J. Phys. Chem. A **2005,** *109,* 6077−6082 **6077**

Orbital Interactions and Their Effects on ^{13}C NMR Chemical Shifts for 4,6-Disubstituted-2,2-dimethyl-1,3-dioxanes. A Theoretical Study

Cláudio F. Tormena,*,† Luiz C. Dias,‡ and Roberto Rittner‡

Departamento de Química, Faculdade de Filosofia Ciências e Letras de Ribeirão Preto, Universidade de São Paulo (USP), Av. Bandeirantes, 3900, 14040-901, Ribeirão Preto SP, Brazil, and Instituto de Química, Universidade Estadual de Campinas (UNICAMP), C. P. 6154, CEP 13084-971, Campinas, SP, Brazil

Received: April 20, 2005; In Final Form: May 17, 2005

A theoretical study is employed to describe the orbital interactions involved in the conformers' stability, the energies for the stereoelectronic interactions, and the corresponding effects of these interactions on the molecular structure (bond lengths) for *cis*- and *trans*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes. For *cis*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes, two $LP_O \rightarrow \sigma^*_{C(2)-Me(8)}$ interactions are extremely important and the energies involved in these interactions are in the range 6.81−7.58 kcal mol^{-1} for the $LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$ and 7.58−7.71 kcal mol^{-1} for the $LP_{O(3)} \rightarrow \sigma^*_{C(2)-Me(8)}$ interaction. These two $LP_O \rightarrow \sigma^*_{C(2)-Me(8)}$ interactions cause an upfield shift, indicating an increased shielding (increased electron density) of the ketal carbon $C_{(2)}$ as well as the axial $Me_{(8)}$ group in the chair conformation. These $LP_O \rightarrow \sigma^*_{C(2)-Me(8)}$ hyperconjugative anomeric type interactions can explain the ^{13}C NMR chemical shifts at 19 ppm for the axial methyl group "$Me_{(8)}$" and 98.5 ppm for the ketal carbon "$C_{(2)}$". The observed results for the trans derivatives showed that for compounds **2a**−**c** (R = −CN, −C≡CH, and −CHO, respectively) the chair conformation is predominant, whereas for **2d**,**f**−**h** [$-CH_3$, −Ph, $-C_6H_4(p\text{-}NO_2)$, $-C_6H_4(p\text{-}OCH_3)$, respectively] the twist-boat is the most stable compound and for **2e** [$-C(CH_3)_3$] is the only form.

Introduction

Chemical reactions involve interactions between electronic orbitals, accounting for the increasingly important role of the concept of stereoelectronic effects in modern organic chemistry.[1,2] Two-electron/two-orbital interactions are important for understanding molecular properties and reactivities and their magnitude depends on (a) the donor ability of the filled (bonding or nonbonding) orbital, (b) the acceptor ability of the antibonding orbital, (c) the energy difference between filled and empty orbitals, (d) the strength of the overlap between donor and acceptor orbitals, and (e) the hybridization of the lone pairs in the case of nonbonding orbitals.[3] These delocalization energies are the stabilizing energies calculated by second-order perturbation theory analysis relative to an idealized Lewis structure and a real molecule, affecting electron density distribution,[4] molecular orbital energies,[4] IR frequencies,[5] and NMR parameters.[6] These two-electron/two-orbital interactions influence conformational preferences,[7] modify reactivity,[2,3] and determine selectivity.[8] Depending on the nature of interacting orbitals, these interactions can provide electron density to electron-deficient centers[9] or withdraw it from electron-rich centers, and can stabilize incipient bonds.[10,11] The hyperconjugative interaction between oxygen lone pairs (nonbonding electronic orbitals) and $\sigma^*_{(C-X)}$ bonds is very well documented and the anomeric effect is a very nice demonstration of such two-electron/two-orbital interactions.[1,12,13]

The conformations of 1,3-dioxanes have been a subject of exciting theoretical and experimental investigation.[14,15] It is observed for the *cis*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes (**1**) that the most stable conformation is the chair with the substituents at $C_{(4)}$ and $C_{(6)}$ in equatorial positions (Figure 1).[14,15] For the *trans*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes (**2**) there are two stable forms, chair and twist-boat, with the stability of these conformations depending on the groups attached at positions 4 and 6. An anti acetonide will preferably adopt a twist-boat conformation in case the chair conformations are destabilized.[14,15]

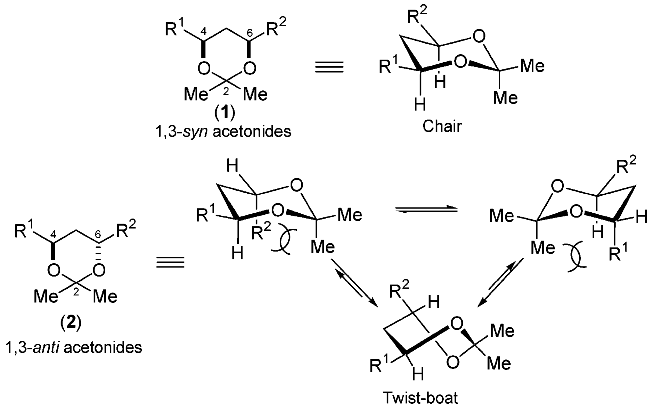

Figure 1. Preferred conformations for *cis*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes (**1**) and *trans*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes (**2**).[16,17]

