JOC Article

Hyperconjugation and the Increasing Bulk of $OCOCX_3$ Substituents in Trans-1,4-Disubstituted Cyclohexanes Destabilize the Diequatorial Conformer

Erich Kleinpeter,*,† Nadja Rolla,† Andreas Koch,† and Ferdinando Taddei‡

Department of Chemistry, University of Potsdam, P.O. Box 60 15 53, D-14415 Potsdam, Germany, and
Dipartimento di Chimica, Universita degli Studi di Modena e Reggio Emilia, Via Campi 183,
I-41100 Modena, Italy

kp@chem.uni-potsdam.de

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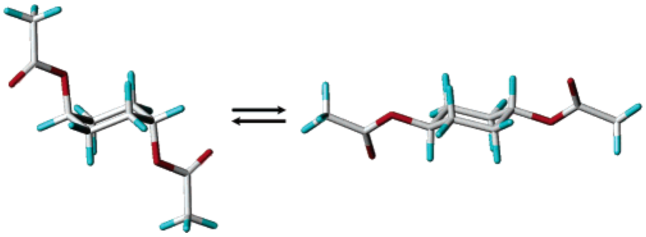

The trans diesters of 1,4-cyclohexanediol with a number of acetic acid analogues, CX_3COOH, of varying steric hindrance and polarity (CX_3 = Me, Et, *iso*-Pr, *tert*-Bu, CF_3, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, CBr_3) were synthesized, and the axial,axial/equatorial,equatorial conformational equilibria were studied by low-temperature ^{1}H NMR spectroscopy in CD_2Cl_2. The structures and relative energies of the axial,axial and equatorial,equatorial conformers were calculated at both the MP2/6-311G* and the MP2/6-311+G* levels of theory, and it was only by including diffuse functions that a good correlation of $\Delta G°_{calcd}$ vs $\Delta G°_{exptl}$ could be obtained. Both the structures and the energy differences of the axial,axial and equatorial,equatorial conformers are discussed with respect to the established models of conformational analysis, viz., steric 1,3-diaxial and hyperconjugative interactions. Interestingly, the hyperconjugative interactions $\sigma_{C-C}/\sigma_{C-H}\rightarrow\sigma^*_{C-O}$, together with a steric effect which also destabilizes the equatorial,equatorial conformers on increasing bulk of the substituents, proved to dominate the position of the conformational equilibria. In addition, the preference of the axial,axial conformers with respect to their equatorial,equatorial analogues was greater than expected from the conformational energies of the corresponding substituents in the monosubstituted cyclohexyl esters. The reason for this very interesting and unexpected result is also discussed.

Introduction

In the very recent discussion concerning the reason for the preferred staggered conformation of ethane,[1-3] the origin of the torsional barrier was attributed to both traditional steric hindrance *and* hyperconjugation, the latter stabilizing by 1 kcal mol^{-1} the *staggered* conformation with respect to the *eclipsed* conformation,[3] whereas 2.9 kcal mol^{-1} of stabilization was attributed to the former. We obtained a similar result when studying the conformational equilibria of monosubstituted cyclohexanes with substituents of variable polarity and volume.[4-7] However, the two substituent influences were active in different directions: (i) there was no perceived influence on the position of the axial/equatorial equilibria **Ia** vs **Ib** (cf. Scheme 1) from

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* To whom correspondence should be addressed. Phone: 0049-331-977-5210. Fax: 0049-331-977-5064.

† University of Potsdam.

‡ Universita degli Studi di Modena e Reggio Emilia.

[1] Bickelhaupt, F. M.; Baerends, E. J. *Angew. Chem.* **2003**, *115*, 4315.

[2] Weinhold, F. *Angew. Chem.* **2003**, *115*, 4320.

[3] Mo, Y.; Wu, W.; Song, L.; Lin, M.; Zhang, Q.; Gao, J. *Angew. Chem.* **2004**, *116*, 2020.

[4] Kleinpeter, E.; Taddei, F. *J. Mol. Struct. (THEOCHEM)* **2002**, *585*, 223.

