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Probing the Anomeric Effect. Trimethylsilyloxy and *tert*-Butoxy Substituents in 1,4-Dioxane Derivatives: Theory vs. Experiment[1]

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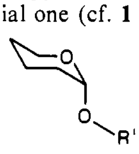
Abstract: A conformational analytical study of a series of trimethylsilyloxy- (TMSO) and *tert*-butoxy- (TBO) substituted 1,4-dioxanes was performed using NMR techniques. It was found that the TMSO and TBO groups (in contrast to MeO, AcO, and PhO substituents[2]) alleviate the anomeric effect. Arguments based on molecular mechanics (MM2-parametrized for the anomeric effect) and MO ab initio calculations of ROCOR′ ($R = CH_3$, H; $R' = SiH_3$) at various levels help rationalize this behavior, by isolating and identifying steric and electronic contributions. The electronic factors are (i) strong attractive nonbonded OSi···O interactions within the R-O-C-O-Si system, which reduce considerably the O-C-O-Si dihedral angle (down to 0°) and the energy of the "*ag*" (equatorial) form vs. the "g^+g^+" one and (ii) inductive electron donation by $SiMe_3$ (or CMe_3) which lowers the electronegativity of TMSO (or TBO). Steric factors and $(p \rightarrow d)\pi$ bonding are negligible. A single-crystal X-ray analysis of 2,5-di-*tert*-butoxy-1,4-dioxane revealed structural data in line with all the above.

The anomeric effect is recently an intensively studied and increasingly documented topic.[1-5,9-11] Phenomenologically, it consists of the tendency of a R-X-C-Y-R′ moiety to assume "gauche" conformations about the X-C-Y bonds or, e.g., of a 2-(R) oxytetrahydropyran-type molecule (as in the ubiquitous carbohydrate-pyranoside system) to prefer the axial form over the equatorial one (cf. **1** vs. **2**). Theoretically, it was first interpreted in terms of electrostatic interactions (e.g., destabilization of **2** by repulsive, parallel dipoles) and later in molecular orbital terms of delocalization of an n_p lone pair of one O into the σ^* orbital of the adjacent C-O bond as in **3**[5c] or in valence bond terms of double-bond - no-bond resonance (**3** ↔ **4**)[5c,d,h] or hyperconjugation.[11,12] It was additionally suggested to be a result of interaction between bonded electron pairs (of R-X and Y-R).[5i] The phenomenon, while well perceived, seems far from being straightforwardly interpreted.



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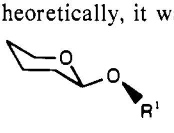

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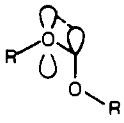

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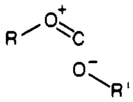

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The existence of an anomeric effect in a system is eminently manifest in its properties,[4] as follows: (i) *structure*, e.g., shorter and/or longer anomeric C-O bonds; (ii) *energy*, i.e., greater stability of gauche (axial) forms (**1**) over anti (equatorial) ones (**2**); (iii) *reactivity*, i.e., variation of rates of attack at or around the anomeric center, all those as a function of geometry.

We have recently started to probe the anomeric effect in some of its manifestations. Thus the first, structural criterion was delineated[1] and is being currently examined in more detail, while the *energy* criterion was examined in di(R)oxy-1,4-dioxanes,[2] e.g., R = Me (**5t**). These, similarly to the earlier studied dihalogeno derivatives,[5c] exhibit an overwhelming prevalence of diaxial conformations in trans 2,3- and 2,5-disubstituted derivatives, with $\Delta G(\text{diax} - \text{dieq}) > 2$ kcal/mol. The principal conclusions were that the energetics of 1,4-dioxanes bearing polar substituents are determined by a combination of anomeric, steric, and gauche

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Table I. ^1H and ^{13}C NMR Data of Various Trimethylsilyloxy and *tert*-Butoxy-Substituted 1,4-Dioxanes[a]

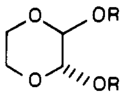
			-(R)oxy-1,4-dioxanes										
			trans-2,3-di			*trans*-2,5-di			*cis*-2,3-di			*cis*-2,5-di	2-
spectral patterns[c]	parameters	R:	**5t**[b] Me	**6t** TMS	**7t** TBU	**8t**[b] Me	**9t** TMS	**10t** TBU	**5c** Me	**6c** TMS	**7c** TBU	**10c** TBU	**12** TMS
C^5H_2	${}^2J_{gem}$		−11.52	−11.78	−11.85	−11.5	−12.15	−11.62	−11.70	−11.60	−11.64	−11.70	−12.10
C^6H_2	${}^3J_{trans}{}^d$		11.30	6.63	6.51	1.45	5.66	6.35	6.35	6.37	6.33	5.40	5.65
(AA′BB′)	${}^3J_{trans}{}^e$		1.47	5.92	6.08				6.35	6.37	6.33		
or													
C^2HOR	${}^3J_{cis}{}^f$		2.99	2.86	2.89	1.85	2.25	2.50	2.98	2.70; 3.26	2.57; 3.23	3.20	2.30
C^3H_2	$\delta_{A(A')}$		3.41	3.34	3.55	3.46	3.94	3.85	3.58	3.37	3.54	3.76	3.88
(ABX)	$\delta_{B(B')}$		4.06	3.79	3.96	4.02	3.39	3.40	3.94	3.79	3.98	3.52	3.41
	δ_X					4.51	4.88	4.79				4.82	4.73
C^2H–OR[g]	${}^3J_{2,3}$		<2	3.2	3.8				1.2	1.2	2.1		
C^3H–OR	$W_{1/2}$		1.3	0.75	1.0				0.40	0.j5	0.95		
	$\delta_{H_{2,3}}$		4.34	4.53	4.47				4.46	4.72	4.61		
	δ_{Me}		3.43	0.09	1.26	3.43	0.08	1.25	3.48	0.07	1.25		0.13
	C_2		96.55	93.90	93.45	93.98		90.89	97.52	91.92	92.10	90.22	
	C_6		58.60	61.19	61.74	59.68		66.54	61.62	61.10	61.54	64.43	
^{13}C	CMe_3				75.26			75.25			74.94	74.83	
	CH_3				28.79			28.56			28.53	28.66	
	${}^1J_{H\text{–}COR}$		171.4	162.6	162.7			159.0	165.5		158.2	160.4	
	R^h		2.13	2.19	2.18				2.13	2.14	2.16		
	ψ, deg		57.7	58.1	58.1				57.7	57.7	57.9		
	equil. comp.,[i] % diax. or ax.		>96	53	51	96	32	23					32[j]

[a] Chemical shifts in ppm, coupling constants in Hz (obtained at 90 or 360 MHz on ca. 5% $CDCl_3$ solutions). The AA′BB′ spectra **6** and **7** were analyzed using simulation techniques; with **9**, **10**, and **12** the data were obtained by direct analysis. [b] Data cited from ref 3 for ready comparison. [c] Cf. Figure 1 for visualization of the two various conformations and notations. [d] $J_{AA'}$ in **6** and **7**: J_{BX} in **9**, **10**, and **12**. [e] $J_{BB'}$ in **6** and **7**. In the cis-2,3 substituted compounds, rapid ring inversion averages the coupling constants to give $^1/_2(J_{AA'} + J_{BB'})$. [f] $J_{AB'} = J_{A'B}$ in **6** and **7**; J_{AX} in **9**, **10**, and **12**. [g] The magnitude of the couplings between the methinic protons (${}^3J_{2,3}$) were evaluated from ^{13}C satellite spectra. The half-width ($W_{1/2}$) of the singlet was taken from the regular spectrum after optimizing the natural bandwidth ($W_{1/2}$ of $CHCl_3$ −0.35 Hz). In the cases where the satellites were poorly resolved we chose to quote upper limits for ${}^3J_{2,3}$. [h] $R = J_t/J_c = {}^1/_2(J_{aa} + J_{ee})/{}^1/_2(J_{ae} + J_{ea})$; $\psi_{deg} = \arccos\,[3/(2 + 4R)]^{1/2}$.[37] [i] Evaluated from the relationship $J_{obsd} = X_{aa}J_{aa} + (1 - X_{aa})J_{ee}$ where J_{obsd} is J_{trans}, X_{aa} the molar ratio of the diaxial (or axial) conformer and J_{aa} and J_{ee} are, respectively, the limiting vicinal diaxial and diequatorial coupling constants for the AA′BB′ spectra (of **6** and **7**) or for the ABX spectra (of **9** and **10**) as taken from ref 3 (cf. also compd **5*t***): J_{aa} = 11.3 and J_{ee} = 1.47 Hz for AA′BB′; J_{aa} = 7.7 and J_{ee} = 1.2 Hz for ABX. It is assumed that these values are solvent and temperature invariant. [j] This value is to be compared with available literature values for 2-methoxy-1,4-dioxane (**11**), viz. 70% axial in $CDCl_3$[5f] and MeCN-d_3[30b] and for 2-*tert*-butoxy-1,4-dioxane (**13**) viz. 50% diaxial in MeCN-d_3.[30b]

effects, with the first being the most important factor in this interplay.