^{13}C NMR spectroscopy is a very useful tool to study substituent effects on the electronic environment of a given carbon.[6] In this sense, Rychnovsky and co-workers described a very useful and simple method for determining the relative stereochemistry of 1,3-diols derived from polyacetate polyols, by analyzing the ^{13}C NMR resonances of their three acetonide carbons.[14−17] They observed that *syn*- and *anti*-1,3-diol ac-

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* Corresponding author. E-mail: tormena@ffclrp.usp.br. Fax: +55-16-633-8151, Phone: +55-16-602-4382.

† Universidade de São Paulo.

‡ Universidade Estadual de Campinas.

10.1021/jp052048a CCC: $30.25

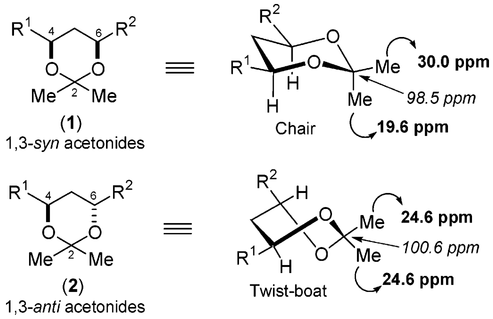


Figure 2. ^{13}C chemical shifts for *cis*- and *trans*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes.[14,15]

etonides can be assigned from the ^{13}C NMR chemical shifts of the ketal methyl groups and from the ^{13}C NMR chemical shifts of the ketal carbon (Figure 2).[14,15] It is observed that *syn*-1,3-diol acetonides have ketal methyl shifts at 19 and 30 ppm and ketal carbon shifts at 98.5 ppm, whereas the *anti*-acetonides have methyl shifts in a range of 24−25 ppm and ketal shifts at 100.5 ppm.[14,15] Later on, Evans et al. extended the method to polypropionate polyols, with the same trends being observed.[18,19] This large difference (about 11 ppm) between the ^{13}C chemical shifts of axial and equatorial methyl groups in *syn*-1,3-diol acetonides is intriguing because the difference in ^{13}C chemical shifts of axial and equatorial methyl groups in methyl cyclohexane and derivatives are in the range of 5 ppm, in agreement with the expectation that carbons which are more sterically perturbed (axial methyl groups) will appear at higher field than those that are not (equatorial methyl groups).[20]

This method relies on the conformational properties of the corresponding 1,3-diol acetonides, as most 1,3-*syn* acetonides exist in a well-defined chair conformation with both substituents (at $C_{(4)}$ and $C_{(6)}$) in equatorial positions (Figure 2). In this preferred conformation, one of the ketal methyl groups is axial and the other is equatorial. An *anti*-acetonide exists in a twist-boat conformation to avoid 1,3-diaxial interactions that would be present in either chair conformation (R_1 vs Me or R_2 vs Me). In this twist-boat conformation, the two-acetal methyl groups are in nearly identical environments.

Rychnovsky and co-workers,[14,15] described some *trans*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes derivatives (Figure 1), applying experimental and theoretical data, and demonstrated that these compounds adopt a twist-boat conformation. Small substituents such as nitriles and alkynes lead to significant population of the chair conformation.[14]

Here, a theoretical approach is applied to describe the orbital interactions involved in conformers' stability, the corresponding energies for these interactions, and the effect of these interactions on molecular structure (bond lengths). To this end, the *cis*- and *trans*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes **1** and **2**, respectively (Figure 3), were chosen to perform these studies.

Computational Details

All structures (chair and twist-boat) for the *cis*- and *trans*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes were fully optimized (Tables 1−4) by applying B3LYP hybrid functional[21,22] and 6-311++G(d,p) basis set using the Gaussian98 program.[23] This basis set includes additional diffuse functions (++), which were used to take into account the relatively diffuse nature of the oxygen lone pairs.

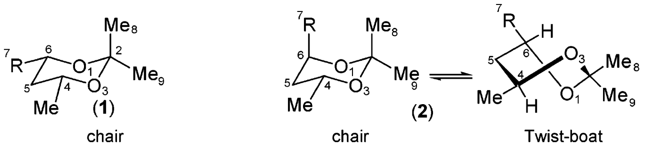
Electronic structures of compounds **1a−h** (cis) and **2a−h** (trans) were studied using natural bond orbital (NBO) analysis.[24] The NBO analysis transforms the canonical delocalized Hartree−Fock (HF) MO, or the corresponding natural orbitals of a correlated description into localized orbitals, which are closely tied to chemical bonding concepts. Filled NBO describe the hypothetical strictly localized Lewis structure. NBO analysis allows for specific lone pairs to antibonding orbital delocalizations to be quantified, from which a detailed picture of their contribution to the energetics of different conformations can be obtained. The interactions between filled and vacant orbitals represent the deviation of the molecule from the Lewis structure and can be used as a measure of delocalization.[25] The NBO energies were calculated at the B3LYP/6-311G(d,p) level.

