

## *trans*- versus *cis*-1,3,5,7-Tetraoxadecalin: A Structural, Thermochemical, and Computational Study<sup>1a</sup>

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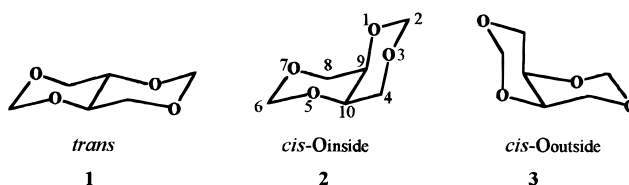
In a multidisciplinary study (low-temperature X-ray diffraction, heats of combustion, and high-level (MP2/6-31+G\*) ab initio calculations), the structure and relative stability of *trans*-1,3,5,7-tetraoxadecalin (**1**) versus its *cis*-diastereomer (**2**) were established. We also calculated the atomic charges and proton affinities of the oxygen sites to predict the probable coordination sites in each isomer. Excellent agreement was found between the experimental and theoretical structural parameters, which were well reproduced by force field calculations using MM3-GE (MM3 reparametrized for the gauche effect). Also, **1** and **2** are largely equienergetic within experimental errors and the computational methods used.

### Introduction

The 1,3,5,7-tetraoxadecalin<sup>1b</sup> (1,3,5,7-TOD) system is a bicyclic diacetal existing in *trans* (**1**) or *cis* (**2**) forms (Scheme 1), the formation of which involves the condensation of a 1,2,3,4-tetrahydroxybutane with formaldehyde under acid catalysis to give **1** or **2** in a stereospecific manner, that is, from erythritol or threitol, respectively.<sup>2,3</sup> The *cis*-1,3,5,7-TOD system can exist in two possible diastereoisomeric chair–chair forms, O<sub>inside</sub> (**2**) and O<sub>outside</sub> (**3**), which may interconvert by conformational ring inversion (**2** ⇌ **3**) or by chemical (acid-catalyzed) isomerization. The *trans* form, however, is both configurationally and conformationally fixed.

This type of diacetal systems has been well known in carbohydrate chemistry for a long time.<sup>4</sup> The reaction of erythritol with formaldehyde was reported 100 years ago,<sup>5</sup> but only more recently have various groups devel-

### Scheme 1. The 1,3,5,7-Tetraoxadecalin Diastereoisomers



oped preparative methods and stereochemically defined both parent TOD molecules and some of their derivatives.<sup>3</sup> None, however, have dealt with the relative stabilities of these diastereoisomeric systems and their intimate structural features. We raised these questions recently<sup>2a,b</sup> in connection with our studies on approaches to new types of host systems based on *cis*-1,3,5,7-TOD “core” units<sup>2</sup>. A low-temperature X-ray diffraction analysis of **2**<sup>2a</sup> provided its structure and bonding details, and a variable-temperature NMR study<sup>3b</sup> probed the equilibrium (i.e., relative stability) between **2** and **3** in solution. As to the relative stability of **1** and **2**, because no isomerization pathway was available, we had to resort to the use of theory and we did this by both QM and MM.<sup>2b</sup> The tetraoxadecalin system is loaded with O–C–O and O–C–C–O units, which are subject to stereoelectronic effects, viz., the anomeric effect and the gauche effect.<sup>6,15–17</sup> The MM3 force field<sup>7</sup> had been parametrized for both,<sup>7b</sup> but when we used it for the TOD system, MM3 preferred **2** by 1.1 kcal/mol, contrary to the results of a fragment analysis<sup>2b,g</sup> of the tetraoxadecalin system, which favored **1** by 1.5 kcal/mol (**1**, **2**, and **3** differ in anti versus

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(1) (a) Reany, O.; Goldberg, I.; Grabarnik, M.; Abramson, S.; Star, A.; Fuchs, B. *New Supramolecular Host Systems*. 8. Part 7. *Tetrahedron Lett.* **1997**, *38*, 8073. (b) We consistently<sup>1a,2</sup> use the 1,3,5,7-tetraoxadecalin nomenclature. Other possible names for **1** are *trans*-2,4,7,9-tetraoxabicyclo[4.4.0]decane or (CA) (4aR)-(4ar,8at)-tetrahydro[1,3]dioxino[5,4-*d*]-1,3-dioxin.

(2) (a) Senderowitz, H.; Linden, A.; Golender, L.; Abramson, S.; Fuchs, B. *Tetrahedron* **1994**, *50*, 9691. (b) Senderowitz, H.; Golender, L.; Fuchs, B. *Tetrahedron* **1994**, *50*, 9707. (c) Abramson, S.; Ashkenazi, E.; Goldberg, I.; Greenwald, M.; Jatzke, H.; Vardi, M.; Weinman, S.; Fuchs, B. *J. Chem. Soc., Chem. Commun.* **1994**, 1611. (d) Frische, K.; Abramson, S.; Ashkenazi, E.; Greenwald, M.; Lemcoff, N. G.; Fuchs, B. *Tetrahedron Lett.* **1995**, *36*, 9193. (e) Jatzke, H.; Frische, K.; Greenwald, M.; Golender, L.; Fuchs, B. *Tetrahedron* **1997**, *53*, 4821. (f) Grabarnik, M.; Goldberg, I.; Fuchs, B. *J. Chem. Soc., Perkin Trans I* **1997**, 3123. (g) Golender, L.; Senderowitz, H.; Fuchs, B. *THEOCHEM* **1996**, *370*, 221. (h) Senderowitz, H.; Fuchs, B. *THEOCHEM* **1997**, *395*/396, 123.