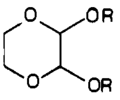
Synthesis and Conformational Analysis

We wish now to elaborate on a rather peculiar phenomenon that we came across in our study of such systems. First, we found that *trans*-2,3- and -2,5-di(trimethylsilyloxy)-1,4-dioxanes consistently exhibit relatively weak anomeric effects.[2a] This was assessed in an NMR study, using various techniques as a diagnostic tool. Thus (Table I), one can readily see that the *trans*-2,3- (**6t**) and the *trans*-2,5-di(trimethylsilyloxy) (**9t**) derivatives as well as 2-trimethylsilyloxy-1,4-dioxane (**12**) show spectra which can be only understood if one assumes almost equimolar dynamic mixtures of axial–equatorial conformations (see Figure 1). This is especially borne out by the AA′BB′ spectra of **6t**, **9t**, and **12** in which values of ${}^3J_{trans}$ and ${}^3J_{trans'}$ are all quite similar and around 6 Hz in contrast to the situation in well-defined systems like the dimethoxy derivative (**5t**) (Table I) in which ${}^3J_{trans}$ is 11.30 Hz (i.e., diaxial) and ${}^3J_{trans'}$ is 1.47 Hz (i.e., diequatorial) because of its well-defined conformation with better than 96% diaxial methoxy (MeO) groups. This is also confirmed by additional criteria which we used to probe the conformations of the TMSO derivatives, namely, ${}^3J_{2,3}$ and ^{13}C data (Table I) (as well as by comparison with fixed analogous systems).[25]

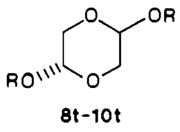


5t-7t

5: R = Me
6: R = SiMe3
7: R = CMe3

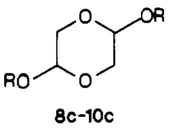


5c-7c

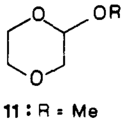


8t-10t

8: R = Me
9: R = SiMe3
10: R = CMe3



8c-10c



11: R = Me
12: R = SiMe3
13: R = CMe3

These results suggested that one deals with an apparent alleviation of the anomeric effect in mono- and di(R)oxy-1,4-dioxanes in which R = $SiMe_3$. To gain a better understanding of the origin of this behavior, it was considered desirable to look also into the behavior of the analogous *tert*-butoxy (TBO) substituted derivatives. It should be mentioned that the 2,3-di-TBO derivatives have been independently and contemporaneously prepared by Bou et al.[6a] and discussed[6b] (see, however, Discussion below). While the 2,3-di(TMSO) derivatives (**6t** and **6c**) had been prepared earlier[7a] from the corresponding 2,3-dihydroxy-1,4-dioxanes and the 2,5-di(TMSO) derivative (**9t**) from *trans*-2,5-dihydroxy-1,4-dioxane,[7b] the analogous *tert*-butoxy derivatives were obtained from the isomeric 2,3- and 2,5-dichloro-1,4-dioxanes[8] with *tert*-butyl alcohol.

We decided to study both the 2,3- and 2,5-di-*tert*-butoxy-1,4-dioxanes using NMR techniques similar to those for the TMSO derivatives. Significantly, the results (Table I) are also very similar to those from the TMS series, implying that *trans*-2,3- and *trans*-2,5-di-*tert*-butoxy-1,4-dioxane (**7t** and **10t**, respectively) also

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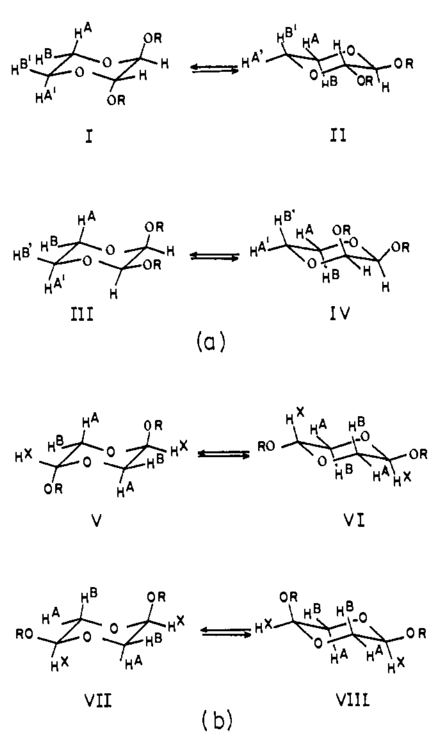

Figure 1. Conformational equilibria in disubstituted 1,4-dioxanes: (a) 2,3-di(R)oxy-1,4-dioxane and (b) 2,5-di(R)oxy-1,4-dioxane [trans (I, II, V, and VI) and cis (III, IV, VII, and VIII)]. The ring protons are labeled for the purpose of NMR analysis (cf. Table I).

occur as diaxial–diequatorial dynamic equilibrium mixtures (Figure 1: I $\rightleftarrows$ II; V $\rightleftarrows$ VI).

In addition to that, we analyzed both the static and dynamic NMR spectra of the cis-2,3- and cis-2,5-disubstituted 1,4-dioxanes **6c**, **7c**, and **10c**. The data (Table I) fully substantiate the configurational (cis) and conformational (ae $\rightleftarrows$ ea) assignments. The dynamic, variable-temperature NMR study of **7c** down to −100 °C ($\Delta\nu_{Me}$ = 49.5 Hz at 360 MHz) showed coalescence at −83 °C. Using the expression for noninteracting two sites ($K_c = \pi\Delta\nu/\sqrt{2}$) and the Eyring equation, one obtains $\Delta G_{190} = 4.56T(10.32 + \log T/k) = 9.15$ kcal/mol for the barrier to ring inversion (Figure 1a, III $\rightleftarrows$ IV).

To quantify the information obtained on the trans-2,3 derivatives, we evaluated the conformational composition of the equilibrium mixtures (Table I) by using the relationship $J_{obsd} = XJ_{aa} + (1 - X)J_{ee}$ and taking J_{aa} = 11.3 Hz and J_{ee} = 1.47 Hz from the 2,3-dimethoxy derivative (**5t**) which has been shown to be a conformationally all but homogeneous system existing in better than 96% diaxial conformation, hence a diaxial $\rightleftarrows$ diequatorial free-energy difference of or over ca. 2 kcal/mol, with very little, if any, temperature and solvent dependence.[2]

As for the mono- and trans-2,5-disubstituted TMSO and TBO derivatives, the limiting J_{aa} and J_{ee} values in the ABX spectra were taken from previous work[3] as 7.7 and 1.2 Hz, respectively. This led to even more striking results (Table I) i.e., predominant contribution of equatorial forms in the conformational equilibria in chloroform.

Ab Initio MO Calculations

The initial theoretical postulates, which were meant to rationalize the anomeric and related effects in MO terms,[5c,10] were followed by a decade of increasingly elaborate efforts from various quarters of theoretical chemistry.[9-12] The goal was to duplicate the experimental results, in particular concerning energies and structural features, and to provide thereby a better understanding of the stereoelectronics of this, both ubiquitous and sophisticated, phenomenon. Gradually, it became clear that quantum chemical (MO) ab initio calculations provide results of (varyingly) good reliability,[9] while early attempts of calculations using semiempirical (MO) methods were largely unsuccessful in tackling the anomeric effect. Recently, however, significant progress was made, indicating an eventual breakthrough in handling larger molecules of this kind by semiempirical MO[13,14] methods.

At this time, ab initio calculations could be performed only on relatively small molecular species,[9] and dimethoxymethane is, understandably, the most studied model for oxygen-containing molecules exhibiting anomeric effects.[9d,e,i-15] Hence, it is clear why we decided to use this as a reference species in order to probe theoretically the problem of alleviation of the anomeric effect by the silyl substituent. We calculated, therefore, the two lowest conformations, viz. "g^+g^+" (related to **1**) and "ag^+" (related to **2**) of dimethoxymethane (DMM) and methoxymethanol (MMO) along with the simplest possible models for our Si-containing systems, namely, methoxysilyloxymethane (MSM) and silyloxymethanol (SMO). This was done using GAUSSIAN 80[16a] with the STO-3G,[16b] 3-21G,[17a,b] 3-21G,*[17c] and 4-21G**[18] (3-3-21G* for Si[18b,c]) basis sets. The latter two include polarization functions for assessing the role of d orbitals in the stereoelectronic interplay. The 3-21G* is a fully polarized basis set, constructed directly from the 3-21G representations[17a,b] (following essentially the guidelines of Pietro et al. for 3-21G$^{(*)}$[17c]) and augmented by a complete set of six d-type functions on all heavy atoms, identical with the set used in the larger 6-31G* basis set (the 3-21G* basis set was recently used also by Bachrach and Streitwieser[19a]). Similarly, 4-21G** was constructed from the 4-21G basis set,[18a] using a 3-3-21 basis set for silicon[18b] and adding a set of d functions on all heavy atoms[18c] as well as a set of p functions on hydrogens (following the procedure of Hariharan and Pople for the 6-31G** basis set[17d]).

The calculated relative energies are assembled in Table II and the relevant structural parameters, i.e., the R–O–C–O–R′ bond lengths and angles and O–C–O–R dihedral angles, in Table III. It should be stressed that these structural features are very sensitive probes of the anomeric effect,[1,4a,5c,9] and, therefore, the calculations were performed at several levels of geometry optimization. First we optimized the relevant bond lengths, bond angles, and torsional angles, and eventually complete optimization was carried out (cf. Table II, items 2 and 3). Some single point calculations of certain significant conformations were also performed at relatively high levels of theory (items 3–5; e.g., 3-21G*//3-21G denotes a single point 3-21G* calculation at the fully optimized 3-21G geometry).

