hz) |
| | | | | | | 7.61 s |
| 9 | 1.25–1.40 m | 2.22 s | 3.21 sept ($J$ = 6 Hz) | 4.40, 4.43 AB q ($J$ = 10.5 Hz) | | 7.30, 7.39 AB q ($J$ = 7.3 Hz) |
| | | 2.23 s | | | | 7.31, 7.40 AB q ($J$ = 7.3 Hz) |
| | | | | | | 7.42, 7.65 AB q ($J$ = 7.3 Hz) |
| 10 | 1.26–1.39 m | 2.22 s | 3.22 m ($J$ = 6 Hz) | 4.38, 4.42 AB q ($J$ = 10.5 Hz) | | 7.33, 7.42 AB q ($J$ = 7.3 Hz) |
| | | | | | | 7.43, 7.67 AB q ($J$ = 7.3 Hz) |
| | | | | | | 7.43, 7.68 AB q ($J$ = 7.3 Hz) |
| 11 | 1.30, 1.37 dd ($J$ = 6.8 Hz) | | 3.26 sept ($J$ = 6.8 Hz) | 4.37, 4.40 AB q ($J$ = 10.5 Hz) | | 7.43, 7.68 AB q ($J$ = 7.3 Hz) |
| 12 | 1.10–1.48 m | | 3.02 m 3.23 sept (1 H) | 4.32–4.52 m | 6.70 s | 7.43, 7.69 AB q ($J$ = 7.3 Hz) |
| | | | | | | 7.47, 7.71 AB q ($J$ = 7.3 Hz) |
| | | | | | | 7.55, 8.15 AB q ($J$ = 8.4 Hz) |

[a] The chemical shifts of all AB q absorptions are of weight centered peaks. [b] Coincident doublets.

Table III. Solvent-Dependent $^1$H NMR Chemical Shift Data for Tribromo-TOT (5)[a]

| solvent[b] | $C(CH_3)_2$ | CH | $CH_2Br$ | aromatic H |
|---|---|---|---|---|
| benzene | 0.90, 1.23 dd | 3.38 h | 4.07, 4.77 AB q | 7.09 s |
| toluene | 0.91, 1.23 dd | 3.32 h | 4.07, 4.72 AB q | 7.09 s |
| xylene | 0.93, 1.22 dd | 3.28 h | 4.06, 4.70 AB q | 7.09 s |
| $CDCl_3$ | 1.34, 1.22 dd | 3.22 h | 4.57, 4.77 AB q | 7.59 s |
| $CDCl_3$/TFA[c] | 1.33, 1.23 dd | 3.23 h | 4.58, 4.73 AB q | 7.62 s |
| TFA:$CDCl_3$[d] | 1.39, 1.29 dd | 3.31 h | 4.61, 4.76 AB q | 7.72, 7.70 AB q |
| THF | 1.32, 1.18 dd | 3.24 h | 4.71, 4.78 AB q | 7.62, 7.69 AB q |
| acetone | 1.35, 1.22 dd | 3.26 h | 4.77, 4.82 AB q | 7.75, 7.83 AB q |
| DMSO | 1.27, 1.17 dd | 3.10 h | 4.75 s | 7.74, 7.86 AB q |

[a] $J$ values for each set of protons are the same as that observed in $CDCl_3$. [b] All solvents are deuterated. [c] Three drops of TFA. [d] The ratio of TFA:$CDCl_3$ was 3:2.

served at a higher chemical shift than that found in TOT. The AB multiplicity of the bromomethyl group indicates the prochiral nature of these two H atoms ($H_d$ and $H_e$). Unlike TOT, the two aromatic protons ($H_f$ and $H_g$) appear as a singlet and are observed at lower field. All these peakes are solvent dependent (see Table III).