(3) (a) Burden, I. J.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. I* **1975**, 666. (b) 675. (c) Lemieux, R. U.; Howard, J. *Can. J. Chem.* **1963**, *41*, 393. (d) Jensen, R. B.; Buchardt, O.; Jørgensen, S. E.; Nielsen, J. U. R.; Schroll, G.; Altona, C. *Acta Chem. Scand.* **1975**, *29B*, 373. (e) Nørskov, L.; Jensen, R. B.; Schroll, G. *Acta Chem. Scand.* **1983**, *37B*, 133 and previous parts in this series. (f) Nougier, R.; Gras, J.-L.; Mchich, M. *Tetrahedron* **1988**, *44*, 2943. (g) Gras, J.-L.; Poncet, A. *Synth. Commun.* **1992**, *22*, 405.

(4) (a) Barker, S. A.; Bourne, E. J. *Adv. Carbohydr. Chem.* **1952**, *7*, 138. (b) Mills, A. *Adv. Carbohydr. Chem.* **1955**, *10*, 1. (c) Stoddart, J. F. *Stereochemistry of Carbohydrates*; Wiley: New York, 1971; p 21. (d) Foster, A. B. In *The Carbohydrates*; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1972; Vol. 1A, Chapter 11. (f) See ref 2e for a review on carbohydrate TOD compounds.

(5) Schulz, M.; Tollens, B. *Annalen* **1896**, *289*, 20.

(6) (a) Aped, P.; Apelöig, Y.; Ellençweig, A.; Fuchs, B.; Goldberg, I.; Karni, M.; Tartakovsky, E. *J. Am. Chem. Soc.* **1987**, *109*, 1486. (b) Senderowitz, H.; Aped, P.; Fuchs, B. *Tetrahedron* **1993**, *49*, 3879 and previous papers cited therein.

**Table 1. Previously Computed Relative Stabilities of 1, 2, and 3 (in kcal/mol)<sup>a</sup>**

	1	2	3
MM3 <sup>i</sup>	1.1	0.0	5.9
QM, ab initio <sup>ii</sup>	0.0	0.6	4.7
MM3-GE <sup>iii</sup>	0.0	0.6	5.0

<sup>a</sup> Calculated<sup>2b</sup> using <sup>i</sup>MM3; <sup>ii</sup>GAUSSIAN92 at the MP2/6-31g\*//6-31g\* level; <sup>iii</sup>MM3-GE, that is, MM3 reparametrized for the relative stability (gauche effect) in dimethoxyethane<sup>2b</sup> (MM2-AE,<sup>6</sup> i.e., MM2 parametrized for the anomeric effect in O-C-O-containing systems gave similar results).

gauche conformations of the interannular fragment constituents of butane [CCCC], oxypropane [CCCO], methyl ethyl ether [COCC], dimethoxymethane [CO-COC], and 1,2-dioxyethane [OCCO]). The MM3 and QM (ab initio, 6-31g\*) results were also conflicting (Table 1), except for the *cis*-O<sub>outside</sub> (**3**) isomer, which was similarly and highly disfavored by all methods. Having found that MM3-92 overestimated the O-C-C-O gauche effect, we reparametrized MM3 for this (MM3-GE),<sup>2b</sup> in accord with ab initio results of dimethoxyethane, and subsequently obtained better results for TOD (Table 1).

We felt compelled, though, to improve the ab initio calculation (vide supra) to a high-level fully optimized one to secure more reliable energies and geometrical

**Table 2. Results from Typical Combustion Experiments<sup>a</sup>**

substance	1	1	2	2
$m_{\text{substance}}^b$ (g)	0.044 264	0.056 721	0.033 992	0.055 965
$m'_{\text{cotton}}^b$ (g)	0.000 715	0.000 733	0.000 627	0.000 554
$m'_{\text{Mylar}}^b$ (g)	0.009 277	0.011 287		
$m''_{\text{paraffin}}^b$ (g)				0.006 844
$\Delta T_c$ (K) <sup>c</sup>	0.789 44	1.001 86	0.499 09	1.030 37
$\epsilon_{\text{calor}}(-\Delta T_c)$ (cal) <sup>c</sup>	-277.70	-352.43	-174.23	-359.70
$\epsilon_{\text{cont}}(-\Delta T_c)$ (cal) <sup>d</sup>	-0.50	-0.64	-0.35	-0.66
$\Delta E_{\text{corr}}$ (cal) <sup>d</sup>	0.19	0.26	0.12	0.22
$-m'\Delta u'_c$ (cal)	2.89	2.97	2.54	2.24
$-m''\Delta u''_c$ (cal)	50.63	61.61		
$-m'''\Delta u'''_c$ (cal)				75.23
$\Delta u_{\text{c(substance)}}^e$ (cal g <sup>-1</sup> )	-5063.1	-5075.3	-5047.1	-5044.3

