

The ratio of the L to the D form of the adduct in the absence of DNA increases with increasing methanol and decreases with the presence of DNA. The finding that deuterium is incorporated selectively into the C2 position of the L form of the thiol–drug adduct suggests that the steric geometry of the thiol which donates the hydrogen is relatively fixed in its relationship to the drug. Accordingly, the mechanism of hydrogen abstraction favors an internal hydrogen transfer into C2 of the drug from the attached L-form thiol at C12.

Although NCS-Chrom is converted into a diradical intermediate upon thiol activation that is capable of bistranded interaction with DNA, it has been puzzling that single-stranded lesions are much more prevalent than double-stranded lesions.¹¹ The finding of significant intramolecular hydrogen abstraction from the adducted thiol by the radical center at C2, resulting in the conversion of a bifunctional agent into a monofunctional one, may provide an explanation.¹² This result is consistent with recent evidence that the C6 radical is specifically responsible for hydrogen abstraction from the C-5' position of deoxyribose of T residues,⁵ the lesion primarily responsible for single-strand breaks.

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- (11) Dedon, P. C.; Goldberg, I. H. *J. Biol. Chem.* **1990**, *256*, 14713.
 (12) Whether or not the amount of deuterium incorporated from the α carbon of the thiol into C2 is sufficient to explain entirely the difference between the double- and single-stranded lesions of DNA depends on the magnitude of the deuterium isotope selection effect. Internal hydrogen transfer, such as from C12 of the drug into C2^{6c} or from the β carbon into C2,⁴ may also contribute to the quenching of the C2 radical. These possibilities are under investigation.

Tri-3-(2-butyl)-6-methylsalicylide. A Novel, Versatile Tri-*o*-thymotide-Based Clathrate Host Having Chiral Centers

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Activity in supramolecular chemistry continues to develop with many impressive achievements being recorded. Clathrate inclusion complexes allow a broad category of host–guest phenomena to be readily studied, and they have also been the subject of increasing recent interest.¹ The unique properties of tri-*o*-thymotide² (TOT, **4**) provide an especially suitable system for study because TOT affords a host lattice for inclusion compounds with guest molecules having a wide variety of sizes, shapes, and functionalities³ and

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(1) *Topics in Current Chemistry: Molecular Inclusion and Molecular Recognition. Clathrates I*, 140; Weber, E., Ed.; Springer-Verlag: New York, 1987.

(2) Gerdil, R. *Top. Curr. Chem.* **1987**, *140*, 71.

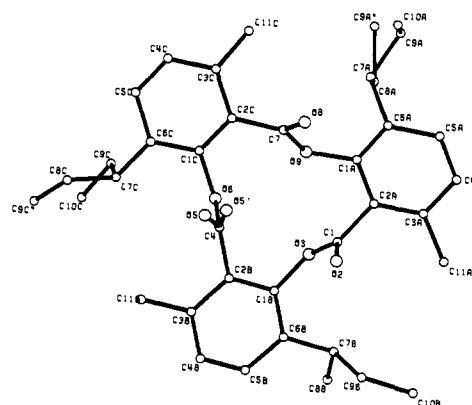
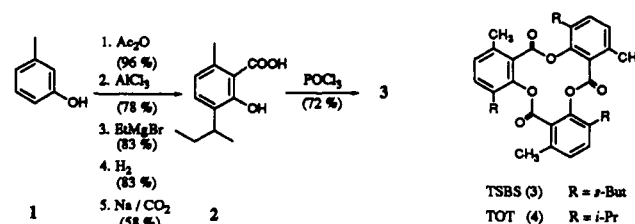


Figure 1. Molecular structure of TSBS (**3**) in the (*S*)-(+)-2-butanol clathrate.¹¹ The hydrogen atoms have been eliminated for clarity. The *sec*-butyl group disorder in subunits A and C is indicated by the extra atoms C_{9A} and C_{9C}, respectively; this is effectively methyl–ethyl substitutional disorder. In addition, one of the three carbonyl oxygens (O₅/O₃) displays positional disorder with 0.5:0.5 occupancy values.