Results and Discussion

The geometries and energies for *cis*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes were optimized. Only one stable chair conformation, with both substituents at $C_{(4)}$ and $C_{(6)}$ in equatorial positions, was obtained (Figure 3).[14] For these systems, the two $LP_O \rightarrow \sigma^*_{C(2)-Me(8)}$ hyperconjugative anomeric type interactions are extremely important and the energy involved in this interaction is in the range 6.81−7.58 kcal mol^{-1} for the $LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$ and 7.58−7.71 kcal mol^{-1} for the $LP_{O(3)} \rightarrow \sigma^*_{C(2)-Me(8)}$ interaction (Figure 4, Table 1) in compounds **1a−h**. These two $LP_O \rightarrow \sigma^*_{C(2)-Me(8)}$ interactions cause an upfield shift, indicating increased shielding (increased electron density) of the ketal carbon $C_{(2)}$ as well as of the axial $Me_{(8)}$ group in the chair conformation. These two $LP_O \rightarrow \sigma^*_{C(2)-Me(8)}$ stereoelectronic interactions may explain the ^{13}C NMR chemical shifts at 19 ppm for the axial methyl group "$Me_{(8)}$" and 98.5 ppm for the ketal carbon "$C_{(2)}$". It is also noteworthy that the $LP_{O(3)} \rightarrow \sigma^*_{C(2)-Me(8)}$ hyperconjugative anomeric type interaction for compounds **1a−h** is stronger than the corresponding $LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$ interactions, as expected from the higher availability of the $O_{(3)}$ lone pair (Figure 4, Table 1).

In the presence of this stereoelectronic interaction, it is expected that the central bond lengths $O_{(1)}-C_{(2)}$ and $O_{(3)}-C_{(2)}$ shorten because they have increased π character, and the acceptor $C_{(2)}-Me_{(8)}$ bond lengthens, because the corresponding antibonding orbital turns populated. In addition, as these interactions become stronger, it is expected to see shorter $O_{(3)}-C_{(2)}$ bonds when compared to $O_{(1)}-C_{(2)}$ bonds, which, in fact, is observed. Thus, for these acetonides derived from 1,3-syn diols, calculated bond lengths for the $C_{(2)}-Me_{(8)}$ bond (1.534−1.536 Å) showed this bond is about 0.015 Å longer than the $C_{(2)}-Me_{(9)}$ bond (1.519−1.521 Å), as expected from these hyperconjugative anomeric type interactions (Table 1).

In an attempt to try to understand the ^{13}C NMR chemical shifts for the methyl groups attached to $C_{(2)}$ in the 1,3-syn



R = (a) -CN, (b) -CCH, (c) CHO, (d) CH_3, (e) $C(CH_3)_3$, (f) Ph, (g) $C_6H_4(p\text{-}NO_2)$, (h) $C_6H_4(p\text{-}OCH_3)$

Figure 3. Chair conformation for *cis*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes (**1a−h**) and chair and twist-boat conformations for *trans*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes (**2a−h**).

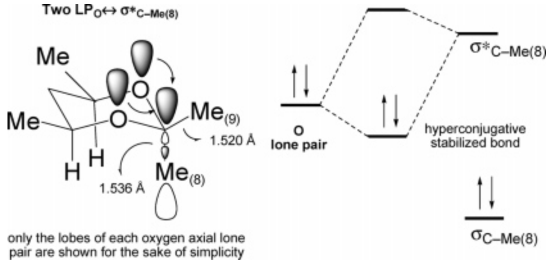


Figure 4. Vicinal hyperconjugatively stabilization by overlap between two occupied (oxygen lone pairs) and an unoccupied orbital $\sigma^*_{C_{(2)}-Me_{(8)}}$.

TABLE 1: Selected Bond Lengths (Å) and Orbital Interactions (kcal mol^{-1}) for the Chair Conformer of the *cis*-4,6-Disubstitued-2,2-dimethyl-1,3-dioxanes (1a−h) Calculated at the B3LYP/6-311++G(d,p) Level