<sup>a</sup> For the definition of the symbols see ref 8b;  $T_h = 298$  K;  $V_{\text{bomb}} = 0.0460$  L;  $p_{\text{gas}}^i = 30.45$  bar;  $m_{\text{water}}^j = 0.23$  g;  $E_{\text{ignition}} = 0.36$  cal;  $m_{\text{platin}} = 2.37$  g. <sup>b</sup> Masses obtained from weight by calculating the buoyancy. <sup>c</sup>  $\Delta T_c = T^f - T^i + \Delta T_{\text{corr}}$ . <sup>d</sup>  $\epsilon_{\text{calor}} = 349.095 \pm 0.052$  cal K<sup>-1</sup> (0.0086%) from calibration runs with benzoic acid;  $\epsilon_{\text{cont}}(-\Delta T_c) = \epsilon_{\text{cont}}^i(T^f - T_h) + \epsilon_{\text{cont}}^f(T_h - T^i + \Delta T_{\text{corr}})$ . <sup>e</sup>  $\Delta E_{\text{corr}}$  is the sum of items 81–85, 87–90, 93, and 94 in r 8b.

parameters and to provide suitable experimental data to corroborate the computational results. To this end, a low-temperature X-ray diffraction analysis of **1** was performed and we probed the relative stability of **1** and **2** using thermochemical methods. All these now constitute a consistent set of results. Moreover, since we are interested in the ability and modes of complexation of these systems, we calculated ab initio at the same high level the proton affinities at the two different oxygen sites in each diastereoisomeric TOD and the corresponding atomic charges, so that the preferred sites of coordination in each isomer could be predicted.

## Experimental Data and Computational Methodology

### Thermochemistry. 1. Combustion Calorimetry.

The heats of combustion were measured with an aneroid isoperibolic calorimeter,<sup>8a</sup> calibrated with benzoic acid (NIST, standard reference sample 39i). The samples of **1** and **2** were purified by recrystallization from methanol/ether. From the analysis of the melting peaks (DSC), a purity of more than 99.99 mol % (**1**) and about 99.98 mol % (**2**) has been derived. The carefully dried samples were pressed into pellets, and the pellets of the more volatile isomer **1** were sealed in Mylar bags. Paraffin oil as an auxiliary material was added to the pellets of **2**. No soot was formed during combustion. Results of a typical combustion experiment for each compound are given in Table 2. For the reduction of the data to standard conditions, conventional procedures<sup>8b</sup> were used. The densities of the compounds,  $d = 1.54$  g cm<sup>-3</sup>, were measured with a pycnometer. Specific heat capacities,  $C_p(298.15$  K) = 0.27 (**1**) and 0.25 (**2**) cal g<sup>-1</sup>, were measured by DSC. The auxiliary quantities for the combustion experiments have been measured in previous experiments:<sup>8c</sup> cotton  $\Delta u_c^\circ(\text{CH}_{1.774}\text{O}_{0.887}) = -(4050.0 \pm 1.0)$  cal g<sup>-1</sup>; paraffin oil  $\Delta u_c^\circ(\text{CH}_{1.940}) = -(10991.2 \pm 3.8)$  cal g<sup>-1</sup>; Mylar  $\Delta u_c^\circ(\text{C}_{10}\text{H}_8\text{O}_4) = -(5462.7 \pm 1.2)$  cal g<sup>-1</sup>,  $m_{\text{(Mylar)}} = m_{\text{moist}} [1 - (4.64 \times 10^{-5})$  (relative moisture of air in %)]. The individual values of the standard specific energies of combustion  $\Delta u_c^\circ$  together with their mean and standard deviation are given in Table 3.

**2. Vapor Pressure Measurements.** The enthalpies of sublimation of compounds **1** and **2** were determined by the method of transference in a saturated N<sub>2</sub> stream.

(7) (a) MM3 is available from QCPE (latest public version); the official distributors are Technical Utilization Corporation, Inc., 235 Glen Village Court, Powell, OH 43065, and Tripos Associates, 1699 S. Hanley Road, St. Louis, MO 63144. (b) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551 and subsequent articles, in particular those on alcohols and ethers. (c) Allinger, N. L.; Rahman, M.; Lii, J.-H. *J. Am. Chem. Soc.* **1990**, *112*, 8293. (d) MM4 is also available from the above agencies.

(8) (a) Beckhaus, H.-D.; Rüchardt, C.; Smisek, M. *Thermochim. Acta* **1984**, *79*, 149. (b) Hubbard, W. N.; Scott, D. W.; Waddington, G. In *Experimental Thermochemistry*; Rossini, F. D., Ed.; Interscience Publishers: New York, 1956; Vol. 1, p 75. (c) Rakus, K.; Verevkin, S. P.; Peng, W.; Beckhaus, H.-D.; Rüchardt, C. *Liebigs Ann. Chem.* **1995**, 2059. (d) Chickos, J. S.; Hesse, D. G.; Panshin, S. Y.; Rogers, D. W.; Saunders, M.; Uffer, P. M.; Liebman, J. F. *J. Org. Chem.* **1992**, *57*, 1897. (e) Cox, J. D.; Pilcher, G. *Thermochemistry of Organic and Organometallic Compounds*; Academic: London, 1970. (f) Cox, J. D., Wagman, D. D., Medvedev, V. A., Eds. *CODATA Key Values for Thermodynamics*; Hemisphere: New York, 1989.