Scheme I



because of its tendency to undergo spontaneous optical resolution on crystallization.⁴ While modification of its chemical structure has been carried out over the past 40 years, none of the analogues retained the versatile properties of TOT itself.⁵ In order to better understand the physical properties which make TOT such a unique host, we report the preparation of tri-3-(2-butyl)-6-methylsalicylide (TSBS), a TOT analogue which is unusual because of the presence of chiral *sec*-butyl units and its broad clathrate-forming properties.

TSBS (**3**) was prepared by the cyclodehydration⁶ of racemic 3-(2-butyl)-6-methylsalicylic acid (**2**),⁷ starting from *m*-cresol (**1**) (Scheme I), and isolated as the TSBS/*n*-hexane complex (mp 132 °C).⁸ Crystallization of TSBS from all solvents used thus far has afforded complexes, and more than 30 clathrates (both cage- and channel-type) have been characterized. The included guests have alcohol, carboxylic acid, ester, ketone, haloalkane, and alkane functionalities and represent sizes and shapes which are common to TOT clathrates.⁹ A few modified TOT analogues form

(3) Lawton, D.; Powell, H. M. *J. Chem. Soc.* **1958**, 2339. Arad-Yellin, R.; Green, B. S.; Knossow, M.; Tsoucaris, G. *J. Am. Chem. Soc.* **1983**, *105*, 4561–4571 and references therein.

(4) Newman, A. C. D.; Powell, H. M. *J. Chem. Soc.* **1952**, 3747.

(5) Harris, T. D.; Oruganti, S. R.; Davis, L. M.; Keehn, P. M.; Green, B. S. *Tetrahedron* **1987**, *43*, 1519–1540 and references therein. Ollis, W. D.; Stoddart, J. F. *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Academic Press: London, 1984; Vol. 2, p 170.

(6) Gnaïm, J. M.; Green, B. S.; Arad-Yellin, R.; Keehn, P. M. *J. Org. Chem.* **1991**, *56*, 4525–4529.

(7) Data for **2**: mp 85–7 °C; ¹H NMR δ 0.86 (3 H, t, *J* = 7 Hz), 1.20 (3 H, d, *J* = 7 Hz), 1.61 (2 H, q, *J* = 8 Hz), 2.59 (3 H, s), 3.15 (1 H, m), 6.72 (1 H, d, *J* = 8 Hz), 7.23 (1 H, d, *J* = 8 Hz), 9.06 (2 H, br s).

(8) Guest-free host **3** was obtained by heating the clathrate crystals under vacuum at 80 °C (30 mmHg) for 7 days or at 100 °C (0.1 mmHg) for 4 h; the microcrystalline powder obtained had mp 178–9 °C: ¹H NMR δ 0.78, 0.92 (9 H, two triplets, *J* = 8 Hz), 1.17, 1.26 (9 H, two doublets, *J* = 8 Hz), 1.60 (6 H, quintet, *J* = 7 Hz), 2.47 (9 H, s), 2.84 (3 H, sextet, *J* = 8 Hz), 7.22 (3 H, d, *J* = 7 Hz), 7.38 (3 H, d, *J* = 7 Hz). Anal. Calcd C, 75.79; H, 7.37. Found: C, 75.95; H, 7.45.

(9) For example, TSBS forms cage-type, 2:1 (space group *P*₃2₁) clathrates with nitromethane, ethyl acetate, 2-butanol, trifluoroacetic acid, and 2-chlorobutane; a channel-type, 2:1 (space group *P*₆), clathrate forms with 2-octanone. The 2:1 clathrates with chloroform, tetrachloromethane, 1-bromobutane, and diiodomethane are believed to be cage-type, but X-ray data has not been collected.

clathrates with a single guest,¹⁰ but this is the first example of a TOT analogue displaying the same versatility in clathrate formation as TOT. The space groups, cell dimensions, and host:guest ratios for the TSBS clathrates and the conformation of the host molecule (see below and Figure 1) are the same as those for the corresponding TOT clathrates.