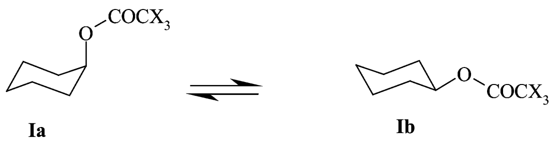
[5] Kleinpeter, E.; Taddei, F.; Wacker, Ph. *Chem.*−*Eur. J.* **2003**, *9*, 1360.

[6] Taddei, F.; Kleinpeter, E. *J. Mol. Struct. (THEOCHEM)* **2004**, *683*, 29.

[7] Taddei, F.; Kleinpeter, E. *J. Mol. Struct. (THEOCHEM)* **2005**, *718*, 141.

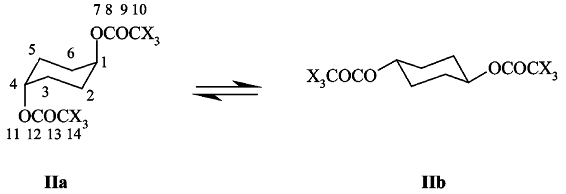
10.1021/jo0600858 CCC: $33.50

SCHEME 1



CX_3 = Me, Et, *iso*-Pr, *tert*-Bu, CF_3, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, CBr_3

SCHEME 2



$$K = \frac{[eq,eq]}{[ax,ax]}; \quad -\Delta G° = RT \ln K$$

No.	CX_3	No.	CX_3	No.	CX_3
1	Me	**5**	CF_3	**9**	CH_2Br
2	Et	**6**	CH_2Cl	**10**	$CHBr_2$
3	*iso*-Pr	**7**	$CHCl_2$	**11**	CBr_3
4	*tert*-Bu	**8**	CCl_3		

the 1,3-diaxial steric effect which should destabilize the axial arrangement (this result is in full contradiction to the generally accepted model of substituent influence on cyclohexane conformational equilibria,[8] but this result has since been proven to be true also by others[9,10]); (ii) substituent influences were found to be partly based on their polarity (hyperconjugation by way of $\sigma_{C2-H2ax}\rightarrow\sigma^*_{C1-O7}$ and $\sigma_{C2-C3}\rightarrow\sigma^*_{C1-O7}$) but also partly based on (iii) their steric effects, but by destabilizing the equatorial conformer with increasing volume of the substituent. Thus, the theoretically formulated pretext that not only in heterosubstituted analogues but also in cyclohexanes substituent influences can also be of electronic origin, i.e., hyperconjugation[11] has been corroborated experimentally and theoretically.[4−7]

Previously,[12] we studied the conformational equilibria of the 1,4-disubstituted analogues **IIa** vs **IIb** (Scheme 2) of the monosubstituted cyclohexanes (CX_3 = Me, CH_2Cl, $CHCl_2$, CCl_3) and found the same influences to be present. However, the effect of substituent polarity on the conformational equilibria was found to be stronger than expected from simple additive considerations. For this reason and to (i) find further support for the stereoelectronic origin of substituent effects in cyclohexane, (ii) obtain fresh information regarding the competition of both steric and electronic substituent effects of ester groups bound to cyclohexane on its conformational equilibrium, and finally (iii) study the differences of the conformational equilibria of **Ia** vs **Ib** and **IIa** vs **IIb**, the full set of trans 1,4-disubstituted cyclohexanes was synthesized and studied accordingly.