It is worth mentioning that polarization functions are essential for calculating reasonably accurate Si–O bond lengths and Si–O–C bond angles[18,19b] (here polarization functions on hydrogen may also be important) which otherwise are both too large.[18b,19b] This is well illustrated in Table III for SMO where both the Si–O bond length and the Si–O–C bond angle are larger by ca. 0.03 Å and ca. 10°, respectively, in the 3-21G structure than in the 4-21G** one; a similar correction would then apply for MSM (for similar findings in other silyloxy systems (cf. ref 18 and 19b). It may also be noted that in both respects, energy and structure, the STO-3G calculation indicates only trends and no quantitative validity.

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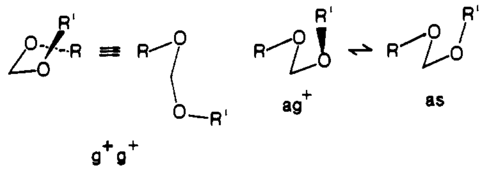
Table II. Relative Energies as Calculated ab Initio of Dimethoxymethane (DMM), Methoxysilyloxymethane (MSM), Methoxymethanol (MMO), and Silyloxymethanol (SMO) in Their Lowest Conformations:[a] g^+g^+ vs ag^+ (as)



			ΔE											
			DMM	MSM		MSM		MMO	SMO		MMO	SMO	
		R:	CH_3	CH_3		SiH_3		H	H		CH_3	SiH_3	
item	basis set	R′:	CH_3	SiH_3	$\Delta\Delta E$	CH_3	$\Delta\Delta E$	CH_3	SiH_3	$\Delta\Delta E$	H	H	$\Delta\Delta E$
1	STO-3G//STO-3G		1.76	0.28	1.48	1.63	0.13	2.83	1.41	1.42	1.28	0.96	0.32
2	3-21G//3-21G		3.90	−0.08	3.98	3.33	0.57	4.29	1.91	2.38	3.58	4.13	−0.55
3	4-21G**//4-21G**[b]							4.04	2.65	1.39	2.76	3.84	−1.08
4	3-21G*//3-21G[c,d]							3.04	2.06	1.02	2.71	4.09	−1.33
5	3-21G(*)//3-21G[c,e]								2.21	0.83		3.66	−0.95
6	3-21G//(3-21G)[f]		3.60	3.16	0.44	3.22	0.38	4.75	4.61	0.14	4.14	4.45	−0.31
7	4-21G//4-21G[g]		4.55[9i]										
8	4-31G//(4-31G)[f,g]		3.18[9d]					4.0[9c]			2.7[9c]		

[a] The values are $\Delta E = E_{ag} - E_{gg}$ and $\Delta\Delta E = \Delta E_{Me} - \Delta E_{Si}$ in kcal/mol; the relevant, lowest geometries are shown for easy reference; cf. also Table III. [b] d functions on all heavy atoms and p functions on hydrogen. [c] Calculated at 3-21G geometries. [d] d functions on all heavy atoms. [e] d functions only on Si.[17d] [f] Partly optimized structures (dihedral angles were kept at 180° (a) and 60° (g)). [g] Literature data for comparison.

The best theoretical results in both tables, i.e., from the most sophisticated calculations of known systems, are in good agreement with literature data for the anomeric effect: the energy difference $\Delta E = E_{gg} - E_{ag}$ of ca. 4 kcal/mol (e.g., in dimethoxymethane) is invariably accompanied by relative C–O bond-length shortening and COR bond-angle opening in the gauche (g) part of the (ag) conformations, as indeed expected from the MO representation of the anomeric effect and well-documented both experimentally[1,4a,5c] and theoretically.[9]

The next task was to attempt to assess the contributions of electronic and steric effects in the described alleviation of the anomeric effect, and it was thought that this could be achieved by judicious combination of the above results with those from molecular mechanics calculations.

Molecular Mechanics Calculations

Calculations of molecular structures and energies using empirical force fields or the so-called molecular mechanics method[20] are becoming increasingly vital in organic-chemical research for both verificative and predictive purposes. One of the currently most popular and useful force fields is undoubtedly Allinger's MM2 program[21] which we also use in this work, with appropriate modifications as discussed below.

It has long been recognized that the incorporation of geminal and vicinal heteroatoms in organic molecules is bound to cause considerable difficulties in force field parametrization because of the strong induced (through-bond and through-space) interactions.[20l,22,25] The anomeric effect is a typical such example and its ubiquity[4,5] was compelling in seeking a proper solution to the problem. The original MM2 program[22a] has been improved for dealing with alcohols and ethers[21,22b] and further parametrized in the torsional terms and in dipole–dipole interactions, enough to lead to reasonable energies in compounds containing also R–O–C–O–R moieties and, hence, anomeric effects. Another such effort had been made by Burkert[2b,23] with similar results. In the meantime, however, it became clear[4,5] that the anomeric effect has far-reaching implications (vide supra) not only concerning relative energies of anomeric isomers but also their structural features.[1] These, viz. bond angles and bond lengths and, in particular, the latter, were inadequately accounted for in the described force fields. Efforts to remedy this situation were made by Jeffrey et al.[24] and most recently by Allinger himself[25] who provided a general scheme of parametrization involving a redetermination of l_0 for the O–C–O bonds as a function of the torsional angles around them.[26a] In the original MM2,[22] l_0 had a fixed value and nothing for torsion–stretch interactions, and the latter were, in fact, simulated by the above-mentioned procedure. It should be noted that a stretch–bend term has been included in MM2, and this, after slight reparametrization, took care of the changes in bond angles in the O–R–C–O–R moiety as the C–O bond lengths are shortened or lengthened.

An impressive list of molecular structures was compiled[25] to test and exemplify the described procedure by comparison of the data from calculated structures with those from experimentally determined ones (by neutron or high-precision X-ray diffraction methods). Indeed, the calculated O–C–O bond lengths matched well the experimental ones—not so, however, the terminal R–O bonds, the calculated lengths of which were systematically shorter than in reality (by more than 0.01 Å).

All available structural data of systems exhibiting R–O–C–O–R′ moieties, stemming from experimental[1,4a,b,5c] or theoretical (ab initio)[9] studies (see also Table III in this work), show what may be called a first-order effect of O–C–O bond lengths and ∠ROC bond angle variations with RO–CO torsion angles. These are readily understood from the structures **3** and **4**: an RO–CO *gauche* conformation causes a shortening of the O–C bond and a lengthening of the adjacent (C–O) one as well as an increase in the ∠ROC bond angle; an *anti* conformation is apparently not

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(21) (a) The earlier version of the MM2 program (MM2(80)) was obtained from the Quantum Chemistry Program Exchange, University of Indiana, Bloomington, Ind. 47401. (b) A later, improved version (which can, in addition, deal with conjugated systems), MM2(82)/MMP2(82), Molecular Design, Ltd., Hayward, CA, includes the recent parametrization for the anomeric effect.[25]

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(26) (a) l_0 for C–O bonds is the "natural" bond length (1.407 Å) used in MM2.[21,22,25] (b) The parametrization scheme is available on request from the Tel-Aviv authors.

Table III. Bond Lengths (Å) and Angles (deg) in DMM, MSM, MMO, and SMO as Calculated ab Initio[a] (cf. Table II)

system	R	R′	conf	basis set	R - - - - - - O - - - - - - - C - - - - - - - O - - - - - - R′						ω	ω′	E (au)
DMM	CH_3	CH_3	*gg*	I[b]	1.435	109.9	1.432	1.432	109.9	1.435	66.6	66.6	−264.55444
				II	1.440	114.3	1.416	1.416	114.3	1.440	65.3	65.3	−266.47383
			ga	I	1.435	110.0	1.427	1.435	109.5	1.432	64.9	179.1	−264.55163
				II	1.442	114.8	1.402	1.424	114.5	1.433	52.4	180.8	−266.46759
MSM	CH_3	SiH_3	*gg*	I	1.430	109.9	1.440	1.420	115.3	1.690	69.3	61.2	−512.77668
				II	1.443	115.9	1.420	1.413	127.4	1.684	81.6	32.5	−516.25386
			ag (*as*)	I	1.430	111.1	1.435	1.412	116.3	1.690	179.9	−0.1	−512.77623
				II	1.436	116.1	1.431	1.398	125.9	1.690	179.7	0.0	−516.25398
			ga	I	1.434	109.9	1.432	1.419	114.8	1.686	62.6	177.0	−512.77407
				II	1.441	114.9	1.404	1.414	136.2	1.670	57.6	156.6	−516.24854
MMO	H	CH_3	*gg*	I	0.990	103.5	1.429	1.433	109.9	1.435	60.7	67.0	−225.97142
				II	0.966	110.0	1.423	1.414	114.3	1.442	61.3	63.6	−227.65981
				IV									−227.80008
				V	0.946	107.6	1.390	1.389	113.4	1.409	59.1	64.0	−228.52221
			ag	I	0.990	103.7	1.434	1.428	109.9	1.435	179.1	64.1	−225.96690
				II	0.964	112.4	1.420	1.416	115.8	1.435	277.6	57.8	−227.65425
				IV									−227.79558
				V	0.945	109.2	1.397	1.378	113.7	1.408	199.7	62.3	−228.51574
			ga	I	0.990	103.1	1.425	1.435	109.9	1.432	47.1	179.3	−225.96938
				II	0.967	108.0	1.413	1.423	115.1	1.435	30.2	181.5	−227.65409
				IV									−227.79574
				V	0.946	107.5	1.379	1.395	113.1	1.402	52.3	180.3	−228.51779
SMO	H	SiH_3	*gg*	I	0.990	103.6	1.434	1.418	115.4	1.690	62.9	60.6	−474.19360
				II	0.966	111.5	1.429	1.411	126.7	1.686	80.9	21.0	−477.44152
				III									−477.55095
				IV									−477.64781
				V	0.946	108.3	1.393	1.396	121.3	1.650	65.0	49.0	−478.24609
			ag (*as*)	I	0.988	105.6	1.433	1.414	116.4	1.690	179.9	0.2	−474.19134
				II	0.965	113.9	1.437	1.398	126.0	1.691	180.0	0.0	−477.43847
				III							178.7	−0.1	−477.54741
				IV							234.9	6.7	−477.64451
				V	0.944	110.0	1.401	1.382	122.0	1.651	220.5	30.3	−478.24216
			ga	I	0.991	102.6	1.431	1.419	115.2	1.687	35.7	177.0	−474.19207
				II	0.967	108.6	1.413	1.414	135.3	1.673	34.5	166.0	−477.43491
				III									−477.54509
				IV									−477.64126
				V	0.946	108.0	1.377	1.401	125.7	1.640	56.3	177.2	−478.24025
DMM	CH_3	CH_3	*gg*	I[c]	1.449	114.5	1.422	1.422	114.5	1.449	62.4	62.4	−267.34299
			ag		1.442	114.3	1.432	1.409	114.9	1.448	179.4	57.4	−267.33570
MMO	H	CH_3	*gg*	II[c]			1.417	1.421		1.444	60.0	60.0	−228.58786
			ag				1.430	1.400		1.444	180.0	60.0	−228.58149
			ga				1.398	1.424		1.435	60.0	180.0	−228.58353
DMM	CH_3	CH_3	*gg*	exptl[d]	1.432	114.6	1.382	1.382	114.6	1.432	63.3	63.3	