The mono-, di-, tetra-, and pentabromo compounds (3, 4, 6, and 7) are not symmetric and all show a complex pattern of peaks in their $^1$H NMR spectra around the standard isopropyl and bromomethyl positions of tribromo-TOT (5). A 12-line pattern (three sets of double doublets) for the isopropyl methyl units in 3, 4, 6, and 7 indicates the nonequivalency of the three distinct *o*-thymotic units in each of these structures. This is corroborated by three independent septets for $H_c$ (two of which are relatively close to each other) and AB quartets for $H_{d,e}$ in each of these structures. The two aromatic protons ($H_{f,g}$) appear either as a singlet or as an AB quartet depending upon the structure (a singlet when the thymotic unit is monobrominated, like that found in 5, and an AB quartet when a thymotic unit is unbrominated or dibrominated). Thus, for example, a singlet and two AB quartets (ratio 1:2) are observed for compounds 3 and 7, while two singlets (coincident) and an AB quartet (ratio 2:1) are observed for 4 and 6.

The $^1$H NMR spectra of TOC (2) and its analogues 9–12 have spectral characteristics similar to TOT (1) and analogues 3–6 but have slightly different chemical shifts for similar protons.

Some comments regarding the $^1$H NMR spectra are in order. The two aromatic protons ($H_{f,g}$) appear as an AB pattern in unbrominated thymotic units (TOT, 3, and 4), while in monobrominated units they appear as a singlet positioned at lower field (as in 3, 4, and 5). When a second bromine atom is added to a given thymotic unit (as in 6 and 7) an AB pattern reappears for these protons and the chemical shift is observed even further downfield. This downfield shift may be explained in terms of the inductive effect of the halogen atom.

The bromine atom also seems to have a nonbonded proximity effect on the methine proton $H_c$. In TOT this proton appears at $\delta$ 3.08, whereas in 5 it appears at lower field ($\delta$ 3.22). The addition of a second bromine atom to the bromomethyl group (as in 6 and 7), however, causes a different effect than above. The proximate methine proton is shifted upfield (to $\delta$ 3.02) rather than downfield as was the case for the aromatic ring protons. This is perhaps due in part to the steric effects of the additional bromine atom which causes the average mass of the bromine atoms to be further from the methine proton.

Another interesting feature is observed when comparing the chemical shifts of the prochiral methyl units in TOT ($Me_{a,b}$) with those of tribromo-TOT (5). In TOT (1), the chemical shift difference is very small both in the $^1$H (0.06 ppm) and the $^{13}$C (0.18 ppm) NMR spectra.[7] In 5, however, the chemical shift difference is 0.11 and 1.25 ppm, respectively, for the comparable prochiral proton and carbon atoms.

Based on the above observations some interesting suggestions can be made regarding the position of the bromine atoms in 5. Since these molecules have a propeller shape, there exists an upper and lower surface to the macrostructure (see Figure 3). The ester carbonyl oxygen atoms point in one direction (up) while the ester ether oxygen atoms point in the opposite direction (down). In TOT (1), the Me group meta to the phenolic oxygen atom is oriented toward the upper surface and the i-Pr group is oriented toward the lower surface. The prochiral methyl units of the latter group ($Me_{a,b}$, Figure 2; C12A and C13A, C12B and C13B, C12C and C13C, Figure 3), however, are oriented toward different sides of the benzene ring plane such that one methyl points toward the upper surface of

(7) The $^{13}$C NMR spectral assignment of tribromo-TOT (5) and some of the unsymmetric analogues were carried out using the APT (attached proton test) program associated with the Varian XL-300 NMR spectrometer.

TOT and the other points toward the lower surface of TOT.

A priori, the bromine atoms in **5** can be oriented toward the upper or lower face of the molecule. Considering the polarities of the carbonyl oxygen and bromine atoms, an anti orientation would be favored. With the oxygen atom on the upper surface the bromine atom would be oriented toward the lower face and thus should influence the upper prochiral methyl unit to a greater extent; the data strongly support this orientation. In the $^1$H NMR spectrum, just one of the prochiral methyl units in **5** ($(CH_3)_a$; C12A, C12B, C12C) appears at a lower field than that in TOT. Since the only difference between **1** and **5** is the presence of the bromine atom, the data imply that this methyl unit is proximate to the bromine atom. The chemical shift of the distal methyl unit of the isopropyl group ($(CH_3)_b$; C13A, C13B, C13C), that which is directed down and away from the lower surface of compound **5**, remains essentially the same as that in TOT. If the Br atom would be directed toward the upper surface the chemical shift of the prochiral methyl units in **5** would be more comparable to those in **1**. $^{13}$C NMR data corroborates this. However, while the van der Waals effect causes a deshielding effect on the hydrogen nuclei, it causes a shielding effect on the associated carbon nuclei.[8]