(9) Sheldrick, G. M. SHELXS-86. *Acta Crystallogr.* **1990**, *A46*, 467–473.

(10) TEXSAN. *Single-Crystal Structure Analysis Software*, Version 5.0; Molecular Structure Corporation: The Woodlands, TX, 1989.

(11) Johnson, C. K. ORTEPII. Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.

(12) Dewar, M. J. S.; Dieter, K. M. *J. Am. Chem. Soc.* **1986**, *108*, 8075.

(13) Ganguly, B.; Fuchs, B. Stereoelectronic Effect in Negatively and Positively (Protonated) Charged 1,3-Dioxo Species: An Ab Initio Study. *J. Org. Chem.* **1997**, *62*, 8892.

(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*; Gaussian Inc.: Pittsburgh, PA, 1995.

(15) (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: Berlin, 1983. (b) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Wiley: New York, 1983. (c) The Anomeric Effect and Associated Stereoelectronic Effects, Thatcher, G. R. G., Ed.; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993. (d) Juaristi, E., Ed. *The Anomeric Effect*; CRC Press: Boca Raton, 1995.

(16) Schleifer, L.; Senderowitz, H.; Aped, P.; Tartakovsky, E.; Fuchs, B. *Carbohydr. Res.* **1990**, *206*, 21.

(17) (a) Wolfe, S.; Tel, L. M.; Haines, W. J.; Robb, M. A.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1973**, *95*, 4863 and earlier papers cited therein. (b) Juaristi, E. *J. Chem. Educ.* **1979**, *56*, 438. (c) Žefirov, N. S. *J. Org. Chem. USSR* **1974**, *10*, 1147. (d) Pinto, B. N.; Leung, R. Y. N. in ref 15c, p 126.

**Table 3. Enthalpies of Combustion ( $H_c$ ) As Resulting from All Combustion Experiments (kcal/mol)**

	1 (cr)	2 (cr)
	-740.22	-737.60
	-742.58	-737.73
	-739.93	-737.17
	-739.78	-737.76
	-741.91	-737.26
	-742.03	-737.40
	-742.20	-737.45
	-742.39	-737.41
		-737.62
		-737.28
mean $\pm$ SD	-741.38 $\pm$ 0.42	-737.58 $\pm$ 0.08

About 0.2 g of the sample was mixed with glass beads and placed in a thermostated U-tube of 20-cm length and 0.5-cm diameter. At constant temperature ( $\pm 0.1$  K), a nitrogen stream was passed through the U-tube and the transported amount of material was condensed in a cooled trap. The amount of condensed product was determined by GC analysis using an internal standard.

The vapor pressure  $p$  at each saturation temperature was calculated from the amount of product collected within a definite time period with the help of the ideal gas equation  $p = mRT/V(N_2)M$ , where  $R = 8.31451$  J K $^{-1}$  mol $^{-1}$ ,  $m$  = mass of the transported compound,  $V(N_2)$  is the volume of transporting gas,  $M$  = molar mass of the compound, and  $T$  = saturation temperature. The measured value of the vapor pressure  $p$  at each temperature was independent of the gas flow in the broad range from 0.1 to 0.8 cm $^3$  s $^{-1}$ , which proved the saturation of the transport gas with the compound. The vapor pressure  $p$  was corrected for the residual vapor pressure at the condensation temperature. The latter was calculated from a linear correlation between  $\ln p$  and  $T^{-1}$  obtained by iteration. The molar enthalpies of sublimation were calculated from the slope of the linear Clausius–Clapeyron correlation:  $\Delta H_{\text{sub}}^{\circ}(T) = -R(d \ln p/d T^{-1})$ . The resulting enthalpies of vaporization  $\Delta H_{\text{sub}}^{\circ}$  at  $T = 298.15$  K are recorded in Table 5. The enthalpies of sublimation, which were measured at higher temperatures, had to be corrected to the reference temperature  $T = 298.15$  K. The corrections were estimated using the Sidgwick correction:  $[\Delta H_{\text{sub}}^{\circ}(T) - \Delta H_{\text{sub}}^{\circ}(298.15 \text{ K})]/(\text{kcal mol}^{-1}) = -0.014((T/\text{K} - 298.15 \text{ K}))$ , as recommended by Chickos et al.<sup>8d</sup> With these corrections and the observed values of  $\Delta H_{\text{sub}}^{\circ}(T)$  from Table 4, the standard molar enthalpies of sublimation at  $T = 298.15$  K were calculated (Table 5).