The crystal structure of the TSBS/(*S*)-(+)-2-butanol clathrate¹¹ (Figure 1) shows that all of the host molecules have identical *P* (or *M*) propeller chirality in the central ring, while the three distinct *sec*-butyl groups predominantly display an *RSR* (or *SRS*) configuration. The presence of the second diastereomer *RRR* (or *SSS*), anticipated to be present in low proportion, is not evident. Designating the three aromatic subunits A, B, and C, one sees no disorder in the B *sec*-butyl groups, which have the *R* configuration, while the A and C *sec*-butyl groups exhibit appreciable substitutional disorder: A has 0.8:0.2 *R*:*S* while C has 0.8:0.2 *S*:*R* occupancy values. Interestingly, the ordered *sec*-butyl group has an anti conformation, while both of the disordered ones have *gauche* conformations.¹² The guest is heavily disordered within the cavity, but separate atoms are discernable exhibiting 2-fold disorder that remains to be elucidated.

When single crystals of the TSBS clathrates are dissolved at 0 °C in chloroform, the solutions have initial optical rotations of $[\alpha]_D^{20} \sim 100^\circ$ (some crystals afford (+) and some (-) rotation values), which over a period of 5 min approach 0°. This is due to the *P* \rightleftharpoons *M* conformational isomerization of the propeller conformation of the host which, in single crystals of space group *P*3₁21, should be homochiral.¹³ The half-life ($\tau_{1/2}$) for this process was determined to be 4.7 min at 0 °C; on the basis of its temperature dependence (via polarimetry), the energy of activation (ΔG^\ddagger) and Arrhenius parameters (E_a , $\log A$) were calculated to be 22.2 and 22.7 kcal/mol and 16.1, respectively.

These results confirm that the structural motif of TOT may be modified in order to engineer improved host structures for clathrates and open up the possibility of obtaining host properties (e.g., chemical reactivity centers, optical properties for nonlinear effects, etc.) which are not observed in TOT. This is of specific importance and interest with regard to difficult resolutions (e.g., halothane) and may provide systematically modified clathrate structures which will allow us to better understand the structural requirements that lead to clathrate formation.

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(10) Edge, S. J.; Ollis, W. D.; Stephanatou, J. S.; Stoddart, J. F.; Williams, D. J.; Woode, K. A. *Tetrahedron Lett.* **1981**, 22, 2229.

(11) Crystal data: C₃₆H₄₂O₆·1/2(C₄H₁₀O), a transparent, prismatic, trigonal crystal, 0.4 mm in all dimensions was used; space group *P*3₁21 (No. 152), $a = b = 13.556$ (2), $c = 31.705$ (8) Å, $Z = 6$, $F_w = 607$, $D_{\text{calc}} = 1.10$ g cm⁻³. Data collected at 90 K on a Rigaku AFC5R four circle diffractometer, R_U300 rotating anode, load 40 KV, 250 mA, Mo *K*α radiation ($\lambda = 0.7114$ Å), graphite monochromator; 5630 reflections collected $2.0^\circ \leq 2\theta \leq 55.0^\circ$; ω scan method, scan width = 1.0°, scan speed 1°/min; typical half-height peak width = 0.34° ω ; 3 standard reflections collected 55 times; no changes in intensity; no absorption correction; 3809 reflections with $I > 3\sigma(I)$. Solution and refinement: structure solved by direct methods (SHELXS-86). Anisotropic refinement for non-hydrogen atoms. Hydrogens were found from a difference Fourier map and refined constrained to regular geometry with an overall temperature factor. Scattering factors from International Tables of X-ray Crystallography, Vol. IV. Prior to attempt to resolve disorder of the guest molecule, $R_w = 0.078$.

(12) For discussion and examples of *sec*-butyl group disorder, see: Addadi, L.; Ariel, S.; Lahav, M.; Leiserowitz, L.; Popovitz-Biro, R.; Tang, C. P. In *Chemical Physics of Solids and Their Surfaces*; Roberts, M. W., Thomas, J. M., Eds.; Royal Society of Chemistry: London, 1980; Vol 8, p 202.