We note also, when comparing the proton spectra of tribromo-TOT and -TOC analogues **5** and **11**, that the methylene proton quartet in **5** appears at a lower chemical shift than that in **11**. This is most probably due to the strong influence of ester carbonyl group which deshields the methylene protons in **5** (positioned on the upper surface) to a greater extent than the same protons in **11** (positioned on the lower surface). It is the bromomethyl rather than the isopropyl group which faces down in **11**, and the influence of the carbonyl groups on these protons is thus greatly reduced. The chemical shifts are observed at relatively higher field strengths and the $\Delta\nu$ values are smaller in tribromo-TOC **11** than in **5**.

The important effect of the ester carbonyl is further demonstrated by other NMR data. Upon addition of trifluoroacetic acid (TFA, 3 drops) to a chloroform-$d_1$ solution of tribromo-TOT (**5**), the lower field methylene H atom absorption shifts upfield by 0.04 ppm. The higher field methylene H absorption remains at the original chemical shift position of the unacidified solvent. Since protonation of the carbonyl groups would remove some of its usual anisotropic influence, the above experiment provides evidence for the influence of the carbonyl group on the lower field methylene protons in **5**. This absorption probably corresponds to the methylene proton which is positioned in the deshielding region of carbonyl group (inward facing), while the higher field peak corresponds to the other methylene proton which is not as proximate to the carbonyl group. At higher TFA concentration (3:2, TFA:$CDCl_3$) a dramatically different spectrum of **5** is observed where all the peaks are shifted to lower field and the two aromatic protons (normally a singlet) appear as an AB quartet (see Table III). This will be discussed in the next section.

**Solvent Effects on the $^1$H NMR Chemical Shifts of Tribromo-TOT (5).** It became evident, during our studies, that the proton chemical shifts of these analogues were very sensitive to solvent polarity. A summary of the $^1$H NMR spectra of tribromo-TOT (**5**) in different solvents is given in Table III.

In deuterated benzene only one of the two prochiral Me absorptions (the lower field doublet) is shifted (upfield, 0.43 ppm) when compared with the spectra in $CDCl_3$. The methine proton absorption is shifted downfield (0.11 ppm), while the higher field absorption of the methylene AB quartet is shifted upfield (0.49 ppm). The aromatic singlet is shifted upfield by 0.50 ppm.

In toluene and xylene, similar chemical shift changes were observed for **5**. The two absorptions in **5** which are not shifted when changing to an aromatic solvent reflect on the position of one of the prochiral isopropyl methyl units and one of the prochiral methylene protons which are both oriented toward the carbonyl group (as mentioned above). The aromatic solvent seems to affect only the protons on the lower and outer surface of the macrostructure of **5**. It is interesting to note that a similar effect of aromatic solvents is observed for the two distinct methyl groups in dimethylformamide.[9] Only the methyl group which is anti to the carbonyl in DMF is shifted. A similar phenomenon is also observed in TOT (**1**).[10]

In nonaromatic solvents, such as deuterated TFA, THF, and acetone (and DMSO), the lower field doublet of the bromomethyl group in **5** remains essentially at the position observed in $CDCl_3$. The upfield portion of the quartet, however, is shifted downfield (rather than upfield as in $C_6D_6$) by a minimum of 0.5 ppm. This effect is emphasized with increasing solvent polarity. In DMSO (largest dipole moment) the bromomethyl group appears as a singlet ($\delta$ 4.75). In polar solvents, the aromatic protons appear as an AB quartet. The latter protons are most downshifted while the isopropyl methine hydrogen atoms are most upshifted in DMSO from their respective values in other solvents. In lieu of our previous statement regarding the effect of the ester carbonyl group on the chemical shift of the prochiral isopropyl and methylene protons, DMSO seems to invert or equalize the electronic and/or magnetic environments of the two different faces of TOT and its analogues.[8]