**3. Enthalpies of Formation.** To derive  $\Delta H_f^{\circ}$  (cr) from  $\Delta H_c^{\circ}$  (Table 3), the following molar enthalpies of formation were used:<sup>8f</sup> for H $_2$ O(l),  $-(285.83 \pm 0.04)$  kJ mol $^{-1}$  and for CO $_2$ (g),  $-(393.51 \pm 0.13)$  kJ mol $^{-1}$ . Table 5 lists the derived standard molar enthalpies of combustion and standard molar enthalpies of formation in the condensed and the gaseous states. The given standard deviations of the mean include the uncertainties from calibration and the uncertainties from the combustion energies of the auxiliary materials. The enthalpies of formation in the crystalline state  $\Delta H_f^{\circ}(\text{cr})$  were calculated from  $\Delta H_c^{\circ}(\text{cr})$  of Table 3 and the values for the gas phase  $\Delta H_f^{\circ}(\text{g}) = \Delta H_f^{\circ}(\text{cr}) + \Delta H_{\text{sub}}^{\circ}$  were calculated therefrom. The energies thus derived are given in Table 6.

**X-ray Diffraction Analysis.** All measurements were made on a Rigaku AFC5R diffractometer using graphite-

**Table 4. Results from Measurements of the Vapor Pressures  $p$  by the Transpiration Method**

	$T^a$ (K)	$m^b$ (mg)	$V(N_2)^c$ (dm $^3$ )	$p^d$ (mbar)	
<b>1</b>	298.2	8.76	27.75	0.0536	
	303.3	10.4	20.12	0.0878	
	308.3	14.9	16.04	0.157	
	313.3	17.0	11.39	0.253	
	318.1	22.8	9.04	0.427	
	323.1	31.	8.26	0.650	
	328.2	44.4	7.48	1.01	
	$\Delta H_{\text{sub}}^{\circ}(313.2 \text{ K}) = (19.25 \pm 0.25) \text{ kcal mol}^{-1}$				
	$\Delta H_{\text{sub}}^{\circ}(298.15 \text{ K}) = (19.47 \pm 0.25) \text{ kcal mol}^{-1}$				
	<b>2</b>	293.5	0.0627	80.41	0.000132
298.3		0.0981	71.00	0.000234	
303.3		0.116	44.40	0.000444	
308.5		0.266	52.73	0.000856	
313.4		0.407	45.14	0.00153	
318.3		0.634	41.00	0.00262	
323.4		1.32	49.14	0.00457	
328.5		1.67	36.64	0.00774	
333.6		3.02	40.55	0.0126	
338.3		3.02	24.25	0.0211	
343.4		4.31	20.42	0.0358	
$\Delta H_{\text{sub}}^{\circ}(318.4 \text{ K}) = (22.40 \pm 0.09) \text{ kcal mol}^{-1}$					
$\Delta H_{\text{sub}}^{\circ}(298.15 \text{ K}) = (22.69 \pm 0.09) \text{ kcal mol}^{-1}$					

<sup>a</sup> Temperature of saturation, N $_2$  gas flow 0.26–0.52 cm $^3$  s $^{-1}$ . <sup>b</sup> Mass of transferred sample condensed at  $T = 243$  K. <sup>c</sup> Volume of nitrogen used to transfer sample. <sup>d</sup> Vapor pressure at temperature  $T$  of experiment; corrections were made for residual vapor pressure at  $T = 243$  K.

**Table 5. Thermochemical Results for cis- and trans-1,3,5,7-Tetraoxadecalin (1 and 2) at  $T = 298.15$  K ( $p^{\circ} = 0.1$  MPa) (in kcal/mol)**

	1	2
$\Delta H_f^{\circ}$ (cr) <sup>a</sup>	-164.5 $\pm$ 0.43	-168.28 $\pm$ 0.10
$\Delta H_{\text{sub}}^{\circ}$ <sup>b</sup>	19.47 $\pm$ 0.25	22.69 $\pm$ 0.09
$\Delta H_f^{\circ}$ m <sup>c</sup>	5.53	6.84
$T_m^c$	374.5 K	450.2 K
$\Delta H_f^{\circ}$ (g)	-145.03 $\pm$ 0.47	-145.59 $\pm$ 0.13

<sup>a</sup> Calculated from the enthalpies of combustion, Table 3. <sup>b</sup> From the measurements of vapor pressures at different temperatures from Table 4 using the Clausius–Clapeyron equation. <sup>c</sup> Enthalpy of fusion was measured by DSC with accuracy 0.05 kcal mol $^{-1}$ .

monochromated Mo K $\alpha$  radiation ( $\lambda = 0.71069$  Å) and a 12-kW rotating anode generator. The structure of **1** was solved by direct methods using SHELXS86,<sup>9</sup> and all calculations were performed using the TEXSAN crystallographic software package.<sup>10</sup> Selected structural parameters are given in Table 7, and an ORTEP<sup>11</sup> view of the molecule and of its packing arrangement is shown in Figure 1.