(13) Although TOT and TSBS are very similar, the correlation of host sign of rotation with guest chirality is the *opposite* for their 2-butanol (BuOH) clathrates. (*S*)-(+)-2-BuOH is preferentially enclathrated by (-)-TSBS and (*R*)-(-)-2-BuOH is associated with (+)-TSBS, whereas (*S*)-(+)- and (*R*)-(-)-2-BuOH are exclusively associated with *P* (+)- and *M* (-)-TOT, respectively.¹⁴

(14) Burlinson, N. E.; Ripmeester, J. A. *J. Am. Chem. Soc.* **1985**, 107, 3713.

Supplementary Material Available: Description of the data collection and tables of atomic coordinates, anisotropic temperature factors, hydrogen atom coordinates, bond lengths, and bond angles for the cage-type clathrate of TSBS (3) with (*S*)-(+)-2-butanol (10 pages). Ordering information is given on any current masthead page.

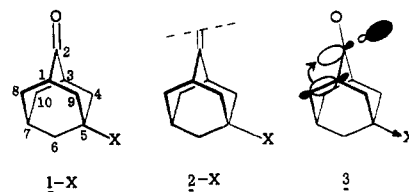
Strongly Enhanced Stereoselectivity in the Reduction of 5-Substituted Adamantanones by Substitution of C₅ by Positive Nitrogen

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Studies of addition to the 5-substituted adamantanone 1-X and its derivatives 2-X have produced insights into the electronic factor influencing the stereochemistry of that process.¹ The results, highly uniform over a very wide variety of reactions,² appear to support the generalization that the reagent prefers attack at that face which is antiperiplanar to the more electron-rich vicinal bond(s). To interpret this phenomenon, we have employed the idea of transition-state hyperconjugation first proposed in 1981 by Cieplak³ to explain the peculiar preference of many nucleophilic reagents for axial attack on cyclohexanone. Probes 2-X have seemed ideal for these studies because from the steric point of view they have virtual C_{2v} symmetry, and the donor bonds are essentially strainless, yet rigidly oriented.



Nevertheless, the concept has not been universally accepted, perhaps in part⁴ because the selectivities in the reactions of electroneutral substrates 2-X have been quite modest:⁵ an *E/Z* alcohol ratio of about 1.5. Such small ratios make it difficult to dismiss the possible responsibility of a host of otherwise inconsequential factors; hence, we sought to design new probes possessing the same advantages of an adamantane skeleton but with a much more powerfully polarizing substituent. We now wish to report our findings in the borohydride reduction of 5-azaadamantan-2-one derivatives 4–6. The known⁶ parent amino ketone (7) is isoelectronic with 1-H, and the configurations of the *E* and *Z* alcohols 8 derived from it have been determined.⁷

(1) (a) Cheung, C. K.; Tseng, L. T.; Lin, M.-h.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, 108, 1598; **1987**, 109, 7239. (b) Li, H.; le Noble, W. J. *Tetrahedron Lett.* **1990**, 31, 4391.

(2) For a summary and references, see: Bodepudi, V.; le Noble, W. J. *J. Org. Chem.* **1991**, 56, 2001.

(3) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, 103, 4540.

(4) For a summary and references, see: Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, 113, 5018.

(5) Much larger ratios (10²⁻³) are encountered when the substrates are cations: (a) Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, 109, 5874. (b) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, 54, 3839. (c) Adcock, W.; Coope, J.; Shiner, V. J.; Trout, N. A. *J. Org. Chem.* **1990**, 55, 1411.

(6) (a) Dekkers, W. J. D.; Verhoeven, J. W.; Speckamp, W. N. *Tetrahedron* **1973**, 26, 1691. (b) Black, R. M. *Synthesis* **1981**, 829.

(7) Fernandez, M. J.; Galvez, E.; Lorente, A.; Iriepa, I.; Soler, J. A. *J. Heterocycl. Chem.* **1989**, 26, 307. The assignments were based on a ¹H NMR analysis of a mixture of 50/50 composition after purification. We succeeded in obtaining highly enriched samples of both alcohols by chromatography (Al₂O₃-methanol); we confirm their assignment.