**Variable-Temperature Studies.** By analogy with TOT, a conformational change between P (+) and M (−) propeller forms in **5** should be possible. Although we were unable to get variable-temperature data above 150 °C, in $C_2D_2Cl_4$, we observed a coalescence of the $H_{d,e}$ absorptions at 150 °C (or slightly higher) and a coalescence of the isopropyl $Me_{a,b}$ absorptions at about 140 °C. The calculated $\Delta G^{\ddagger}$ for molecular inversion (racemization) is thus 21.1 kcal/mol.[11] This value is essentially the same as that found for TOT itself ($\Delta G^{\ddagger}$ 21.4 kcal/mol).[12,13]

(8) Lambert, J. B.; Shurvell, H. F.; Verbit, L.; Cooks, R. G.; Stout, G. H. *Organic Structural Analysis*; Macmillan Publishing Co., Inc.: New York, 1976.

(9) Reference 8, p 45.

(10) The $^1$H NMR chemical shift data for TOT in other solvents is as follows. Benzene-$d_6$: $\delta$ 1.17, 0.94 (dd, 18 H), 2.39 (s, 9 H), 3.17 (sept, 3 H), 6.87, 7.09 (AB q, 6 H). DMSO-$d_6$ (+ 5 drops $CDCl_3$): $\delta$ 1.17, 1.22 (dd, 18 H), 2.40 (s, 9 H), 2.97 (sept, 3 H), 7.39, 7.60 (AB q, 6H). At 70 °C (benzene-$d_6$), all peaks that were initially shifted (up or downfield) relative to deuteriochloroform returned slightly (0–0.11 ppm) to their normal positions. This temperature effect was observed both for TOT (**1**) and for tribromo-TOT (**5**).

(11) The equations used to calculate $K_c$ and $\Delta G^{\ddagger}$ are as follows:

$$K_c = \frac{\pi}{\sqrt{2}}\Delta\nu$$

$$\Delta G^{\ddagger} = -RT \ln \frac{k_c h}{K T_c}$$

where $h$ = Planck's constant, $6.626 \times 10^{-27}$ erg·s, $R$ = gas constant, 1.987 cal/mol·K, $K$ = Boltzmann constant, $1.38 \times 10^{-16}$ erg·K, $T_c$ = coalescence temperature, K.

(12) (a) Downing, A. P.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc. B*, **1970**, 24. (b) Ollis, W. D.; Stoddart, J. F.; Sutherland, I. O. *Tetrahedron* **1974**, *30*, 1903. (c) Ollis, W. D.; Stephanatou J. S.; Stoddart, J. F. *J. Chem. Soc. Perkin Trans. 1* **1982**, 1629.

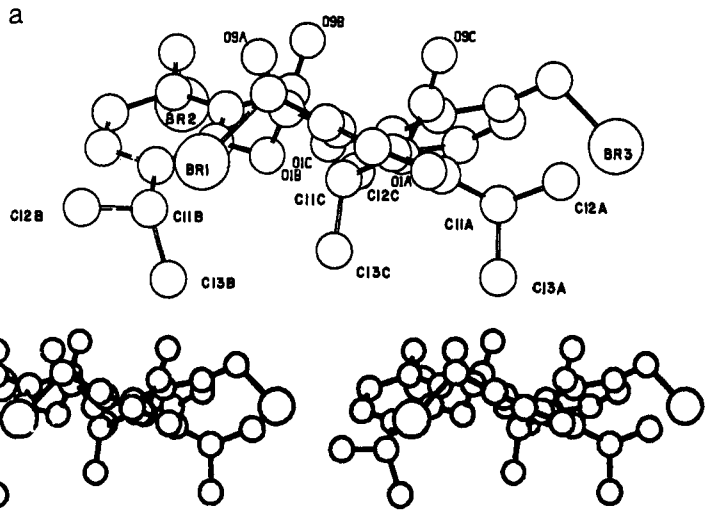



**Figure 3.** Upper and lower faces of tribromo-TOT (5). (a) View of 5 along an axis 5° off the mean molecular plane. (b) Stereoview of the same.