Cyclohexyl acetates are of special interest in pharmaceutical chemistry because they can act, for example, as substrates for acetylcholinesterase, wherein their conformation and stereochemistry are of decisive influence on their activity.[13] Although the conformational peculiarities of cyclohexanes have been reviewed,[8,14] not so much is known about 1,4-disubstituted derivatives despite their behavior being of interest. For example, the conformation of trans 1,4-disubstituted cyclohexane derivatives determines their liquid crystalline properties,[15−17] wherein participation of the 1,4-diaxial conformer lowers considerably the corresponding clearing points. In the solid state, a strong general preference for the diequatorial form has been ascertained[14,18] and only in the cases of *trans*-1,4-diisocyanocyclohexane and two organometallic and inorganic complexes have the 1,4-diaxial conformers been isolated.[19] In that compound, slight bending (5.1−8.2°) from the $C_1-C_3-C_5$ plane was observed indicating steric hindrance between the axial NC substituents and the axial protons at C3/5 and C2/6, respectively. Interestingly, *trans*-1,4-dibromo-1,4-dicarboxymethylcyclohexane is a rigid chair conformer with the Br and $COOCH_3$ substituents axially and equatorially orientated, respectively.[20] The chance to observe trans 1,4-ax,ax-disubstituted cyclohexanes in solution, obviously, is much greater: Wood et al.,[21] Borsdorf et al.,[12] and Zefirov et al.[22] studied the conformational equilibria of trans 1,4-disubstituted cyclohexanes substituted symmetrically by polar substituents and found the diaxial form to be more stable than expected by simple addition of the conformational energies of the singly substituted compounds. Furthermore, this additional stabilization increased with increasing polarity of the substituents. This nonadditivity of the $-\Delta G°$ values was discussed in terms of transannular polar[12,22] and electrostatic interactions.[21] Later, Wiberg[23] ab initio MO calculated the conformational equilibria of *trans*-1,4-dihalocyclohexanes (in addition to the 1,2- and 1,3-analogues) and obtained results in good agreement with experimental measurements;[24−28] the conformational equilibria of the 1,4-dihalocyclohexanes were predictable by simple addition,[29] and deviations were considered to stem from the additional contribution of electrostatic effects.[23] Similar transannular interactions were found to be responsible for the preferred axial orientation of polar substituents in 4-substituted cyclohexanones.[30] On the other hand, dipole−dipole interactions between two ester substituents in cyclohexane

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(8) Bushweller, C. H. In *Conformational Behaviour of Six-Membered Rings*; *Stereodynamics of Cyclohexane and Substituted Cyclohexanes. Substituent A Values*; Juaristi, E., Ed.; VCH: New York, 1995; p 25.

(9) Salzner, U.; von R. Schleyer, P. *J. Org. Chem.* **1994**, *59*, 2138.

(10) Wiberg, K. B.; Hammer, J. D.; Castejon, H.; Bailey, W. F.; DeLwon, E. L.; Jarrett, R. M. *J. Org. Chem.* **1999**, *64*, 2085.

(11) (a) Alabugin, I. V. *J. Org. Chem.* **2000**, *65*, 3910. (b) de Oliveira, P. R.; Rittner, P. *J. Org. Chem.* **2003**, *68*, 6780.

(12) Borsdorf, R.; Arnold, M.; Kleinpeter, E. *Z. Chem.* **1977**, *17*, 378.

(13) Kay, J. B.; Robinson, J. B.; Cox, B.; Polkonja, D. *J. Pharm. Pharmacol.* **1970**, *22*, 214.

(14) Kleinpeter, E. *Adv. Heterocycl. Chem.* **2004**, *86*, 41 and references therein.

(15) Kleinpeter, E.; Köhler, H.; Tschierske, C.; Zaschke, H. *J. Prakt. Chem.* **1988**, *330*, 484.

(16) Kleinpeter, E.; Köhler, H.; Krieg, R.; Deutscher, H.-J. *J. Prakt. Chem.* **1989**, *331*, 171.

(17) Thiem, J.; Vill, V.; Fischer, F. *Mol. Cryst. Liq. Cryst.* **1989**, *170*, 43.

(18) Remillard, P. B.; Brisse, F. *Acta Crystallogr.* **1982**, *B38*, 1220.

(19) Steiner, Th.; Saenger, W. *J. Chem. Soc., Perkin Trans. 2* **1998**, 371.

(20) Echeverria, G. A.; Baron, M.; Punte, G. *Struct. Chem.* **2000**, *11*, 35.

(21) Wood, G.; Woo, E. P.; Miskow, M. H. *Can. J. Chem.* **1969**, *47*, 429.

(22) Zefirov, N. S.; Samoshin, V. V.; Nikulin, A. V.; Zyk, N. V. *Zh. Org. Khim.* **1978**, *14*, 2617.

(23) Wiberg, K. B. *J. Org. Chem.* **1999**, *64*, 6387.

(24) Richardson, A. D.; Hedberg, K.; Wiberg, K. B. *J. Phys. Chem. A* **1999**, *103*, 7709.

(25) Eliel, E. L.; Kandasamy, D. *J. Org. Chem.* **1976**, *44*, 3899.