[a] See footnote *a* and geometries depicted in Table II: g = gauche$^+$, *a* = anti, *s* = syn; ω, ω′ = dihedral angles RO–CO and OC–OR′ respectively. [b] This work: (I) STO-3G//STO-3G; (II) 3-21G//3-21G; (III) 3-21G(*)//3-21G; (IV) 3-21G*//3-21G; (V) 4-21G**//4-21G**. [c] Literature data: (I) 4-21G//4-21G;[9i] (II) 4-31G.[9c] [d] Electron diffraction data.

affecting these parameters. All this is superimposed upon a basic bond shortening occurring in any geminal CX_2 unit (X = electronegative atom).[1]

There is, however, an additional structural feature, namely, an increase in the outer R–O bond length in any gauche (RO–CO) segment which may possibly be rationalized as a hybridization phenomenon connected to the above-mentioned C–O bond shortening. While this may be seen as a second-order effect, it is real, general, and by no means negligible.

We have decided therefore to incorporate this feature in a parametrization of MM2(80)[21a] for the anomeric effect. This was done essentially along the lines set by Nørskov-Lauritsen and Allinger[25] but redefining l_0 also for the terminal R–O bonds[26] as an empirical function of the adjacent O–C bond:

$$l_0'{}_{(\mathrm{OR})} = l_0 + \Delta$$

where

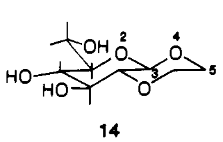
$$\Delta = aX_{(\mathrm{OC})} + b$$

and

$$X_{\mathrm{OC}} = l_0'{}_{(\mathrm{OC})} - l_0$$

The results are given in Table IV for six structures (**14–19**) taken from ref 25, representing all (g^+g^+, g^+g^-, and $ag^\pm$) conformations. While the fit with the experimental data is still not perfect and further work should be done for improving it, the problem of the outer (R–O) bonds is largely rectified. We take it, hence, as good enough for probing the subject of our immediate interest.

We calculated, using MM2 (parametrized as above), the mono-, 2,3-di-, and 2,5-di-*tert*-butoxy-1,4-dioxanes as well as the analogous methoxy derivatives for comparison (Figure 2i–iii). The relevant data for the two lowest (axial/diaxial and equatorial/diequatorial) conformations in each series are given, namely, the relative energies and dihedral angles as calculated by MM2 along with the recognized steric and electronic interactions operating in such systems, which can be regarded as six-membered rings made up of (dialkoxymethane) COCOC and (dialkoxyethane) COCCOC fragments.[2b] It is worth recalling the interactions inherent in such moieties. (i) COCOC is the basic grouping subject to *anomeric* effects (vide supra) and preferring the $g^\pm g^\pm$ form, where two anomeric effects obtain. In dimethoxymethane itself, these are degenerate by virtue of C_2 symmetry, which is



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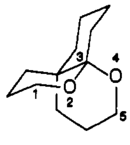

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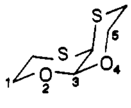

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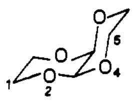

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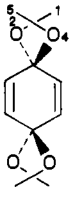

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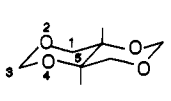

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destroyed in such compounds as 2-methoxytetrahydropyran or -1,4-dioxane (Figure 2i). (ii) COCCOC is the basic grouping subject to gauche effects[27] and preferring the aaa and $ag^{\pm}a$ forms almost equally well (by more than 85%) over all the other forms.[28]

As a further test of the reliability of our approach as well as of the modified MM2 force field we are using, we calculated (Table V) these basic moieties including terminal *tert*-butyl; i.e., in the ROCOR′ series (with R, R′ = methyl and/or *tert*-butyl), dimethoxymethane (DMM), *tert*-butoxymethoxymethane (TBMM), and di(*tert*-butoxy)methane (DTBM); and in the ROCCOR′ series, 1,2-dimethoxyethane (DME), 2-*tert*-butoxymethoxyethane (TBME), and 1,2-di(*tert*-butoxy)ethane (DTBE). The results, viz. relative energies vs. dihedral angles (Table V), are very interesting, in that the relative energies show little change in each series notwithstanding *tert*-butyl substitution, the molecular relaxation taking place mainly by increasing bond angles and dihedral angles.

Discussion

Before going into a thorough analysis of our results and for the sake of clarity it is deemed useful to stress certain significant principles and implications of the (generalized[5f,h]) anomeric effect.

To start with, its quantification turned out to be not at all a straightforward matter. Since the anomeric effect had been defined as the preference of an electronegative substituent at the anomeric center of pyranoside derivatives for the axial conformation,[4,5] its magnitude has been taken[29,30] as the sum of the free-energy difference for the axial–equatorial equilibria in a 2-substituted tetrahydropyran (e.g., $\Delta G^{\circ}_{1\rightarrow 2}$) and the corresponding "*A* value" in an appropriate cyclohexyl derivative. In time, this procedure was critically discussed[30,31] and adjusted[31] so that the anomeric effect for, e.g., an alkoxy group was evaluated at ca. 2.1 kcal/mol. To be sure, this is a $\Delta\Delta G^{\circ}$ value and includes a medium- and temperature-dependent $\Delta\Delta S$ term, whereas the anomeric effect is of enthalpic nature.[1b,32]. In this context, some $\Delta\Delta H$ data have been most recently reported[32] and smaller values were obtained, but further elaboration and a larger data base is needed before passing final judgment. As to the theoretically (ab initio) calculated values, they are consistently higher, viz., 2.7–4.5 kcal/mol (cf. Table II and ref 9) for an "anomeric effect" in a basic R-O-C-O-Me unit, which in this case is the energy difference between its "ag" and "g^+g^+" conformations.

At this point one should recall that any R-O-C-O-R′ unit has two halves, each capable of exhibiting such an anomeric effect. In cyclic systems (e.g., of the pyranoside type) this is well-perceived: while the anomeric effect represents the prevalence of the axial (**1**) over the equatorial (**2**) form, both show a clear preference of the glycosidic substituent for the "gauche" (over the "anti") form, and this is known as the exo-anomeric effect.[33a] The latter is, in fact, competitively stronger than the anomeric effect,[33a,1b,32] apparently because of the rotational freedom of the glycosidic substituent to attain the optimal geometry in each case.

In this work, the experimentally studied cyclic systems exhibit, of course, both the anomeric effect and its exo counterpart, but in our measurements we can assess only the first since the second is operating in both axial and equatorial conformations.[1,33] In the theoretical ab initio calculations of ROCOR′ systems (Table II), this is evaluated by the magnitude of ΔE, i.e., the energy difference between the two lowest "g^+g^+" and "g^+a" conformations. For R $\neq$ R′ there are two such values (Table II), with $\Delta\Delta E$ measuring the substituent effect, i.e., when H or Me is replaced by SiH_3.

It may be useful to note that in MO terms[11,12] the ΔE values can be considered as representing mainly the acceptor properties of the σ^*(C–OR′) relative to the σ^*(C–H) orbitals (i.e., in the "g^+g^+" vs. the "g^+a" conformations)[33b] along with the donor properties of the n_p(RO–C) lone pair. Following the superjacent orbital control theory,[9a,b,33b] the lower the σ^*(C–OR′) orbital and the higher the level of the n_p(RO–C) lone pair, we should expect enhancement of the anomeric effect (i.e., higher ΔE) and vice versa. Furthermore, the more electronegative an X substituent is, the lower is the corresponding σ^*(C–X) orbital.[12] At the same time, the less electronegative an R substituent on Y is, the more available a lone pair in $R\ddot{Y}$ is bound to be (a useful criterion for this property is the ionization potential of molecules containing RY units) with corresponding enhancement of the anomeric effect. For a more detailed and historical recent account on the origins of the anomeric effect and its interpretations, cf. ref 9f as well as ref 4a,b.