parameters	**a**	**b**	**c**	**d**	**f**	**g**	**h**
$r_{O_{(1)}-C_{(2)}}$	1.441	1.433	1.435	1.427	1.430	1.435	1.429
$r_{C_{(2)}-O_{(3)}}$	1.422	1.425	1.423	1.427	1.426	1.423	1.426
$r_{O_{(3)}-C_{(4)}}$	1.434	1.434	1.436	1.434	1.434	1.434	1.435
$r_{C_{(4)}-C_{(5)}}$	1.530	1.529	1.529	1.529	1.529	1.529	1.529
$r_{C_{(5)}-C_{(6)}}$	1.536	1.536	1.532	1.529	1.536	1.537	1.535
$r_{C_{(6)}-O_{(1)}}$	1.422	1.432	1.421	1.434	1.430	1.425	1.432
$r_{C_{(6)}-C_{(7)}}$	1.468	1.460	1.520	1.519	1.514	1.513	1.512
$r_{C_{(2)}-C_{(8)}}$	1.534	1.535	1.534	1.536	1.536	1.535	1.536
$r_{C_{(2)}-C_{(9)}}$	1.519	1.520	1.519	1.521	1.521	1.520	1.521
$LP_{O_{(1)}}\rightarrow\sigma^*_{C_{(2)}-Me_{(8)}}$	6.81	7.30	7.11	7.58	7.47	7.18	7.54
$LP_{O_{(3)}}\rightarrow\sigma^*_{C_{(2)}-Me_{(8)}}$	7.71	7.67	7.68	7.58	7.67	7.71	7.66
$LP_{O_{(1)}}\rightarrow\sigma^*_{C_{(2)}-Me_{(9)}}$	0.84	1.01	0.88	0.94	1.06	1.02	1.06
$LP_{O_{(3)}}\rightarrow\sigma^*_{C_{(2)}-Me_{(9)}}$	0.99	1.09	0.97	0.94	1.09	1.10	1.08
$\sigma_{C_{(6)}-O_{(1)}}\rightarrow\sigma^*_{C_{(2)}-Me_{(9)}}$	1.38	1.55	1.43	1.51	1.51	1.42	1.53
$\sigma_{C_{(4)}-O_{(3)}}\rightarrow\sigma^*_{C_{(2)}-Me_{(9)}}$	1.54	1.61	1.54	1.51	1.67	1.64	1.62
$\sigma_{C_{(2)}-Me_{(9)}}\rightarrow\sigma^*_{O_{(1)}-C_{(6)}}$	2.95	3.49	2.83	2.95	3.49	3.45	3.48
$\sigma_{C_{(2)}-Me_{(9)}}\rightarrow\sigma^*_{O_{(3)}-C_{(4)}}$	3.04	3.47	2.93	2.95	3.47	3.51	3.46
$\sigma_{O_{(1)}-C_{(6)}}\rightarrow\sigma^*_{C_{(7)}-R_{(10)}}$	4.14	3.91	1.40	1.09	1.73	1.88	1.68
$\sigma_{C_{(7)}-R_{(10)}}\rightarrow\sigma^*_{O_{(1)}-C_{(6)}}$	4.79	6.41	0.54	4.12	1.22	1.27	1.11

acetonides, the hyperconjugative anomeric type interactions showed in Table 1 are the most important. However, it is very important to point out that the following hyperconjugative anomeric type interactions: $LP_{O_{(1)}}\rightarrow\sigma^*_{C_{(2)}-O_{(3)}}$ (11.5 kcal mol^{-1}), $LP_{O_{(3)}}\rightarrow\sigma^*_{C_{(2)}-O_{(1)}}$ (11.5 kcal mol^{-1}), $LP_{O_{(1)}}\rightarrow\sigma^*_{C_{(6)}-C_{(5)}}$ (6.5 kcal mol^{-1}), $LP_{O_{(3)}}\rightarrow\sigma^*_{C_{(4)}-C_{(5)}}$ (6.5 kcal mol^{-1}), might also influence the charge density as well as the bond lengths in these systems.

Other important values from NBO analysis that can be used to explain ^{13}C NMR chemical shifts for methyl groups $Me_{(8)}$ and $Me_{(9)}$, as well as for the ketal carbon $C_{(2)}$, are the occupancies of the antibonding orbitals (electronic density) and the atomic charges. For 1,3-*syn*-acetonides **1a−h** the occupancy for $\sigma^*_{C_{(2)}-Me_{(8)}}$ is around 0.0479 whereas for $\sigma^*_{C_{(2)}-Me_{(9)}}$ the value is 0.0225 (almost half the value observed for $\sigma^*_{C_{(2)}-Me_{(8)}}$). This high occupancy for $\sigma^*_{C_{(2)}-Me_{(8)}}$ is because of the strong $LP_{O_{(1)}}\rightarrow\sigma^*_{C_{(2)}-Me_{(8)}}$. An electronic density over the $Me_{(8)}$, higher than over $Me_{(9)}$, can explain why this methyl group appears upfield, in comparison to $Me_{(9)}$, in ^{13}C NMR spectrum. This effect also explains why the $C_{(2)}$ ketal carbon, for the 1,3-*syn*-acetonides, appears upfield when compared with the same ketal carbon in 1,3-*trans*-acetonides. The atomic charges can be used as well to explain this behavior. The atomic charge for the axial $Me_{(8)}$ is around −0.627 whereas for the equatorial $Me_{(9)}$ the atomic charge is around −0.584. It is important to point out that these values for atomic charges were observed for all compounds **1a−h**. Moreover, it was observed for 1,3-*trans*-acetonides that the $C_{(2)}$ is downfield (100 ppm) whereas for 1,3-*cis*-acetonides the $C_{(2)}$ is upfield (98 ppm). This behavior was observed for all compounds and is due to the atomic charges, because for the trans isomer it is 0.60 and for cis it is 0.58. These results explain the experimental ^{13}C NMR data.