(26) Kozima, K.; Yoshino, T. *J. Am. Chem. Soc.* **1953**, *75*, 166.

(27) Abraham, R. J.; Rossetti, Z. L. *Tetrahedron Lett.* **1972**, 4965.

(28) Meyer, A. Y. *J. Mol. Struct.* **1977**, *40*, 127.

(29) Abraham, R. J.; Bretschneider, E. In *Internal Rotation in Molecules*; Orville-Thomas, W. J., Ed.; Wiley: New York, 1974.

(30) Borsdorf, R.; Arnold, M.; Kleinpeter, E. *Z. Chem.* **1977**, *17*, 378.

TABLE 1. Diaxial/Diequatorial Conformational Equilibria (K = [eq,eq]/[ax,ax]) and $\Delta G°$ ($\Delta G°_{\text{exptl}} = -RT \ln K$) for Diesters 1−11

compd	K^{170}	$-\Delta G°$ (kcal mol^{-1})
1	7.96	0.70
2	7.82	0.70
3	3.77	0.45
4	0.92	−0.03
5	1.58	0.16
6	3.17	0.39
7	1.08	0.03
8	0.41	−0.30
9[a]	3.19	0.42
10[a]	1.20	0.07
11	0.37	−0.33

[a] At 183 K.

proved to be negligible and inductive effects, due to the low polarizability of the intervening aliphatic ring, were also considered minimal.[31]

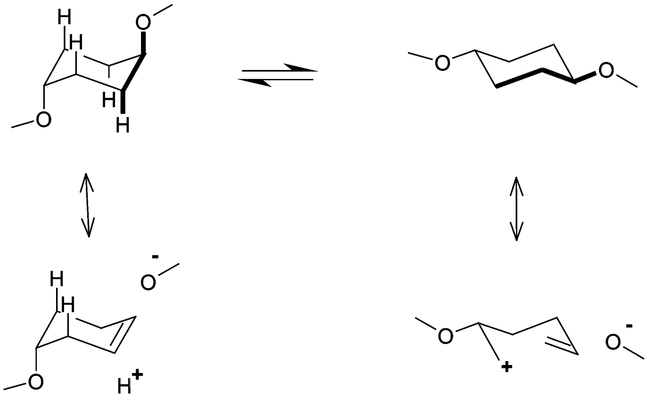
Results and Discussion

Synthesis of the Compounds and NMR Spectroscopic Studies. The cyclohexyl diesters were prepared from a mixture of *cis*- and *trans*-1,4-cyclohexane diols and the corresponding carboxylic acid either in dry toluene (for acid-catalyzed conditions) or diethyl ether (for base-catalyzed conditions) and were obtained as white solids after separation from the monosubstituted and cis disubstituted products by column chromatography. The purity of the products was confirmed by ^{1}H and ^{13}C NMR spectroscopy and mass spectral analysis.

For determination of the equilibrium constants K (cf. Scheme 2), the ^{1}H and ^{13}C NMR spectra of the *trans*-diesters were recorded in CD_2Cl_2 at low temperature, wherein two sets of signals, one for each of the diaxial and diequatorial conformers, were obtained. The set of cyclohexane ring carbon atoms that were more shielded was assigned to the diaxial conformers in each case because of the steric compression effects they experience.[32] The equilibrium constants (K = [**1eq**,**eq**]/[**1ax**,**ax**]) of the conformational equilibria were evaluated by careful integration of the well-separated H-1 and H-4 signals at both 170 and 183 K which subsequently provided the free-energy differences ($\Delta G° = -RT \ln K$). ^{13}C chemical shifts of the two conformers for **1**−**11** are given in Table S1 of the Supporting Information. For the ^{1}H NMR, only the chemical shifts of H-1/H-4 and the protons of the R substituents (H-10) are provided, as protons H-2, H-3, H-5, and H-6 furnished subspectra of higher order which, because of the poor state of homogeneity at the lower temperatures, were not amenable to simulation. In Table 1, the conformational energy differences between the diaxial and diequatorial conformers of **1**−**11** are summarized. These values differ appreciably from those reported previously[12] as they are dependent both on the method used and on the solvent employed. However, the sequence order with respect to the R substituent remains intact. From standard HMQC spectra without proton decoupling, $^1J_{\text{H,C}}$ coupling constants were determined (also given in Table S1 of the Supporting Information).