Turning back to our own work, the NMR results (Table I) unequivocally indicate a considerable increase in the population of equatorial conformations of trimethylsilyloxy- (TMSO) and *tert*-butoxy- (TBO) substituted 1,4-dioxanes as compared with corresponding alkoxy (e.g., MeO) derivatives.[2] The latter, one may recall, as well as the phenoxy-,[2] acetoxy-,[2] or halogeno-substituted[2a,5c] 1,4-dioxanes (in 2 and/or 3 position) overwhelmingly prefer (di)axial conformations over (di)equatorial ones as a consequence of the anomeric effect.[4] While our main concern is the origin of the above alleviation of the anomeric effect by TMSO and TBO, the results and the techniques we used to obtain them carried us far beyond that.

A careful literature search revealed some early, albeit sporadic reports showing increased populations of the equatorial conformation of trimethylsilyloxy-[34] and *tert*-butoxy-substituted[35] 1,4-dioxanes and 2-*tert*-butoxytetrahydropyran;[30,36] the latter cases were taken to indicate a weaker than usual anomeric effect but were not further investigated. Also, before going into a more elaborate discussion, we had to make sure that we did not deal with spurious effects involving nonchair conformations; this was taken care of by applying the R-value criterion[37] (Table I), which indicated that ours are veritable chair structures.

A first attractive and obvious factor to invoke in the explanation of the phenomenon we deal with was the classic steric effect, viz., an apparent weakening of the anomeric effect by the possible preference of the bulky TMSO or TBO groups for the equatorial

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Table IV. Bond Lengths (Å) and Angles (deg) in the COCOC Fragment of Structures **14–19** as Calculated by MM2 (Parametrized for the Anomeric Effect)[a]

no.	C1–O2	O2–C3	C3–O4	O4–C5	C1–O2–C3	O2–C3–O4	C3–O4–C5	C1–O2–C3–O4	O2–C3–O4–C5
14	1.443	1.414	1.413	1.439	111.4	105.2	109.6	176.9	178.8
15	1.435	1.428	1.414	1.440	114.9	104.9	115.2	179.5	−62.9
16	1.436	1.420	1.408	1.441	112.7	106.2	114.9	166.4	64.0
17	1.432	1.420	1.403	1.441	110.1	106.5	112.2	178.7	70.8
18	1.438	1.420	1.420	1.438	115.8	108.2	115.9	69.6	69.4
19	1.436	1.419	1.420	1.441	109.7	111.4	111.2	−62.9	63.0

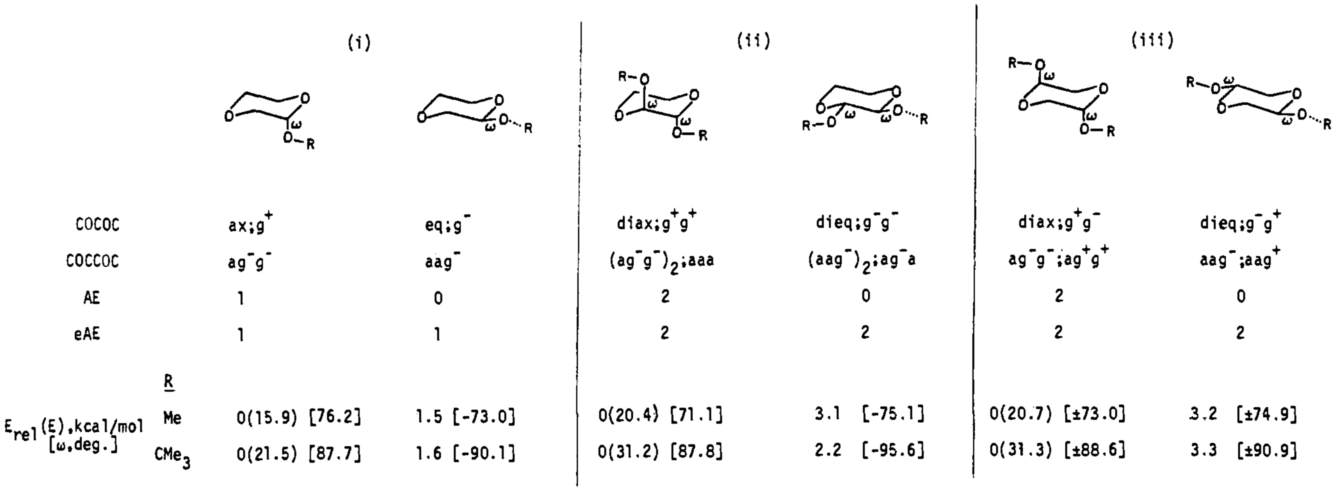
	average differences	average abs. differences:[b] calcd − exptl [MM2(82) − exptl][25]
anomeric C–O bonds	0.0002 [−0.0024]	0.0052 [0.0044]
outer C–O bonds	0.0011 [−0.0155]	0.0039 [0.0155]
bond angles	−0.40 [−0.26]	0.61 [0.55]
dihedral angles	1.55 [2.05]	2.40 [2.89]

[a] The molecules (see formulas and the numbering of the COCOC fragments therein) were taken from the collection in ref 25 for comparison with the MM2(82) as well as the experimental data. **14**, ethyleneglucopyranose (*a*,*a*): Norrestam, R., et al., *Acta Cryst., Sect. B: Struct. Sci.* **1981**, *37*, 1689 (No. 12 of ref 25). **15**, 2,10-dioxatricyclo[4.4.4.0]tetradecane (*a*,*g*): Dunitz, J. D., et al. *Ibid.* **1982**, *38*, 1241 (No. 21 of ref 25). **16**, *cis*-1,8-dioxa-4,5-dithiadecalin (*a*,*g*): Norskov-Lauritsen, L., unpublished (cited in No. 22 of ref 25). **17**, *cis*-1,4,5,8-tetraoxadecalin (*a*,*g*): Fuchs, B., et al. *J. Chem. Soc., Perkin Trans. 2* **1972**, 357 (No. 24 of ref 25). **18**, 3,3,6,6-tetramethoxycyclohexa-1,4-diene (g^+,g^+): Liebich, et al., *Acta Cryst., Sect. B: Struct. Sci.* **1976**, *32*, 269 (No. 31 of ref 25). **19**, *trans*-1,3,5,7-tetraoxadecalin (g^+,g^-): Nilsson, K., unpublished (cited in No. 41 of ref 25). [b] Differences and absolute differences between calculated and experimental results are given to stress the reliability of the approach.

Table V. Energies as Calculated by MM2 (Parametrized for the Anomeric Effect) of Dimethoxymethane (DMM), *tert*-Butoxymethoxymethane (TBMM), Di(*tert*-butoxy)methane (DTBM), Dimethoxyethane (DME), *tert*-Butoxymethoxyethane (TBME), and Di(*tert*-butoxy)ethane (DTBE)

	E_{rel} (E),[a] kcal/mol					
conformation	DMM	TBMM	DTBM	DME	TBME	DTBE
g^+g^+	0.00 (8.24)	0.00 (14.00)	0.00 (19.30)			
ga	1.96	2.05	1.99			
aa	4.00	3.72	2.51			
aaa				0.00 (9.07)	0.00 (13.92)	0.00 (18.72)
aga				0.32	0.27	0.22
ag^+g^+				2.35	2.08	4.12
ag^+g^-				1.94	1.65	4.19
aag				2.02	2.00	4.11

[a] Relative energies (total energies).



		(i)		(ii)		(iii)	
COCOC		ax;g^+	eq;g^-	diax;g^+g^+	dieq;g^-g^-	diax;g^+g^-	dieq;g^-g^+
COCCOC		ag^-g^-	aag^-	$(ag^-g^-)_2$;aaa	$(aag^-)_2$;ag^-a	ag^-g^-;ag^+g^+	aag^-;aag^+
AE		1	0	2	0	2	0
eAE		1	1	2	2	2	2
	R						
E_{rel}(E),kcal/mol [ω,deg.]	Me	0(15.9) [76.2]	1.5 [−73.0]	0(20.4) [71.1]	3.1 [−75.1]	0(20.7) [±73.0]	3.2 [±74.9]
	CMe_3	0(21.5) [87.7]	1.6 [−90.1]	0(31.2) [87.8]	2.2 [−95.6]	0(31.3) [±88.6]	3.3 [±90.9]

Figure 2. Two (one axial/diaxial and one equatorial/diequatorial) most stable conformations of (i) 2-methoxy- and 2-*tert*-butoxy-1,4-dioxane (**11** and **13**), (ii) *trans*-2,3-dimethoxy- and di(*tert*-butoxy)-1,4-dioxane (**5t** and **7t**), and (iii) *trans*-2,5-dimethoxy- and di(*tert*-butoxy)-1,4-dioxane (**8t** and **10t**) with the steric and electronic interactions within and energies of the optimized geometries (cf. dihedral angles ω) as calculated by MM2 (parametrized for the anomeric effect). The notation for the (dimethoxymethane) COCOC fragments defines the two O–C–O dihedral angles and that in the (diethoxyethane) COCCOC fragments defines the three O–C–C–O dihedral angles: ax = axial, eq = equatorial, a = anti, g = gauche, AE = anomeric effect, eAE = exo-anomeric effect, E = energy, E_{rel} = relative energy with the lowest form taken as zero in each case.