A priori, it seemed that the bulk of the $CH_2Br$ group would have an effect on the $\Delta G^{\ddagger}$ of P/M interconversion. This seemed evident since this group along with the isopropyl and carbonyl groups pass each other during the conformational flip. The experimental results prove otherwise, however. Adding bromine atoms to the three methyl groups in TOT does not have any significant effect on the $\Delta G^{\ddagger}$ of inversion. This implies that the greater part of the activation energy in 1 and 5 must arise from interactions involving the ester carbonyl and isopropyl groups as they pass one another. The substituents (at least methyl and bromomethyl) at the $R_{4,8,12}$ positions (see Figure 1) seem to have little effect on the inversion barrier. This corroborates what has previously been suggested by Ollis.[12]

Compound 5 also interchanges P and M propeller forms through helical type conformations as was found previously for TOT.[12] This was confirmed by the NMR data. The helical conformation is indicated by small absorptions around the methyl, isopropyl, and bromomethyl peaks. By integration of these smaller absorptions (especially those around the Me groups) it was determined that the concentration of helical form at ambient temperature in $CDCl_3$ is 18.8% and 14.8% for 3 and 4, respectively. These concentrations are lower than that found for TOT (1) (28.6%).[12] The helical form concentration for 5 was more difficult to determine because there are no free Me groups. However, integration around the bromomethyl absorption indicated between 11 and 20% of the helical form. Although the data is not sufficient to define a trend, it seems that the greater the number of bromine atoms that are present the lower the concentration of the helical conformation.[14]

The activation energies for P/M propeller interconversion in tribromo-TOC (11) was found to be 18.4 kcal/mol. This value is essentially identical with that for TOC (2) (18 kcal/mol).[12] Both values, however, are nearly 3 kcal/mol less than that for TOT and its tribromo analogue (5). As with TOT, the $CH_2Br$ groups do not seem to affect the energy barrier for P/M interconversion in TOC.

(13) In a separate determination of $\Delta G^{\ddagger}$ for inversion in TOT, we also obtained 21.3 kcal/mol.[12]

(14) Other TOT analogues isolated by us show approximately the same concentration of the helical conformation as that found in TOT. For example, in the desmethyl analogue of TOT (1, $R_4$ = H, see Figure 1) the helical conformation is present to the extent of 23.5%; in 2 ($R_1$ = Me, $R_4$ = i-Pr) it is 27.8%. The percent helical conformation for TOC (2) is 40.5%.[12]

## Conclusion

A method is defined for the preparation of brominated TOT and TOC analogues which eliminates the need for preparing brominated thymotic and carvacrotic acid precursors for cyclotrimerization. Direct bromination of TOT and TOC affords 3–7 and 9–12 in reasonable yield and represents the first example of functional group transformation in these cyclic triesters. Despite the presence of the formally more active isopropyl group, and the different orientation of the methyl groups in TOT and TOC (upper and lower face of the molecular propeller, respectively), bromination takes place exclusively in the Me group. The conformational barriers between the two chiral propeller forms in 5 and 11 are similar to those found in TOT and TOC, respectively. This indicates that the bromine atom(s) have no important effect on propeller inversion. The dependence of the chemical shift on solvent emphasizes the differences between the upper and lower surface of the TOT macrostructure and the chiral nature of these hosts. The brominated compounds obtained in this study provide a number of new TOT and TOC analogues for host/guest studies and now affords an opportunity for preparing a larger number of analogues by nucleophilic substitution processes. Some nucleophilic substitution reactions have already been carried out on 3–5 with nitrogen nucleophiles, giving a variety of nitrogen substituted derivatives.[15] We are presently studying the chemical and physical properties of these derivatives and collecting X-ray data for the newly prepared analogues and clathrates.[16] It remains to be seen whether a variety of guests can be included into these new analogues and

(15) For example, the mono-, di-, and tripyridinium salts as well as the mono-, di-, and tritrimethylammonium salts have been prepared by the treatment of 3–5 with pyridine and trimethylamine, respectively. The results of these and other displacement reactions will be published in a future paper.