Computational Studies. Ab initio MO calculations were performed using the Gaussian 98 program package.[33] Different levels of theory were previously tested on three of the compounds (**1**, **3**, and **6**) and a number of sulfur analogues.[4] The results at the MP2/6-311G*//MP2/6-311G* and MP2/6-311+G*//MP2/6-311G* theoretical levels proved to be the most reliable and were therefore used to calculate the energies of the fully relaxed structures for both the diaxial and diequatorial conformers of **1**−**11**. In addition, the solvent effect of dichloromethane was considered; a self-consistent isodensity polarized continuum model (SCIPCM)[34] in a solvent of the dielectric constant $\epsilon = 8.93$ was employed in the MP2/6-311G* calculations. The results are collected in Table S2 of the Supporting Information. In Table 2, some structural parameters (inclination angles α and $C_1{-}O_7$ bond lengths) of the two conformers subject to $OCOCX_3$ are collected.

SCHEME 3



The hyperconjugative effect was studied using the NBO option included in the Gaussian 98 package, performed on the MP2 density, following the same protocol as that reported previously.[6,7] A number of interactions between filled NBOs and antibonding orbitals were considered as most representative for delocalization and were retained for all the molecules studied. The interactions considered are those between the filled and antibonding NBOs of the exocyclic $C_1{-}O_7$ bond and those of the $C_2{-}H_{ax}$, $C_6{-}H_{ax}$, $C_2{-}C_3$, and $C_5{-}C_6$ bonds for the substituent at C-1 and those between the $C_4{-}O$ bond and the $C_3{-}H_{ax}$, $C_5{-}H_{ax}$, $C_2{-}C_3$, and $C_5{-}C_6$ bonds for the substituent at C-4. The stabilization of the two conformers by hyperconjugation is given in Table S3 of the Supporting Information; the different hyperconjugative interactions are represented by the Lewis bond/nonbonded structures depicted in Scheme 3 (only $\sigma_{C2-Hax} \rightarrow \sigma^*_{C1-O7}$ hyperconjugation for the diaxial and $\sigma_{C2-C3} \rightarrow \sigma^*_{C1-O7}$ for the diequatorial conformers are given; another three identical interactions are active).

Relative Stability of Diequatorial and Diaxial Conformers of 1,4-Disubstituted Cyclohexanes. With internal rotation about

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[31] Salz, E.; Hummel, J. P.; Flory, P. J. *J. Phys. Chem.* **1981**, *85*, 3211.

[32] Pihlaja, K.; Kleinpeter, E. In *Carbon-13 NMR Chemical Shifts in Structural and Stereochemical Analysis; Methods in Stereochemical Analysis*; Marchand, A. P., Ed.; VCH: New York, 1994; p 207.

[33] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.12; Gaussian, Inc.: Pittsburgh, PA, 1998.

[34] Forseman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098.

TABLE 2. Selected Geometrical Parameters for Compounds 1−11 as Calculated at the MP2/6-311G* Level of Theory

compd	CX_3	conformer	a ax[a]	a eq[a]	C−Oax[b]	C−Oeq[b]	CO⋯H[c]
1	Me	ax,ax	90.96		1.453		2.382
		eq,eq		157.67		1.445	2.369
		ax	91.13		1.452		2.381
		eq		157.80		1.447	2.365
2	Et	ax,ax	90.96		1.453		2.383
		eq,eq		157.67		1.446	2.370
		ax	91.14		1.453		2.382
		eq		157.79		1.448	2.366
3	*i*-Pr	ax,ax	90.87		1.453		2.387
		eq,eq		157.75		1.445	2.367
		ax	91.07		1.452		2.386
		eq		157.88		1.447	2.364
4	*t*-Bu	ax,ax	90.87		1.453		2.380
		eq,eq		157.73		1.446	2.360
		ax	91.07		1.453		2.379
		eq		157.87		1.448	2.357
5	CF_3	ax,ax	89.67		1.461		2.453
		eq,eq		157.44		1.453	2.419
		ax	90.10		1.462		2.451
		eq		157.66		1.457	2.418
6	CH_2Cl	ax,ax	90.12		1.457		2.426
		eq,eq		157.45		1.448	2.390
		ax	90.50		1.457		2.418
		eq		157.42		1.452	2.387
7	$CHCl_2$	ax,ax	89.73		1.460		2.431
		eq,eq		157.89		1.448	2.396
		ax	90.19		1.460		2.428
		eq		157.60		1.454	2.400
8	CCl_3	ax,ax	89.73		1.461		2.430
		eq,eq		157.36		1.452	2.400
		ax	90.20		1.462		2.427
		eq		157.59		1.457	2.400
9	CH_2Br	ax,ax	90.34		1.457		2.421
		eq,eq		157.45		1.448	2.388
		ax	90.71		1.457		2.412
		eq		157.63		1.451	2.386
10	$CHBr_2$	ax,ax	89.89		1.460		2.426
		eq,eq		157.37		1.451	2.399
		ax	90.36		1.460		2.421
		eq		157.56		1.454	2.397
11	CBr_3	ax,ax	89.96		1.462		2.422
		eq,eq		157.35		1.453	2.396
		ax	90.44		1.463		2.419
		eq		157.57		1.457	2.395