Crystallographic data of **1**: colorless plates of **1**, prepared by known procedures<sup>2a,3a</sup> and crystallized from ethanol; empirical formula, C $_6$ H $_{10}$ O $_4$ ; formula weight, 146.14; temperature 158(1) K; crystal dimensions 0.05  $\times$  0.12  $\times$  0.35 mm, monoclinic, space group  $P2_1/n$ ,  $Z = 2.25$  reflections for cell determination, in a  $2\theta$  range of 36–39°; unit cell parameters,  $a = 5.740(2)$ ,  $b = 4.521(3)$ , and  $c = 12.349(2)$  Å,  $\beta = 95.41(2)^\circ$ ;  $V = 319.1(2)$  Å $^3$ ,  $D_{\text{calc}} = 1.521$  g cm $^{-3}$ ,  $F(000) = 156$ ,  $\mu(\text{Mo K}\alpha) = 0.128$  mm $^{-1}$ , scan type  $\omega/2\theta$ ,  $2\theta_{\text{max}} = 60^\circ$ . Total reflections measured 2084, 934 unique reflections,  $R_{\text{int}} = 0.043$ , 578 observed reflections [ $I > 2\sigma(I)$ ], refinement on F, non-H-atoms anisotropic, H-atoms isotropic. At convergence: final  $R = 0.0340$ ,  $wR = 0.0294$ ; weights,  $w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$ ; goodness of fit = 1.347; 67 parameters;  $\Delta\rho$  (max; min) = 0.36;  $-0.16$  e Å $^{-3}$ .

**Table 6. Relative Stability Values of 1 and 2. Experimental Enthalpies of Formation ( $\Delta H_f^\circ$ ) and Calculated Relative Energies ( $\Delta E_{\text{tot}}$ , ab initio) and ( $\Delta E_{\text{ster}}$ ,  $\Delta H_f^\circ$ ,  $\Delta G^\circ$ , MM3) in kcal/mol**

	<i>trans</i> (1)		<i>cis</i> -O <sub>inside</sub> (2) <sup>a</sup>
thermochemistry		$\Delta H_f^\circ(\text{trans} \rightarrow \text{cis})$	
$\Delta H_f^\circ(\text{gas})$	$-145.0 \pm 0.5$	$-0.6 \pm 0.5$	$-145.6 \pm 0.1$
$\Delta H_f^\circ(\text{liquid})$		$-2.4$	
$\Delta H_f^\circ(\text{crystal})$		$-3.7$	
calculations		$\Delta E(\text{trans} \rightarrow \text{cis})$	
$\Delta E_{\text{tot}}$ (MP2/6-31+G*) <sup>a</sup>		0.9	
$\Delta E_{\text{ster}}$ (MM3-92) <sup>b</sup>		$-1.1$ ( $-1.8$ ) <sup>c</sup>	
$\Delta E_{\text{ster}}$ (MM3-GE) <sup>b</sup>		0.6	
$\Delta H_f^\circ(\text{gas})$ (MM3-GE)		0.5	
$\Delta G_{298}^\circ$ (MM3-GE)		0.6	
$\Delta H_f^\circ$ (MM3-GE)		0.6	

<sup>a</sup> *cis*-O<sub>outside</sub> (3) has  $E_{\text{rel}} = 4.9$  kcal/mol; cf. Figure 2 for total energies. <sup>b</sup> Cf. data in Table 1 and ref 2b. <sup>c</sup> Calculated using MM3-94.<sup>7d</sup>

**Table 7. Selected Structural Parameters: Bond Lengths ( $L$ , Å), Bond Angles ( $A$ , deg), Torsion Angles ( $T$ , deg) of *trans*- and *cis*-1,3,5,7-Tetraoxadecalin (1 and 2)**

	<i>trans</i> (1)			<i>cis</i> -O <sub>inside</sub> (2)		
	X-ray	MP2/6-31+G*	MM3-GE <sup>a</sup>	X-ray <sup>b</sup>	MP2/6-31+G*	MM3-GE <sup>a</sup>
$L^c$						
O1–C2	1.419	1.421	1.419	1.41	1.414	1.414
O1–C9	1.430	1.428	1.436	1.436	1.427	1.438
C2–O3	1.417	1.413	1.418	1.414	1.408	1.414
O3–C4	1.441	1.436	1.437	1.434	1.427	1.435
C4–C10	1.518	1.515	1.517	1.511	1.517	1.518
C9–C10	1.523	1.523	1.519	1.529	1.532	1.521
$A^c$						
C2–O1–C9	108.9	108.9	108.8	110.8	111.1	110.4
C2–O3–C4	110.8	111.4	110.5	109.9	110.4	110.1
O1–C2–O3	112.5	112.8	112.5	112.1	112.6	111.4
O3–C4–C10	107.2	107.3	107.2	111.3	111.2	110.0
O1–C9–C8	110.9	110.8	110.3	108.6	107.7	108.1
O1–C9–C10	108.9	109.0	106.6	110.2	110.8	109.1
C4–C10–C9	108.6	109.0	109.6	110.1	110.5	112.0
$T^c$						
C2–O1–C9–C8	$-179.0$	$-179.1$	179.5	176.5	175.3	178.5
C2–O1–C9–C10	$-59.6$	$-59.0$	$-61.5$	55.8	54.4	56.5
O3–C2–O1–C9	61.8	61.2	63.9	$-63.3$	$-62.3$	$-65.4$
C2–O3–C4–C10	59.0	57.9	57.4	$-56.5$	$-55.8$	$-55.8$
O1–C2–O3–C4	$-62.4$	$-61.6$	$-62.0$	63.0	62.5	64.7
O3–C4–C10–O5	177.3	$-176.9$	$-175.4$	$-69.9$	$-71.7$	$-70.5$
O3–C4–C10–C9	$-57.6$	$-56.8$	$-58.2$	50.8	49.4	49.7
O1–C9–C10–O5	180.0	180.0	180.0	69.6	70.6	69.9
O1–C9–C10–C4	59.2	58.8	60.6	$-50.0$	$-48.6$	$-49.8$
C4–C10–C9–C8	180.0	180.0	$-179.9$	$-169.7$	$-167.9$	$-169.4$