(16) Though this aspect of our study is still in progress, preliminary experiments show that monobromo-TOT (3) forms a clathrate with benzene. In addition, even after heating the clathrate for 18 h at 100 °C, the $^1H$ NMR spectrum of the heated material continues to show the presence of benzene. NMR and X-ray crystal studies of 3 after crystalization from EtOAc show that it encapsulates ethyl acetate as well. (Crystallographic data was kindly provided by Dr. J. V. Silverton, NIH, Bethesda, MD. We are presently refining the data.) Dibromo-TOT (4) also behaves as a host and encapsulates benzene. Heating this clathrate, too, does not remove all the solvent. Finally, tribromo-TOT (5) also exhibits host properties when crystallized from benzene and EtOAc. However, the benzene is lost more readily from 5 upon heating. Crystallographic data for 4 and 5 has been collected and will be reported elsewhere.

whether they have enhanced host properties relative to TOT.

## Experimental Section

Melting points are uncorrected. Elemental analyses were determined by Galbraith Laboratories Inc., Knoxville, TN. 1,1,2,2-Tetrachloroethane-$d_2$, was used as the solvent in the variable temperature NMR studies and was purchased from Cambridge Isotope Laboratories. Benzene-$d_6$ was purchased from Wilmad Glass Co. All other chemicals were obtained from Aldrich Chemical Co. TLC plates were purchased from Analtech Inc.

**Bromination of TOT. Brominated Analogues 3–7.** TOT[2b,17] (0.22 g, 0.4 mmol), acetone (100 mL), and $H_2O$ (3 mL) were stirred at 47–50 °C for several minutes to allow dissolution of TOT. While irradiating the contents of the flask (UV lamp, 300-W, 120-V flood, Sylvania), and while maintaining a constant temperature (45–47 °C), NBS (1.32 g, 7.4 mmol, freshly crystallized from water and mixed with a trace of AIBN (about 1 mg)) was added in several portions (8–10) over a 30–40-min period. During this procedure the reaction mixture changed from colorless to yellow. When all the NBS was added, irradiation was discontinued. After sudden disappearance of the yellow color, stirring was continued for 10 more min followed by evaporation of the acetone.

$CCl_4$ (200 mL) was then added, and the mixture washed with $NaHCO_3$(3 × 100 mL of 0.05 M). The combined aqueous fractions were extracted with $CCl_4$ (50 mL). All $CCl_4$ fractions were combined, washed with water (100 mL), and dried with $MgSO_4$. Evaporation of the solvent gave crude brominated product (0.40 g) as a pale yellow, oily solid.

Separation of the bromides was carried out by preparative TLC (20 × 20, 1000-μm silica gel, developed in benzene). The elution order from the top to the bottom of the TLC plate was: penta-, tetra-, tri-, di-, and monobromo-TOT. The silica gel fractions were washed with chloroform and the extracted residues crystallized giving the products mentioned below:

**Monobromo-TOT (3).** 7.9%. Mp (from benzene/hexane): 164–172 °C melted and resolidified, remelted 238–240 °C dec. Anal. Calcd for $C_{33}H_{35}O_6Br + C_3H_3$ ($^1/_2$ benzene): C, 66.87; H, 5.92; Br, 12.36; Found: C 67.05, H 5.87, Br 12.56. MS: *m/e* 608, 606 ($M^+$) ($C_{33}H_{35}O_6Br$), 431, 429 ($C_{22}H_{22}O_4Br$), 352 ($C_{22}H_{24}O_4$), 257, 255 ($C_{11}H_{11}O_2Br$ + H), 176 ($C_{11}H_{12}O_2$), 148 (100) ($C_{10}H_{12}O$). $^{13}C$ NMR ($CDCl_3$): δ 10.3, 19.5, 19.6, 23.2, 23.4, 23.6, 23.8, 24.0, 26.2, 26.4, 26.5, 28.6, 126.0, 129.0, 129.2, 130.0, 135.8, 136.0, 136.2, 139.0, 139.2, 142.0, 144.3, 144.5, 164.2, 164.5, 164.6. IR (NaCl, $cm^{-1}$): 3050, 3040 (w), 2970 (s), 2930 (s), 2870 (w), 2850 (w), 1765 (s), 1470, 1455, 1425, 1385, 1365, 1340, 850–810 (m), 600 (w), 590 (w) (C–Br).