[a] Inclination angle of the C_1-O_7 bond to the $C_1-C_3-C_5$ plane. [b] Bond length of C_1-O_7. [c] Spatial distance between $C_8{=}O_9$ and H_1.

the C_1-O_7 (O_4-C_{11}) and O_7-C_8 ($C_{11}-C_{12}$) bonds [rotation about the C_8-C_{10} ($C_{12}-C_{14}$) bond was not taken into consideration], a number of nondegenerate, but stable, conformers were assessed for each of the orientations of the ester group. Only two conformers, syn and anti (cf. Figure 1), were found to be significant for each of the diequatorial and diaxial orientations (cf. Scheme 2). The four conformers (ax,ax and eq,eq in both syn and anti orientations) adopt staggered orientations for the groups at C-1 (C-4) and O-7 (C-11) with, in each case, an oxygen lone pair oriented toward the cyclohexane ring (see Figure 1).[4] That cyclohexyl acetates intrinsically prefer a staggered conformation,[35,36] whereas eclipsed exocyclic C−O bonds are preferred in methoxycyclohexanes and their heterocyclic analogues,[37,38] has already been reported. In addition, the dihedral angle $H_1-C_1-O_7-C_8$ for the various conformers proves to be nearly constant (37.5−41°) and corroborates the stable conformation of the substituents in all conformers studied.

The ester group was generally found to be in the *Z* configuration.[39] The effect of the syn or anti orientation of the substituents is negligible (anti is more stable by less than 0.05 kcal mol^{-1}) when compared with the difference in stability of the eq,eq and ax,ax conformers. The more stable orientation of syn and anti was checked for all the compounds examined, and the results reported refer to the global minimum.

The free-energy differences of the 1,4-disubstituted cyclohexanes **1**−**11** exhibit distinct trends: (i) The more polar/

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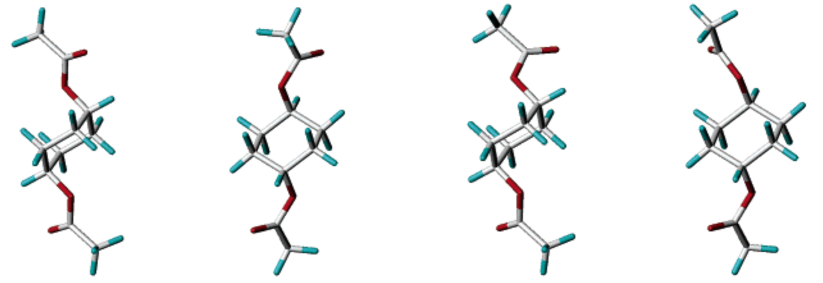
(35) Schneider, H.-J.; Freitag, W.; Weigand, E. *Chem. Ber.* **1978**, *111*, 2656.

(36) Gonzalez-Outeirino, J.; Nasser, R.; Anderson, J. E. *J. Org. Chem.* **2005**, *70*, 2486.