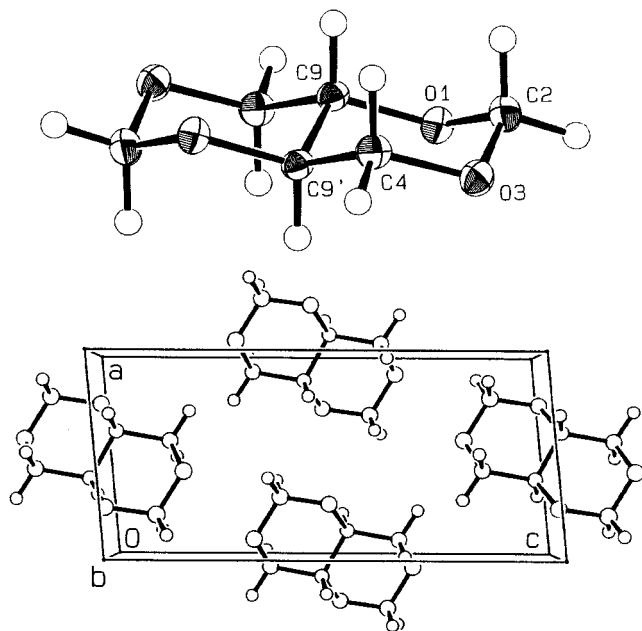
<sup>a</sup> Taken from ref 2b. <sup>b</sup> Taken from ref 2a. <sup>c</sup> Cf. also Figure 1. Notwithstanding symmetry and for the sake of consistency, all data and the discussion are in line with our general numbering (cf. 2), i.e., C9' = C10, etc.; esd's are 2–3 at the significant figure for bond lengths and 1–2 for bond and torsional angles.

The molecule is centrosymmetric and lies across a crystallographic center of inversion located at the midpoint of the bridging bond, C9–C9'. (Notwithstanding symmetry and for the sake of consistency, the discussion and Table 7 are in line with our general numbering (cf. 2), i.e., C9' = C10, etc.) The crystals were quite thin and fairly weakly diffracting and fractured after a couple of hours at 123 K; therefore, it was necessary to perform the measurements at the slightly warmer temperature of 158 K. For these reasons, it was not feasible to collect reasonable high angle data for a detailed electron density analysis. It was found, however, that the largest peak of residual electron density ( $0.36 \text{ e } \text{Å}^{-3}$ ) lies at the midpoint of the bridging C9–C9' bond, which corresponds with the center of inversion. The second highest residual peak ( $0.25 \text{ e } \text{Å}^{-3}$ ) lies almost at the midpoint of the C4–C9' bond. All other residual peaks are  $0.19 \text{ e } \text{Å}^{-3}$  or less. These features are similar to those observed in the earlier *cis*-TOD structure,<sup>2b</sup> in which a concentration of electron density was observed in the central C–C bonds.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. Fax, +44-(0)1223-336033; email, deposit@ccdc.cam.ac.uk.

**Computations. 1. Ab Initio: Proton Affinities, Atomic Charges, and Bond Orders.** QM ab initio calculations of 1 and 2 have been performed using RHF methods with various high basis sets and correlation energy corrections, until we settled on the MP2/6-31+G\*, at which level all conformers were fully optimized. The results (relative energies and selected structural parameters) are shown in Tables 6 and 7.

Proton affinities have been obtained from the difference between the calculated total energies of the parent molecule and the derived cation or anion, all of course after full geometry optimization, following Dewar and Dieter's definition<sup>12</sup> of the proton affinity (PA) of a



**Figure 1.** ORTEP drawing of *trans*-1,3,5,7-tetraoxadecalin (**1**) and its molecular packing diagram projected down the *b*-axis.

compound (B), that is, when  $B + H^+ \rightarrow HB^+$ ,  $PA(B) = E(H^+) + E(B) - E(HB^+)$ .

The validity of the approach has been shown in a previous paper<sup>13</sup> in which we had calculated the proton affinities of many reference systems with different basis sets to evaluate the influence of polarization and diffuse functions and had concluded that the MP2/6-31+G\* results are in best agreement with the experimental data.

Natural charges were calculated using the NBO 3.0 program,<sup>18</sup> including Wiberg<sup>19</sup> bond order calculations, all at the MP2/6-31+G\* level (prior to that, a Mulliken population analysis was tried and abandoned after obtaining very unreasonable results<sup>20</sup>).

All calculations ab initio have been performed using the Gaussian 94<sup>14</sup> program on Cray J932 and IBM SP-2 supercomputers.

**2. Molecular Mechanics.** All molecular mechanics calculations were performed using MM3-GE, that is, the MM3(92) force field,<sup>7</sup> reparametrized by us<sup>2b</sup> for the gauche effect.