**Dibromo-TOT (4).** 14.0%. Mp (from $CCl_4$): 251–253 °C dec. Anal. Calcd for $C_{33}H_{34}O_6Br_2$: C, 57.74; H, 4.99; Br, 23.28. Found: C, 57.64; H, 5.04; Br, 21.85. MS: *m/e* 688, 686, 684 ($M^+$) ($C_{33}H_{34}O_6Br_2$), 512, 510, 508 ($C_{22}H_{22}O_4Br_2$), 431, 429 ($C_{22}H_{22}O_4Br$), 350 ($C_{22}H_{22}O_4$), 256, 254 ($C_{11}H_{11}O_2Br$), 175 ($C_{11}H_{11}O_2$) (100). $^{13}C$ NMR: δ 19.8, 23.03, 23.35, 23.60, 24.08, 24.26, 24.29, 27.01, 27.06, 27.51, 29.09, 29.13, 129.73, 129.76, 130.50, 130.55, 130.57, 130.68, 122.2, 125.3, 125.4, 135.99, 136.24, 136.66, 139.49, 142.34, 142.57, 145.08, 145.21, 145.26, 164.75, 164.82, 164.95. IR (NaCl, $cm^{-1}$): 1760, 600 (w), 590.

**Tribromo-TOT (5).** 48%. Mp (from $CCl_4$): 282–284 °C dec. Anal. Calcd for $C_{33}H_{33}O_6Br_3$: C, 51.76; H, 4.31; Br, 31.37. Found: C, 52.04; H, 4.41; Br, 30.99. MS: *m/e* 768, 766, 764, 762 ($M^+$) ($C_{33}H_{33}O_6Br_3$), 687, 685, 683 ($C_{33}H_{33}O_6Br_2$), 512, 510, 508 ($C_{22}H_{22}O_4Br_2$), 431, 429 ($C_{22}H_{22}O_4Br$), 350 ($C_{22}H_{22}O_4$), 256, 254 ($C_{11}H_{11}O_2Br$), 175 ($C_{11}H_{11}O_2$) (100). $^{13}C$ NMR ($CDCl_3$): δ 22.68, 23.91, 27.10, 28.64, 125.11, 130.30, 130.44, 136.01, 142.22, 144.86, 164.36. IR (NaCl, $cm^{-1}$): 1760, 590, 570.

**Tetrabromo-TOT (6).** 5.7%. Mp (from $CHCl_3$): 172–174 °C. MS: $C_{33}H_{32}O_6Br_4$ *m/e* $M^+$ calcd 843.8895, obsd 843.8882[18,19] (847.9, 845.9, 843.9, 841.9, 839.9), 768, 766, 764, 762 ($C_{33}H_{32}O_6Br_3$), 592, 590, 588, 586 ($C_{22}H_{21}O_4Br_3$), 512, 510, 508 ($C_{22}H_{22}O_4Br_2$), 431, 429 ($C_{22}H_{22}O_4Br$), 256, 254 ($C_{11}H_{11}O_2Br$), 175 ($C_{11}H_{11}O_2$), 28 (100). $^{13}C$ NMR ($CDCl_3$): δ 22.77, 22.80, 22.82, 23.95, 23.98, 24.01, 27.26, 27.29, 27.47, 28.65, 28.69, 35.04, 121.07, 124.90, 124.96, 135.91, 136.38, 139.66, 141.72, 142.27, 143.26, 143.43, 144.80, 163.79, 164.5, 164.14.