conformation. A first, admittedly circumstantial indication that this is not so was the fact that the conformational (axial–equatorial) free-energy difference $-\Delta G_{conf} = A$ for the $-OSiMe_3$ group (in cyclohexane derivatives) was reported to be a mere 0.75 kcal/mol[38] which is in between the OH and OMe groups (surprisingly, the A value of the $-OCMe_3$ group is not known and we hope to remedy this situation soon). A recent paper,[6b] however, raised some rather tenuous arguments in favor of a steric origin to the above-mentioned alleviation, by inferring from an MNDO calculation of the geometry of 2-methoxy-1,4-dioxane (**11**) in its axial form (showing a 87° dihedral angle in the anomeric OC-OCH_3 fragment) that a similar *tert*-butoxy derivative would exhibit so much steric interference with the axial ring hydrogens on C_6 as to distort even more the OC-O-*t*-Bu dihedral angle; it was speculated that this may prevent the exo-anomeric effect from operating in the axial form, destabilizing it in favor of the

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[38] Schneider, H. J. *J. Am. Chem. Soc.* **1972**, *94*, 3636.

equatorial one. We were not convinced by both the inference and the speculation, but it was clear that a thorough investigation is needed, leading to a separation of electronic from steric effects in order to assess their respective contribution to the origin of the described phenomenon.

Another electronic effect we had to reckon with was the possibility of (p $\rightarrow$ d)π bonding in Si–O. This was given, however, very little importance as soon as we found that corresponding TMSO and TBO derivatives show very similar behavior concerning the weakening of the anomeric effect and as we learned that recent ab initio calculations[18c,19b] showed (p $\rightarrow$ d)π bonding to be a minor factor in the Si–O bond. Moreover, even the involvement of dipole–dipole interactions were considered of little importance in this context, after a cursory search,[39] which revealed that MeOH and *t*-BuOH have practically the same dipole moments (1.70 and 1.67 D, respectively) and that of Me_3SiOH is not too different (1.53 D).

We start the analysis of our theoretical results with a scrutiny of Table II, i.e., the relative energies of the two lowest conformations in ROCOR′ groupings: "g^+g^+" vs. "ag^+" ("g" = gauche, "a" = anti), as calculated ab initio. Items 2 and 3 represent the best calculations, both fully optimized; item 2 is the most complete set, i.e., for dimethoxymethane (DMM), methoxysilyloxymethane (MSM), methoxymethanol (MMO), and silyloxymethanol (SMO) at 3-21G//3-21G; and item 3 is the highest level (4-21G**//4-21G**) calculation of MMO and SMO. In both, the ΔE values (which are a measure of the anomeric effect) of DMM and MMO are around 4 kcal/mol in accord with the best available literature values (items 7 and 9).[9c,i] Substitution of R′ = CH_3 by SiH_3, which is taken to model the problem we are facing (by representing closely the relationship between, say, **11** and **12**) brings about a dramatic decrease of ΔE. At 3-21G//3-21G (item 2), ΔE is nearly zero in MSM and 1.9 kcal/mol in SMO. Hence, $\Delta\Delta E$ values are 4.0 and 2.4 for the pairs DMM–MSM and MMO–SMO, respectively; at higher level (items 3 and 4), $\Delta\Delta E$'s for the latter (MMO–SMO) pair are smaller (1.4 and 1.0) but trend-preserving. These results amount to a considerable *alleviation* of the anomeric effect, as experimentally observed.

At the same time, however, we examined the behavior of R–O–C–O–R′ with R = SiH_3 vs. CH_3 in order to assess the donor properties of the $OSiH_3$ substituent in such systems. Notably, the ΔE values are *all* high and (in the best calculations, especially those including polarization functions; cf. items 2–5 in Table II) the $\Delta\Delta E$ values diminish appreciably, down to negative values in the last column. Thus, when R = methyl is substituted by silyl, $\Delta\Delta E$ = 0.6 for MSM (R = SiH_3, R′ = CH_3; item 2) and −0.6, −1.1, −1.4, and −1.0 for SMO (R = SiH_3, R′ = H; items 2, 3, 4, and 5, respectively). This is, in fact, tantamount to an *enhancement* of the anomeric effect, which is actually related to the so-called exo-anomeric effect in ring systems[33] (such as **1** or **2** with R′ = SiH_3).

The rationalization of these results is, prima facie, straightforward. The alleviation of the anomeric effect in the silyloxy-substituted systems can be taken as a manifestation of SiO–C being a poorer σ^* acceptor relative to σ^*(CO–C), because of the inductive electron-donating effect of silicon. Thus, the electronegativity of R′O is lowered (when R′ = SiH_3 as compared to CH_3), raising the energy of the σ^*(SiO–C) level and, implicitly, the n_p–σ^* energy gap.[9a,b,19c] It appears, furthermore, that the enhancement of the exo-anomeric effect is equally consistent with the above rationale since by virtue of the same inductive effect Si–O may be a better n_p donor, raising the n_p level by increasing the electron density on oxygen. All this is in line with the theory[5c,9a,b,f,10–12] of (hyperconjugative) O lone-pair electrons delocalization into the adjacent C–O σ^* orbital.[19c]

At this point, however, a closer examination of Table II along with a careful perusal of the geometrical parameters in Table III reveal some surprising features and a caveat. Geometry optimization (at any level) of methoxymethanol (MMO) and dimethoxymethane (DMM) shows that the "g^+g^+", "ag", and "ga" conformations (with $g = 60 \pm 8°$) are local minima on the rotational potential surface; not so the corresponding silyloxymethanol (SMO) and methoxysilyloxymethane (MSM) in which geometry optimizations reveal extensive distortion of the gauche O–C–O–Si dihedral angle (ω') toward a syn conformation. At 3-21G, this reaches, in fact, 0°, i.e., full eclipsing, turning the "ag" geometries of MSM and SMO into actual "as" ("s" stands for syn) geometries, but this phenomenon is less drastic at higher level (e.g., 4-21G**) and in the "g^+g^+" forms.

An attractive explanation of this behavior is the existence of a relatively strong bonding interaction between Si and the nonbonded γ-O (while we are not aware of other instances where such behavior in Si–O–C–O systems was reported it finds some analogy in the preferred syn conformation calculated for Li–CH_2–CH_2–F[40]). The above suggestion is supported by the calculated overlap populations; e.g., in SMO the interatomic distances OSi- - -O are 3.27 Å in "g^+g^+" (Table II, item 6), 2.97 Å in "g^+g^+", and 2.79 Å in "as" (Table II, item 2). The corresponding overlap populations are 0.01, 0.04, and 0.05, respectively (for comparison, the overlap population of the *covalently bonded* O–Si atoms is ca. 0.26). It appears, therefore, that the geometry of minimum energy is imposed by an interplay of OSi- - -O attractive forces, anomeric effects, as well as a certain steric effect. An estimation of the relative importance of these factors can be obtained from item 6 in Table II (see also footnote *f* there). In these 3-21G calculations the O–SiH_3 group is held in the gauche (60°) conformation where OSi- - -O interactions are bound to be relatively small owing to the relatively large separation. With these constraints the calculated ΔE value for R′ = SiH_3 in MSM is 3.16 kcal/mol, only $\Delta\Delta E$ = 0.44 kcal/mol lower than for R′ = CH_3 in DMM; similarly, $\Delta\Delta E$ = 0.14 kcal/mol for the MMO–SMO pair. We cannot but conclude that much of the anomeric effect alleviation in R–O–C–O–Si-type molecules (manifested by the large $\Delta\Delta E$ values for MSM and SMO in the fully optimized structure) originates in the OSi- - -O attractive forces which result in a propensity for O–C–O–Si eclipsing and lower the energy of the "ag" (or equatorial, e.g., **2**) forms appreciably more than that of the "g^+g^+" (or axial, e.g., **1**) forms. The latter's smaller tendency for eclipsing and higher energy may be due to a lower negative charge on the γ-oxygen and to steric interference of the two termini in R–O–C–O–Si as O–C–O–Si eclipsing is approached. Since the experimental data are on trimethylsilyloxy- (TMSO) (and not H_3SiO-) substituted systems, the bulky terminus in such *real* systems is bound to exert considerable steric hindrance to eclipsing in both "ag" and "g^+g^+" forms (perhaps still more in the latter). This should restore the O–C–O–$SiMe_3$ dihedral angle to a more conventional value and diminish the OSi- - -O attractive contribution to the molecular energy. This may also contribute to the similar behavior of TMSO and TBO groups in alleviating the anomeric effect (vide infra).

The above argument is well-supported by the structural data in Table III. Thus, focusing on MSM as calculated with the 3-21G//3-21G basis set (no. II there), the "ag" ("as") form has ω = 180°, ω' = 0°, and MeO–C–OSi bond lengths, of 1.431 and 1.398 Å, respectively, indicating a strong "exo"-anomeric interaction.[1b] In contrast, the "g^+g^+" form exhibits ω = 82°, ω' = 33°, and MeO–C–OSi bond lengths of 1.420 and 1.413 Å, respectively. Turning to SMO as calculated at the highest level, viz. 4-21G**//4-21G** (Table III, no. V), the "ag" ("as") form exhibits ω = 220°, ω' = 30°, and HO–C–OSi bond lengths of 1.40 and 1.38 Å, respectively, whereas the "g^+g^+" form has ω = 65°, ω' = 49°, and HO–C–OSi bond lengths of 1.393 and 1.396 Å, respectively. In the latter case, the "ga" conformation features normal dihedral angles and the bond lengths are characteristic of a strong "exo"-anomeric effect.