## Discussion

First, the experimental (combustion calorimetry) gas-phase enthalpies of formation of the *trans*- (**1**) and *cis*-TOD (**2**) isomers show (Table 6) that they are largely equienergetic within the experimental error, with a slightly lower value for **2**. This is still in good agreement with our MM3-GE results and in fair agreement with the new ab initio results. The fact that **2** is more stable than **1** in the liquid and crystalline phases is probably and largely due to its high measured<sup>3c</sup> and calculated (MM3-

GE) dipole moment of 4.0 and 3.96 D, respectively. Altogether, there is a striking alleviation of the energy differences between *trans*- (**1**) and *cis*-TOD (**2**) (approximately  $-0.5$  kcal/mol) as compared to those of *trans*- and *cis*-decalin ( $\sim 2.7$  kcal/mol).<sup>21</sup> This is evidently due mainly to the different angular moieties: O–C–O in the former and C–C–C–C in the latter (vide infra).

As to the geometrical parameters (Table 7), the X-ray structure and the new ab initio calculation now provide an unusually consistent set and are in excellent agreement also with the MM3-GE data. As expected, electron correlation ameliorated the strong bond shortening obtained earlier<sup>2b</sup> from RHF calculations. We conclude that MM3-GE is indeed a reliable tool for predictive calculations for TOD and related polyoxy systems.

Two stereoelectronic effects operate in the 1,3,5,7-tetraoxadecalin (TOD) system: the anomeric effect,<sup>8c,15,16</sup> in the (two)  $g^+g^-$  CO–C–OC intraannular moieties, and the gauche effect,<sup>2b,15c,17</sup> in the (three) CO–C–C–OC interannular arrangements. It is now well known (as previously discussed and reviewed<sup>13,15,16</sup>) that the anomeric effect in a R–O–C–O–R' system consists of a difference of properties and behavior between its anti (*a*) and gauche (*g*) forms. One of the main structural manifestations is an appreciable inner O–C–O bond shortening,<sup>15a,16</sup> and this is well expressed in both the experimental and computational data here (Table 7). This is usually due to an  $On_\pi - \sigma^*_{C-O}$  two electron–two orbital interaction, except in the  $g^-g^+$  form, for example, in the case of the fixed geometry of the C–O–C–O–C part in 1,3-dioxane systems. There, the operation of a double anomeric effect “of the second kind” in the O–C–O moiety is possible, that is, involving the equatorial lone pairs in  $On_\sigma - \sigma^*_{C-O}$  interactions and leaving the axial lone pairs free. This is bound to be a less stabilizing effect than the classic anomeric effect (due to the lower  $n_\sigma$  level and the consequently larger  $n_\sigma - \sigma^*_{C-O}$  energy gap). Indeed, in the calculated 1,3-dioxane<sup>13</sup> (Figure 3), the symmetrical C–O bonds underwent little shortening but the computed proton affinity for axial protonation<sup>13</sup> was 2.1 kcal/mol more than that for the equatorial, reflecting the fact that the axial lone pair is much more available for protonation than the equatorial.

As to the gauche effect, we had found in a statistical analysis of data retrieved from the Cambridge Structural Database<sup>2b</sup> a correlation between the gauche geometry and the shortening of the OC–CO bond. We see, however, that in TOD the C9–C10 bond in the *trans* isomer (**1**) is slightly shorter than that in the *cis*-O<sub>inside</sub>-TOD (**2**) form (Table 7). In any case, the C9–C10 and the C4–C10 (C8–C9) bonds are considerably shortened, in line with the increased electron density found (vide supra) in these bonds in both isomers. It appears, though, that the flexibility of **2** allows alleviation of ring strain caused by these short bonds, by a flattening of the interannular region, viz., O3–C4–C10–C9 = 50.8° and O3–C4–C10–O5 =  $-69.9^\circ$ .

We turn now to another aspect of the 1,3,5,7-tetraoxadecalins of much interest to us, namely, their planned role as the core of macrocyclic host systems. The *cis* diastereoisomer (**2**) has been the first to be tried as such

(18) (a) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735. (b) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211. (c) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.

(19) Wiberg, K. *Tetrahedron* **1968**, *24*, 1083.

(20) Bachrach, S. M. Population Analysis and Electron Densities from Quantum Mechanics. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH: New York, 1994; Vol. 5, Chapter 3.

(21) Eliel, E. L.; Willen, S. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

(22) (a) Eliel, E. L.; Kaloustian, M. K. *Chem. Commun.* **1970**, 290. (b) Jochims, J. C.; Kobayashi Y. *Tetrahedron Lett.* **1976**, 2065 and earlier papers cited therein.



culations, as were the atomic charges and proton affinities of **1** and **2** at their different oxygen sites, to predict the probable coordination sites in each isomer. Excellent agreement was found between the experimental and theoretical structural parameters, which were also well reproduced by MM3-GE (i.e., MM3 reparametrized for the gauche effect). We think of this combination of approaches as an admirable and recommended tool for the evaluation of structure, charges, and proclivity for coordination of polyhetero (TOD) systems.

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**Supporting Information Available:** X-ray crystallographic data of *trans*-1,3,5,7-tetraoxadecalin (**1**) (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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