**Pentabromo-TOT (7).** Trace. Mp (from hexane/ethyl acetate): decomposes but does not melt lower than 320 °C. MS: $C_{33}H_{31}O_6Br_5$ *m/e* $M^+$ calcd 923.7983, obsd 923.7839.[18,19] $^{13}C$ NMR ($CDCl_3$): δ 23.29, 24.42, 24.50, 27.88, 27.98, 28.06, 29.14, 30.38, 35.43, 130.30, 130.54, 131.15, 131.28, 131.77, 131.83, 121.30, 121.40, 124.90, 137.10, 140.29, 140.77, 142.56, 143.70, 143.95, 143.97, 144.28, 145.56, 164.39, 164.53, 164.62.

**Bromination of TOC.[20] Brominated Analogues 9–12.** The same procedure was used as for the bromination of TOT described above.

**Monobromo-TOC (9).** 7.9%. Mp (from hexane/ethyl acetate): 93–96 °C (with effervescence). MS: $C_{33}H_{35}O_6Br$ *m/e* $M^+$ calcd 608.1603, obsd 608.1589.[18,19]

**Dibromo-TOC (10).** 38.5%. Mp (from $CCl_4$): 214–215 °C. Anal. Calcd for $C_{33}H_{34}O_6Br_2$: C, 57.74; H, 4.99; Br, 23.28. Found: C, 57.94; H, 5.01; Br, 23.18. MS: *m/e* 688, 686, 684 ($M^+$) ($C_{33}H_{34}O_6Br_2$), 607, 605 ($C_{33}H_{34}O_6Br$), 528 ($C_{33}H_{33}O_6$ + 3 H), 431, 429 ($C_{22}H_{22}O_4Br$), 351 ($C_{22}H_{22}O_4$ + H) (100), 256, 254 ($C_{11}H_{11}O_2Br$), 175 ($C_{11}H_{11}O_2$).

**Tribromo-TOC (11).** 21.0%. Mp (from $CCl_4$): 222–225 °C. Anal. Calcd for $C_{33}H_{33}O_6Br_3$: C, 51.76; H, 4.31; Br, 31.37. Found: C, 52.03; H, 4.34; Br, 31.25. MS: *m/e* 768, 766, 764, 762 ($M^+$) ($C_{33}H_{33}O_6Br_3$); 687, 685, 683 ($C_{33}H_{33}O_6Br_2$); 607, 605 ($C_{33}H_{33}O_6Br$), 512, 510, 508 ($C_{22}H_{22}O_4Br_2$); 431, 429 ($C_{22}H_{22}O_4$ Br); 351 ($C_{22}H_{22}O_4$ + H); 256, 254 ($C_{11}H_{11}O_2Br$); 175($C_{11}H_{11}O_2$) (100). $^{13}C$ NMR ($CDCl_3$): δ 23.3, 25.2, 26.0, 31.2, 125.1, 126.0, 128.1, 132.2, 145.2, 150.2, 164.0.

**Tetrabromo-TOC (12).** 8.4%. MS: *m/e* $M^+$ 846, 844, 842 ($C_{33}H_{32}O_6Br_4$, 848 and 840 were difficult to observe due to the extremely weak molecular ion cluster), 767, 765, 763, 761 ($C_{33}H_{32}O_6Br_3$); 687, 685, 683 ($C_{33}H_{33}O_6Br_2$); 511, 509, 507 ($C_{22}H_{21}O_4Br_2$); 431, 429 ($C_{22}H_{22}O_4Br$); 351 ($C_{22}H_{23}O_4$); 255, 253 ($C_{11}H_{10}O_2$); 175 ($C_{11}H_{11}O_2$) (100).

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**Supplementary Material Available:** High-resolution mass spectra of the $M^+$ ion area of compounds 6, 7, and 9 and proton NMR spectra of compounds 6, 7, 9, and 12 (14 pages). Ordering information is given on any current masthead page.

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(18) The value is given for the most abundant peak in the $M^+$ ion cluster of the halogenated material.

(19) The shape of the $M^+$ isotope peaks and their intensities are in full agreement with the assigned bromine-containing structure.

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