Our next worry was how to isolate the overall steric effect in order to assess if, how, and to what extent it contributes to the observed behavior. It is to this end that we undertook to improve

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Table VI. Final Positional and Thermal Parameters (×10^4) of *trans*-2,5-Di-*tert*-butoxy-1,4-dioxane (**10t**)

	x	y	z	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	−1047 (3)	1989 (3)	4713 (1)	318 (11)	359 (12)	495 (13)	58 (10)	82 (9)	71 (10)
C(2)	1260 (4)	1988 (5)	4803 (1)	293 (15)	366 (16)	415 (17)	−24 (15)	82 (13)	2 (15)
C(3)	1890 (5)	350 (5)	5386 (2)	314 (16)	431 (18)	444 (19)	14 (15)	14 (14)	−28 (15)
O(7)	2296 (3)	1244 (3)	4204 (1)	367 (12)	311 (10)	412 (11)	5 (9)	125 (9)	44 (10)
C(8)	2679 (5)	2981 (5)	3665 (1)	421 (17)	386 (16)	378 (17)	83 (15)	106 (15)	50 (16)
C(9)	577 (6)	4041 (7)	3388 (2)	562 (24)	787 (25)	633 (24)	283 (21)	24 (19)	113 (21)
C(10)	3768 (6)	1524 (6)	3113 (2)	687 (23)	592 (22)	489 (19)	7 (18)	201 (17)	8 (21)
C(11)	4203 (6)	4896 (5)	3942 (2)	590 (22)	451 (22)	649 (24)	50 (16)	131 (18)	−105 (19)

the parametrization of MM2 (as described above) for optimal accuracy in geometry calculations of the molecules under scrutiny. The leading thought was that, having a force field accurately parametrized for the anomeric effect but not for electronic inductive effects of, say, *tert*-butyl, we would take advantage, in fact, of what it *cannot do*. The calculated *tert*-butoxy (TBO) substituted systems and the relevant results are depicted in Figure 2 and are taken to indicate that steric effects play no significant role in the observed alleviation of the anomeric effect.

Indeed, the molecular mechanics calculations (Figure 2i–iii) give ΔE = 1.5 kcal/mol in favor of the axial form of 2-methoxy-1,4-dioxane and nicely double this value for both *trans*-2,3- and 2,5-dimethoxy-1,4-dioxane, in good agreement with experimental observations.[2b,5f] Similar calculations of the corresponding *tert*-butoxy derivatives leave these energy differences almost unchanged (the only exception, viz., 2.2 kcal/mol for *trans*-2,3-di(*tert*-butoxy)-1,4-dioxane still means net preference for the diaxial form and is partially accounted for below), in flagrant conflict with the experimental results (vide supra and Table I). For the record, in each case of the three in Figure 2 the entire potential surface was calculated, but all other conformations were deleted for being more than 4 kcal/mol above the ground state; hence, only the two lowest forms in each case were given. The most stable is always the axial or diaxial where both the anomeric effect and an exo-anomeric effect operate, and the next one is the equatorial or diequatorial form with no anomeric but with an exo-anomeric effect; all other rotamers are much less stable. Interestingly, the same energetic *trends* are preserved in calculations using MM2(80). We take the above results to suggest that steric effects per se do not account for the observed alleviation of the anomeric effect.

For additional evidence, the basic fragments ROCOR′ and ROCCOR′ were calculated with the same force field (Table V); *tert*-butyl vs. methyl substitution for R(R′) does not affect the energy differences in ROCOR′ ($E_{ga} - E_{gg}$) but shows some decrease for ROCCOR′ ($E_{aga} - E_{aaa}$) in the same direction as that observed in Figure 2ii.

Furthermore, the torsional angles ω increase in all cases where *tert*-butyl takes the place of methyl *both in axial and* (*even more so*) *in equatorial conformations*, without altering the energetic order. Hence, this relaxation process cannot account for the observed weakening of the anomeric effect, as inferred by Giralt et al.[6b] Furthermore, the details of our calculation of the *trans*-2,3-di(R)oxy derivatives (Figure 2ii) show that, contrary to the assumption of Giralt et al.,[6b] the axial OR substituents experience no repulsive interaction with the axial hydrogens on C_5 or C_6, the closest interatomic distance (H···H) being 3 Å.

The slight deviation from the trend observed in the 2,3-di-*tert*-butoxy derivative in Figure 2ii is, therefore, attributed to a balance of steric interactions, including the one (Table V) which causes a decrease of the energy difference $E_{aga} - E_{aaa}$ for 1,2-di(*tert*-butoxy)ethane (DTBE) as compared with 1,2-dimethoxyethane (DME).

At this point, we present and discuss the structural data of *trans*-2,5-di-*tert*-butoxy-1,4-dioxane (**10t**) since (while this paper was being written up) we succeeded in growing a single crystal of **10t** and subjecting it to X-ray diffraction analysis. The results are rather interesting and gratifying.

Table VII. Geometrical Parameters of *trans*-2,5-Di-*tert*-butoxy-1,4-dioxane (**10t**) (Crystallographic Inversion at 0, 0, $^1/_2$)

	(a) Bond Lengths (Å)		
O(1)–C(2)	1.424 (3)	O(7)–C(8)	1.450 (3)
O(1)–C(6)	1.427 (3)	C(8)–C(9)	1.508 (4)
C(2)–C(3)	1.496 (4)	C(8)–C(10)	1.515 (4)
C(2)–O(4)	1.400 (3)	C(8)–C(11)	1.515 (4)
	(b) Bond Angles (deg)		
C(6)–O(1)–C(2)	111.9 (2)	O(7)–C(8)–C(9)	111.4 (2)
O(1)–C(2)–C(3)	109.1 (2)	O(7)–C(8)–C(10)	102.8 (2)
O(1)–C(2)–O(7)	112.0 (2)	O(7)–C(8)–C(11)	109.9 (2)
C(3)–C(2)–O(7)	108.7 (2)	C(9)–C(8)–C(10)	110.9 (3)
C(2)–C(3)–O(4)	112.6 (2)	C(9)–C(8)–C(11)	111.0 (3)
C(2)–O(7)–C(8)	118.4 (2)	C(10)–C(8)–C(11)	110.5 (2)
	(c) Torsion Angles (deg)		
C(6)–O(1)–C(2)–C(3)	−54.8 (3)	O(7)–C(2)–C(3)–O(4)	−67.3 (3)
C(6)–O(1)–C(2)–O(7)	65.6 (3)	C(2)–O(1)–C(3′)–C(5)	56.7 (3)
O(1)–C(2)–O(7)–C(8)	84.1 (3)	C(2)–O(7)–C(8)–C(9)	−60.2 (3)
C(3)–C(2)–O(7)–C(8)	−155.3 (2)	C(2)–O(7)–C(8)–C(10)	179.1 (2)
O(1)–C(2)–C(3)–O(4)	55.1 (3)	C(2)–O(7)–C(8)–C(11)	63.2 (3)

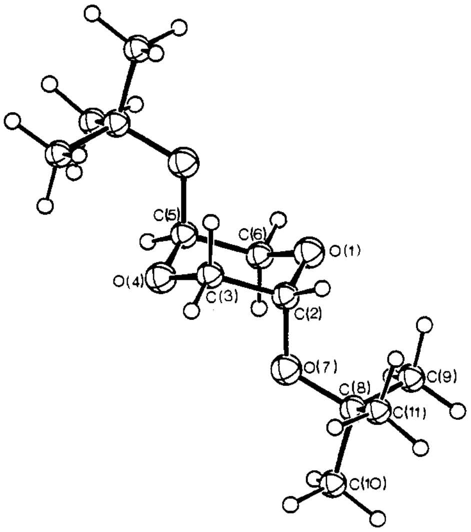

Figure 3. X-ray (ORTEP) structure of *trans*-2,5-di-*tert*-butoxy-1,4-dioxane (**10t**).

As evident from the data in Tables VI and VII and from the ORTEP drawing (Figure 3) of the molecule (**10t**), the latter exists in the crystal in the diaxial form, which in $CDCl_3$ solution at room temperature contributes only 23% to the equilibrium mixture. While this may well be due to favorable packing forces, it is of interest to examine the relevant structural parameters in comparison with known literature values, e.g., in analogous carbohydrates, viz. α-glycosides.[1,41] The latter exhibit characteristic (average) bond lengths of C_6–O_1 1.437, O_1–C_2 1.415, and (exo) C_2–O_7 1.403 Å, and bond angles of (endo) C_2–O_1–C_6 ≃ (exo) C_2–O_7–C_8 = 113.5° (cf. Figure 3 for atom numbering, which differs from the usual carbohydrate numbering, for better convenience).

The corresponding values observed in **10t** are C_6–O_1 1.427, C_2–O_1 1.424, C_2–O_7 1.400 Å; C_2–O_1–C_6 = 111.9°, C_2–O_7–C_8 =

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(41) Jeffrey, G. A. In ref 4a, p 50.