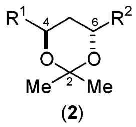
Figure 5 shows the conformational equilibrium for *trans*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes. The energies (Table 2) and geometries for the most stable forms, chair (Table 3) and twist-boat (Table 4), are shown.

Data from Table 2 show that the chair conformer is more stable than twist-boat for compounds **2a−c**. The energy difference decreases from −1.75 kcal mol^{-1} for **2a** to −0.66 kcal mol^{-1} for **2c**. The greater stability for the chair conformer could be, in principle, attributed to a small 1,3-diaxial interaction. These substituents (R = −CN, −C≡CH, and −CHO) present almost the same size, especially cyano and acetylene groups. However, the chair conformer for compound **2a** (cyano derivative) is 0.8 kcal mol^{-1} more stable than the chair form for compound **2b** (acetylene derivative).

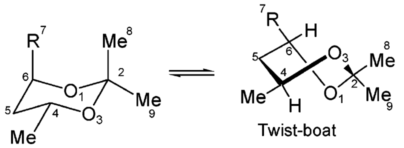
For compounds **2d−h** the twist-boat is the most stable conformer (Table 1). The chair form is present with less than 3% in the equilibrium between chair and twist-boat. For compound **2e** only the twist-boat conformer was found as a stable form. Table 2 shows that, for *trans*-4-methyl-6-phenyl-2,2-dimethyl-1,3-dioxane (**2f**), the energy difference between twist-boat and chair is 2.15 kcal mol^{-1}. When an electron-withdrawing group (NO_2) is attached to the phenyl ring at a para position, a small reduction (0.15 kcal mol^{-1}) in energy difference is observed. When an electron donor group (CH_3O) is attached to the phenyl ring (at its para position), the energy difference between chair and twist-boat increases.

If only the steric interactions are taken as responsible for the conformation stability, compounds **2a−c** and **2f−h**, should present similar energy differences. Therefore, the conformational stability for the studied compounds cannot be explained only by 1,3-diaxial interactions. In this instance, orbital interactions (anomeric type hyperconjugative interactions) must be considered to explain the theoretical data.

The orbital interactions (NBO analysis) can be invoked to explain the stability of the chair conformer for compounds **2a−c** and the energy difference in compounds **2f−h** (Table 4). The orbital interactions that are involved in the conformational stability are those present in the $C_{(7)}-C_{(6)}-O_{(1)}-C_{(2)}-O_{(3)}$



(**2**)
1,3-*anti* acetonides



R = (a) -CN, (b) -CCH, (c) CHO, (d) CH_3, (e) $C(CH_3)_3$, (f) Ph, (g) $C_6H_4(p\text{-}NO_2)$, (h) $C_6H_4(p\text{-}OCH_3)$

Figure 5. Most stable chair and twist-boat conformations for *trans*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes (**2a−h**), including atom numbers.

TABLE 2: Absolute (hartrees) and Relative (kcal mol^{-1}) Energies between Chair and Twist-Boat Conformers for *trans*-4,6-Disubstituted-2,2-dimethyl-1,3-dioxanes (2a−h) Calculated at the B3LYP/6-311++G(d,p) Level

compounds	chair	twist-boat	ΔE^a
a (R = −CN)	−518.0048998	−518.0021046	−1.75
b (R = −CCH)	−501.9029252	−501.9013485	−0.98
c (R = −CHO)	−539.0951215	−539.0940676	−0.66
d (R = $-CH_3$)	−465.069761	−465.0732482	2.18
e (R = $-C(CH_3)_3$)	unstable	−583.0432292	
f (R = −Ph)	−656.8483445	−656.8517791	2.15
g (R = $-C_6H_4(p\text{-}NO_2)$)	−771.4045774	−771.4077679	2.00
h (R = $-C_6H_4(p\text{-}OCH_3)$)	−861.4123174	−861.4164581	2.59

[a] $\Delta E = E_{chair} - E_{twist-boat.}$

TABLE 3: Selected Bond Lengths (Å) and Orbital Interactions (kcal mol^{-1}) for the Chair Conformer of the *trans*-4,6-Disubstituted-2,2-dimethyl-1,3-dioxanes (2a−h) Calculated at the B3LYP/6-311++G(d,p) Level

parameters	**a**	**b**	**c**	**d**	**f**	**g**	**h**
$r_{O(1)-C(2)}$	1.449	1.439	1.442	1.430	1.434	1.440	1.433
$r_{C(2)-O(3)}$	1.420	1.423	1.419	1.425	1.425	1.423	1.426
$r_{O(3)-C(4)}$	1.435	1.435	1.438	1.434	1.434	1.434	1.434
$r_{C(4)-C(5)}$	1.527	1.526	1.527	1.527	1.528	1.527	1.527
$r_{C(5)-C(6)}$	1.538	1.539	1.529	1.535	1.533	1.533	1.533
$r_{C(6)-O(1)}$	1.418	1.431	1.425	1.439	1.440	1.435	1.442
$r_{C(6)-C(7)}$	1.483	1.473	1.530	1.533	1.531	1.532	1.529
$r_{C(2)-C(8)}$	1.532	1.534	1.535	1.537	1.535	1.534	1.535
$r_{C(2)-C(9)}$	1.520	1.521	1.520	1.523	1.522	1.521	1.522
$LP_{O(1)} \rightarrow \sigma^*_{C(6)-C(7)}$	9.14	8.07	8.34	7.41	7.14	7.45	7.02
$LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$	6.81	7.35	7.13	7.93	7.55	7.31	7.61
$LP_{O(3)} \rightarrow \sigma^*_{C(2)-Me(8)}$	7.56	7.52	7.77	7.61	7.45	7.52	7.43
$LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(9)}$	0.72	0.80	0.90	1.56	1.09	1.05	1.10
$LP_{O(3)} \rightarrow \sigma^*_{C(2)-Me(9)}$	1.01	0.98	0.99	0.94	1.09	1.10	1.08
$\sigma_{C(6)-O(1)} \rightarrow \sigma^*_{C(2)-Me(9)}$	1.10	1.20	1.26	1.20	1.31	1.24	1.33
$\sigma_{C(4)-O(3)} \rightarrow \sigma^*_{C(2)-Me(9)}$	1.55	1.55	1.62	1.50	1.63	1.65	1.63
$\sigma_{C(2)-Me(9)} \rightarrow \sigma^*_{O(1)-C(6)}$	2.94	3.03	2.85	3.02	3.53	3.49	3.53
$\sigma_{C(2)-Me(9)} \rightarrow \sigma^*_{O(3)-C(4)}$	3.04	2.99	3.03	2.98	3.50	3.54	3.49

framework (Figure 5). Thus, only the orbital interactions present in this molecular fragment will be discussed here. The energies for the orbital interactions were calculated by applying NBO analysis and the results are presented in Tables 3 and 4.

It can be observed from Table 3 that, for compounds **2a**−**c** as well as **2g**, one of the most important orbital interactions is $LP_{O(1)} \rightarrow \sigma^*_{C(6)-C(7)}$. The energy for the $LP_{O(1)} \rightarrow \sigma^*_{C(6)-C(7)}$ interaction decreases from 9.14 kcal mol^{-1} for **2a** to 7.45 kcal mol^{-1} for **2g** and is larger than that for $LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$ for the same compounds. However, for compounds **2d**, **2f**, and **2h** the $LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$ interactions become more important because the antibonding orbitals $\sigma^*_{C(2)-Me(8)}$ are lower in energy in comparison to the corresponding $\sigma^*_{C(6)-C(7)}$ orbitals. For compounds **2d**−**h** a competition between steric and electronic interactions is also expected. It must be noted that, for compounds **2a**−**c** and **2g**, the $LP_{O(3)} \rightarrow \sigma^*_{C(2)-Me(8)}$ is stronger than $LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$ as the $O_{(1)}$ lone pair is also involved in an orbital interaction with the $\sigma^*_{C(6)-C(7)}$ orbital.

The preference for chair or twist boat conformation, for compounds **2a**−**h**, is dependent on the acceptor ability for the group attached to carbon $C_{(6)}$. This behavior can be observed from a comparison of compound **2g** with **2h** (Table 3). For compound **2g**, bearing an electron withdrawing group (NO_2), the $LP_{O(1)} \rightarrow \sigma^*_{C(6)-C(7)}$ interaction becomes more important than the $LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$ interaction, although the strongest observed interaction is the $LP_{O(3)} \rightarrow \sigma^*_{C(2)-Me(8)}$. An opposite behavior is observed for compound **2h**, where the CH_3O group is present.

For compounds **2d**−**f** and **2h**, the same trend is observed, with $LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$ interaction being favored, the nature of the "R" group being important to increase the electron density at $O_{(1)}$. It is clear from these results that the $O_{(1)}$ lone pair is being delocalized to different extents into different antibonding orbitals ($\sigma^*_{C(6)-C(7)}$ and $\sigma^*_{C(2)-Me(8)}$).