118.4°, C_6–O_1–C_2–O_7 = 65.6°, and O_1–C_2–O_7–C_8 = 84.1°. The relatively long C_2–O_1 bond and small C_2–O_1–C_6 angle indicate an alleviated anomeric effect, but with a strong exo-anomeric effect, as expected.[1b] We proceed now to compare these with the corresponding calculated data (by MM2, parametrized for the anomeric effect) in **10t** (cf. Figure 2iii): C_6–O_1 1.443, O_1–C_2 1.411, C_2–O_7 1.409 Å; C_6–O_1–C_2 = 112.4°, C_2–O_7–C_8 = 116.9°, C_6–O_1–C_2–O_7 = 66.8°, and O_1–C_2–O_7–C_8 = 88.6°. These results are, in our opinion, significant in that indeed they *did not* succeed to duplicate the experimental bond lengths, and are logically attributed to the above-stressed fact that MM2 accounts for steric and anomeric effects but *not* for the electronic inductive effect of *tert*-butyl. Therefore, no intrinsic steric effect is at the roots of the observed alleviation of the anomeric effect, since otherwise our MM2 calculations would have reflected it.

It is novel and revealing that by also applying the structural criterion[1b] one can observe that *tert*-butoxy (TBO) anomeric substitution weakens the anomeric effect. This, in fact, strengthens the argument that we deal with an electron-donating inductive effect of *tert*-butyl which lowers the electronegativity of TBO, but an electrostatic attraction between the positively charged quaternary carbon in $OCMe_3$ and the γ-oxygen could still operate and be stronger in equatorial than in axial form. In fact, our above-presented findings and arguments may well make it worth reevaluating the role of electrostatic attraction between a terminal (carbon, silicon) atom in a R–O–C–X–R′ moiety and the γ-heteroatom, i.e., $RO^{\delta-}\cdots{}^{\delta+}R'X$ or $OR^{\delta+}\cdots{}^{\delta-}XR'$, in the framework of the anomeric effect.[3b,47] We believe that taking into account such a contribution may help rationalize some features of the anomeric effect, which are still unaccounted for, such as the elongation of the terminal (O–R) bond lengths (cf. section on molecular mechanics calculations). This aspect is being looked into presently and will be reported in due time.

In conclusion, we have shown experimentally that *tert*-butoxy- and trimethylsilyloxy derivatives of 1,4-dioxane exhibit weaker than usual anomeric effects. We have improved the parametrization of MM2 for the anomeric effect and used it in conjunction with ab initio MO calculations to show that no steric effects but rather electronic factors cause this phenomenon. These electronic factors involve an inductive electron donation by TBU or TMS and also a peculiar γ-O- - -SiO attractive interaction for the latter case (entropy could have some significance in this picture, but we have no information, as yet, what role it plays, if at all; we plan to deal with this problem presently). Finally, we secured corroborative X-ray structural data (for **10**).

One may well expect the described phenomenon to become useful for directing both conformational behavior and, even more significantly, reactivity by judicious introduction of trimethylsilyl or *tert*-butyl in anomeric positions.

Experimental Section

NMR spectra were measured on Bruker WH-90 and AM-360 WB instruments. Theoretical spectra were calculated using either the original LAOCON 3 simulation program[42] or its PANIC (Bruker-ASPECT 2000) version and tested for reliability at various field strengths. Mass spectra were taken on a DuPont 21-491 B mass spectrometer. Gas chromatography was performed on a Packard-427 instrument using a Carbowax capillary column and a Spectrophysics System I electronic integrator. The NMR data are assembled in Table I.

Preparative Work. The diastereoisomeric 2,3-di(trimethylsilyloxy)-1,4-dioxanes (**6t**, **6c**) were prepared according to a published procedure.[7a]

trans-2,5-Di(trimethylsilyloxy)-1,4-dioxane (**9t**) was prepared by trimethylsilylation of the 2,5-dihydroxy derivative made by dimerization of glycolaldehyde.[43] It was isolated from the isomeric mixture by preparative GLPC (R_T = 25 min on a 20% Carbowax-20M/Chromosorb W column at 125 °C and 100 mL/min carrier flow) and exhibited largely the reported properties.[34]

2-Trimethylsilyloxy-1,4-dioxane (**12**) was prepared by trimethylsilylation (1.9 g of TMSCl + 1.4 g of pyridine) of 2-hydroxy-1,4-dioxane[44] (3.9 g in 20 mL of benzene). The crude product (1.1 g) was distilled in vacuo (130-150 °C (25 torr)) and purified by preparative chromatography as above (R_T = 8 min) to give 0.7 g (16%) of product (**9**) as a colorless oil: MS *m/z* 176 (5, M^+); IR ν_{max} (neat) 1270, 1255 cm^{-1}.

The diastereoisomeric 2,3-di(*tert*-butoxy)-1,4-dioxanes (**7t**, **7c**) were prepared using a recently published procedure.[6a] Earlier we had used a somewhat less efficient procedure. A mixture of absolute *tert*-butyl alcohol (400 mL), *trans*-2,3-dichlorodioxane[8a] (12.85 g), and pyridine (13 g) was stirred under nitrogen at 50 °C for 20 h. Most of the *tert*-butyl alcohol was evaporated in vacuo and the residue taken up in CH_2Cl_2. This solution was washed with water (three times) and dried over anhydrous K_2CO_3. After filtration, the organic solvents were removed to leave a crude residue of 14.6 g (92%) consisting of a roughly 2:1 mixture of *trans*- and *cis*-2,3-di(*tert*-butoxy)-1,4-dioxane (**7t** and **7c**, respectively). These were resolved by HPLC (SI-1000, 8% ethyl acetate in cyclohexane); **7t** was recrystallized from petroleum ether, mp 60–62 °C and **7c** remained a colorless oil, properties as given[6a] (Table I).

The diastereoisomeric 2,5-di(*tert*-butoxy)-1,4-dioxanes (**10t**, **10c**) were prepared by adding 2,5-dichloro-1,4-dioxane[8b] (5.5 g) to a solution of dry pyridine (5.7 g) in dry *tert*-butyl alcohol (150 ml). The mixture was stirred under nitrogen at 30 °C for 24 h after which the *tert*-butyl alcohol was evaporated; the residue was taken up in methylene chloride. The resulting solution was washed with 0.5% HCl and water, dried, and evaporated to dryness. The crude mixture of diastereoisomers (4.2 g, 50%) consisting of 65% cis (**10c**) and 35% trans (**10t**) (by NMR) was resolved by fractional crystallization from hexane. The trans isomer (**10t**) crystallized first: mp 110 °C; *m/z* 232 (M^+ 12%), 57 ($C_4H_9^+$, 100%); ^1H and ^{13}C NMR in Table I. The pure cis isomer (**10c**) was obtained free of trans contamination after repeated recrystallizations: mp 70 °C; *m/z* 232 (M^+, 8%), 57 ($C_4H_9^+$, 100%); ^1H and ^{13}C NMR in Table I.

X-ray Diffraction Work. Intensity data were collected at ca. 291 K on an Enraf-Nonius CAD-4 diffractometer, using monochromatized Mo Kα radiation (0.7107 Å) in the ω–2θ mode with a scan width 1.25 + 0.3 tan θ out to 2θ = 54°.

The structure was solved by direct methods (MULTAN 80)[46] and refinement of the asymmetric unit (one-half of the molecule which is located on a crystallographic center of inversion) was performed by full-matrix least-squares calculations.[47] All hydrogens were located directly on the difference maps; the methyls were refined as geometrically rigid groups.

Crystal data for 10t ($C_{12}H_{24}H_4$): M = 232, monoclinic, space group $P2_1/c$; a = 6.148 (4), b = 5.632 (1), c = 19.270 (3) Å; β = 91.67 (3)°; Z = 2; V = 667.0 (5) Å^3; D_x = 1.157 g cm^{-3}. Of 1731 measured reflections, 1111 were unique (R_{int} = 0.333); $F(000)$ = 256, R = 0.042, R_w = 0.044 for 621 observations with $I > 3\sigma(I)$. Final atomic coordinates and thermal parameters are given in Table VI and relevant bond lengths, bond angles, and torsion angles are given in Table VII. The average esd's are 0.004 Å, 0.2°, and 0.3° for bond lengths, bond angles, and torsion angles, respectively. The full list along with the structure tables are deposited as supplementary material.

Acknowledgment. The computations were performed at the Tel-Aviv University Computational Center on IBM-4381 and CYBER-855 computers and at the Technion Computer Center on an IBM-3081 computer. We are grateful to Dr. Drora Cohen, Bar-Ilan University, for her gracious and helpful assistance with some of the (MO) calculations.

Registry No. 6t, 53226-11-2; **6c**, 53226-10-1; **7t**, 68470-79-1; **7c**, 68470-78-0; **9t**, 6891-61-8; **10t**, 100604-28-2; **10c**, 106064-19-1; **12**, 100604-29-3; DMM, 109-87-5; MSM, 106064-17-9; MMO, 4461-52-3; SMO, 106064-18-0; TBMM, 24209-75-4; DTBM, 2568-93-6; DME, 110-71-4; TBME, 66728-50-5; DTBE, 26547-47-7; *t*-BuOH, 75-65-0; *trans*-2,3-dichloro-1,4-dioxane, 3883-43-0; 2,3-dichloro-1,4-dioxane, 57791-59-0.

Supplementary Material Available: Lists of crystal data, atomic coordinates, and thermal parameters (2 pages); list of structure factors (3 pages). Ordering information is given on any current masthead page.

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