The orbital interaction energies for twist-boat conformation presented almost the same values for all compounds (Table 4), indicating that the most important interactions that stabilize the electronic system for these compounds are $LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$ and $LP_{O(3)} \rightarrow \sigma^*_{C(2)-Me(9)}$ (Table 4). Compounds **2a**−**c** prefer the chair conformation because the $LP_{O(1)} \rightarrow \sigma^*_{C(6)-C(7)}$ hyperconjugative anomeric type interactions predominate over any other interaction observed for the twist-boat conformation. This is in perfect accordance with recently published results by Alabugin and Zeidan.[2a] These authors reported a theoretical study regarding general trends in hyperconjugative acceptor abilities of σ bonds using NBO analysis at the B3LYP/6-31G** level, and they found that σ^*_{C-C} bond orbitals are very good acceptors.

As expected, bond lengths for $C_{(2)}-Me_{(8)}$ and $C_{(6)}-C_{(7)}$ in compounds **2a**−**c** and **2g** are longer (Table 4), and bond lengths for $O_{(1)}-C_{(6)}$ are shorter in the chair conformation (Table 3), when compared to the same bond lengths in the twist-boat conformation (Table 4). For compounds **2a**−**c** (R = −CN, −C≡CH, and −CHO) and **2g** [R = $C_6H_4(p\text{-}NO_2)$] the anomeric interaction $LP_{O(1)} \rightarrow \sigma^*_{C(6)-C(7)}$ is stronger than $LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$. As expected, the interaction $LP_{O(3)} \rightarrow \sigma^*_{C(2)-Me(8)}$ is stronger than $LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$, as this is the only possible anomeric interac-

TABLE 4: Selected Bond Length (Å) and Orbital Interactions (kcal mol^{-1}), for the Twist-Boat Conformer of the *trans*-4,6-Disubstituted-2,2-dimethyl-1,3-dioxanes (2a−h) Calculated at the B3LYP/6-311++G(d,p) Level

parameters	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
$r_{O(1)-C(2)}$	1.444	1.436	1.439	1.430	1.430	1.434	1.439	1.433
$r_{C(2)-O(3)}$	1.427	1.429	1.426	1.430	1.430	1.429	1.427	1.429
$r_{O(3)-C(4)}$	1.437	1.436	1.438	1.436	1.435	1.436	1.436	1.436
$r_{C(4)-C(5)}$	1.543	1.542	1.539	1.540	1.539	1.542	1.542	1.542
$r_{C(5)-C(6)}$	1.545	1.546	1.537	1.540	1.543	1.546	1.548	1.545
$r_{C(6)-O(1)}$	1.424	1.435	1.424	1.436	1.436	1.431	1.426	1.436
$r_{C(6)-C(7)}$	1.466	1.459	1.518	1.518	1.549	1.512	1.511	1.509
$r_{C(2)-C(8)}$	1.524	1.526	1.525	1.527	1.527	1.526	1.525	1.526
$r_{C(2)-C(9)}$	1.525	1.526	1.525	1.527	1.527	1.527	1.526	1.527
$LP_{O(1)} \rightarrow \sigma^*_{C(6)-C(7)}$	1.37	0.77	1.54	0.81		0.81	0.86	0.75
$LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(8)}$	6.63	7.07	6.83	7.38		7.34	7.05	7.44
$LP_{O(3)} \rightarrow \sigma^*_{C(2)-Me(8)}$	1.67	1.71	1.83	1.78		1.82	1.79	1.81
$LP_{O(1)} \rightarrow \sigma^*_{C(2)-Me(9)}$	1.62	1.67	1.65	1.77		1.87	1.84	1.88
$LP_{O(3)} \rightarrow \sigma^*_{C(2)-Me(9)}$	7.54	7.44	7.53	7.39		7.65	7.72	7.63
$\sigma_{C(6)-O(1)} \rightarrow \sigma^*_{C(2)-Me(9)}$	1.30	1.44	1.31	1.43		1.38	1.30	1.42
$\sigma_{C(4)-O(3)} \rightarrow \sigma^*_{C(2)-Me(8)}$	1.47	1.45	1.46	1.43		1.52	1.53	1.50
$\sigma_{C(2)-Me(9)} \rightarrow \sigma^*_{O(1)-C(6)}$	2.51	2.57	2.51	2.55		3.06	3.02	3.05
$\sigma_{C(2)-Me(8)} \rightarrow \sigma^*_{O(3)-C(4)}$	2.67	2.60	2.58	2.55		3.13	3.18	3.13

tion for the $O_{(3)}$ lone pair. This makes the $O_{(3)}-C_{(2)}$ bond shorter than the $O_{(1)}-C_{(2)}$ bonds for **2a**−**c** and **2g** (Table 3).

The bond length for $C_{(2)}-Me_{(8)}$ is longer (1.532−1.537 Å) than for $C_{(2)}-Me_{(9)}$ (1.520−1.523 Å) in the chair conformations of compounds **2a**−**h** (Table 3). This is not the case for the twist-boat conformation (Table 4), as the $C_{(2)}-Me_{(8)}$ and $C_{(2)}-Me_{(9)}$ bonds in this conformation present approximately the same bond lengths (1.524−1.527 Å). These results, together with orbital interactions, antibonding orbital occupancies and atomic charges can be invoked to explain the ^{13}C NMR behavior for the methyl groups and the ketal $C_{(2)}$ carbons in both conformations.

The $C_{(2)}-Me$ bond lengths present different values because of the stronger interaction between $LP_{(O)}\rightarrow\sigma^*_{C(2)-Me(8)}$, leading to high electronic density over $C_{(2)}-Me_{(8)}$, for the chair conformation. The occupancy for $\sigma^*_{C(2)-Me(8)}$ is 0.0467 and the occupancy for the $\sigma^*_{C(2)-Me(9)}$ is 0.0253. The electronic density over these bonds leads to an atomic charge for $Me_{(8)}$ equal to −0.631, whereas for $Me_{(9)}$ the value is −0.587. This behavior of occupancy and atomic charge was observed for all compounds (**2a**−**h**). For the twist-boat conformer, these occupancies and atomic charges are almost the same, because for $\sigma^*_{C(2)-Me(8)}$ it is 0.0376 and for $\sigma^*_{C(2)-Me(9)}$ it is 0.0381, whereas the atomic charge for $Me_{(8)}$ and $Me_{(9)}$ are equal, −0.608.

Conclusions

Theoretical calculations on *cis*- (**1**) and *trans*-4,6-disubstituted-2,2-dimethyl-1,3-dioxanes (**2**) showed that compounds **1** occur in the chair form whereas **2** are in equilibrium between a chair and twist-boat, which is dependent on the substituents at the 4 and 6 positions. The chair conformation of the cis derivatives is stabilized by the $LP_{O(3)}\rightarrow\sigma^*_{C(2)-Me(8)}$ (7.58−7.71 kcal mol^{-1}) and by the $LP_{O(1)}\rightarrow\sigma^*_{C(2)-Me(8)}$ (6.81−7.58 kcal mol^{-1}) interactions. These interactions lead to changes in the bond lengths and on the atomic charges, which are in agreement with the observed ^{13}C NMR chemical shifts at 19 ppm for the axial methyl group "$Me_{(8)}$" and 98.5 ppm for the ketal carbon "$C_{(2)}$".

The observed results for the trans derivatives showed that for compounds **2a**−**c** (R = −CN, −C≡CH, and −CHO, respectively) the chair conformation is predominant, whereas for **2d** and **2f**−**h** [$-CH_3$, −Ph, $-C_6H_4$(*p*-NO_2), $-C_6H_4$(*p*-OCH_3), respectively] the twist-boat is the most stable compound and, for **2e** [$-C(CH_3)_3$], is the only form.

The conformational stability of this later series is also dependent on the orbital interactions, besides the 1,3-diaxial steric interactions. The differences between these two groups of trans derivatives (**2a**−**c** and **2d**−**h**) relies mostly on the involved orbital interactions. For the former (**2a**−**c**) $LP_{O(1)}\rightarrow\sigma^*_{C(6)-C(7)}$ predominates, although the $LP_{O(1)}\rightarrow\sigma^*_{C(2)-Me(8)}$ and $LP_{O(3)}\rightarrow\sigma^*_{C(2)-Me(8)}$ are also important, whereas for the other group (**2d**−**h**) the more important interactions are $LP_{O(1)}\rightarrow\sigma^*_{C(2)-Me(8)}$ and $LP_{O(3)}\rightarrow\sigma^*_{C(2)-Me(9)}$.

However, it was also concluded that the preference for chair or twist boat conformation, for compounds **2a**−**h**, is very dependent on the acceptor ability of the group attached to carbon $C_{(6)}$. This was clearly shown by the energies involved in the orbital interactions of compounds **2g** ($-PhNO_2$) and **2h** ($-PhCH_3O$). The $LP_{O(1)}\rightarrow\sigma^*_{C(6)-C(7)}$ interaction for **2g** became more important than the $LP_{O(1)}\rightarrow\sigma^*_{C(2)-Me(8)}$ interaction, in the chair conformation, although the strongest observed interaction was the $LP_{O(3)}\rightarrow\sigma^*_{C(2)-Me(8)}$. An opposite behavior is observed for compound **2h**.

The stabilizing effects for the twist-boat conformation are $LP_{O(1)}\rightarrow\sigma^*_{C(2)-Me(8)}$ and $LP_{O(3)}\rightarrow\sigma^*_{C(2)-Me(9)}$ interactions, which are by far more important than any other interactions. Here, $C_{(2)}-Me_{(8)}$ and $C_{(2)}-Me_{(9)}$ bond lengths are almost the same for the whole series, which together with antibonding orbital occupancies and atomic charges (also almost the same for all derivatives), can be invoked to explain the ^{13}C NMR behavior for the methyl groups and the ketal $C_{(2)}$ carbons, for these trans derivatives, which occur mostly in twist-boat conformation.

Acknowledgment. We are grateful to FAPESP and CNPq (Brazil) for financial support. We also thank Prof. Carol H. Collins, from IQ-UNICAMP, for helpful suggestions about English grammar and style.

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