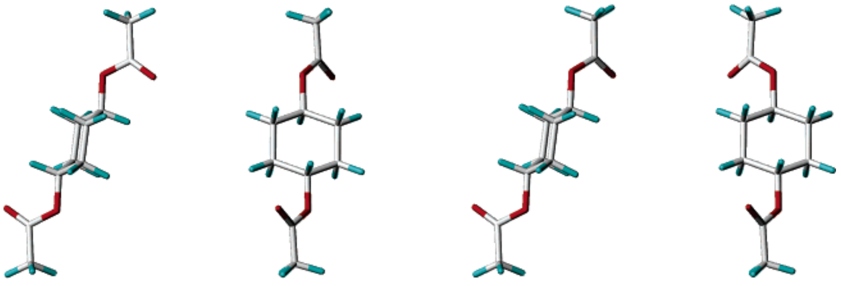
(37) Anderson, J. E.; Iljeh, A. I. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1965.

(38) Anderson, J. E.; Angyal, St. J.; Craig, D. C. *J. Chem. Soc., Perkin Trans. 2* **1997**, 729.

(39) Neuvonen, H.; Neuvonen, K.; Koch, A.; Kleinpeter, E. *J. Phys. Chem. A* **2005**, *109*, 6279.



***ax,ax* (*anti*)** ***ax,ax* (*syn*)**



***eq,eq* (*anti*)** ***eq,eq* (*syn*)**

FIGURE 1. Preferred conformers of the 1,4-disubstituted cyclohexanes **1** (CX_3 = Me).

voluminous the substituents are, the greater the preference of the diaxial conformer (Table 1). For example, with an increasing number of halogen atoms, the free-energy differences are $COCH_3$ (0.70 kcal mol^{-1}) < $COCH_2Cl$ (0.39 kcal mol^{-1}) < $COCHCl_2$ (0.03 kcal mol^{-1}) < $COCCl_3$ (−0.30 kcal mol^{-1}); the same sequence was obtained for the bromo analogues **9**−**11**. (ii) Similarly, the more voluminous the substituents are, the more they prefer the diaxial conformer; $COCH_3$ (0.70 kcal mol^{-1}) = COC_2H_5 (0.70 kcal mol^{-1}) < $COCH(CH_3)_2$ (0.45 kcal mol^{-1}) < $COC(CH_3)_3$ (−0.03 kcal mol^{-1}). This result corroborates the observations obtained for the monosubstituted analogues **Ia** and **Ib** and, in particular, does not bode well for the interpretation of substituent influences on the cyclohexane ring in terms of destabilizing steric 1,3 nonbonding interactions. Finally, (iii) the substituent influences on the conformational equilibria of **1**−**11** are obviously larger than those in the monosubstituted analogues (cf. Table 1).

The free-energy differences of the global minima of the two conformers ax,ax and eq,eq are given in Table S2 of the Supporting Information, together, for reasons of comparison, with the energies of the corresponding monosubstituted analogues as calculated at the same levels of theory. The correlation between the experimental $\Delta G°$ values for **1**−**11** and the theoretically calculated values is only reasonable if calculations take into consideration both electron correlation and diffuse functions; the best results were obtained using MP2/6-311+G* calculations ($R^2 = 0.72$; the correlation considering the solvent effect is less successful, $R^2 = 0.68$), and the corresponding plot is depicted in Figure 2. In this case, the correct order of the conformational energies as a function of the $-OCOCX_3$ substituent was obtained. However, the theoretical calculations obviously overestimate the ax,ax conformer, by 2−2.5 kcal mol^{-1}, in comparison to the experimental results, and more so if polar (**5**−**11**) rather than nonpolar CX_3 substituents (**1**−**4**) are present.

Molecular Geometries. In Table 2, selected geometrical parameters of the preferred conformers of **1**−**11** resulting from MP2/6-311+G* calculations are presented. Of note, the inclination angle (i.e., the angle between the axis of the C_1-O_7 bond and the plane defined by C-3, C-1, and C-5), employed as a sensible measure of the CH(1,3)···O7 intramolecular interactions,[19] was found to lie in the range 90−91° in the diaxial conformers, which is the smallest distortion obtained so far, and therefore, negligible strain only can be expected. Obviously, destabilizing 1,3-diaxial interactions play no role at all because of the 1,4-positioning of the substituents; in the 1,3-positioning of two substituents, however, there is steric destabilization competing with stabilization via intramolecular hydrogen bonding.[40]

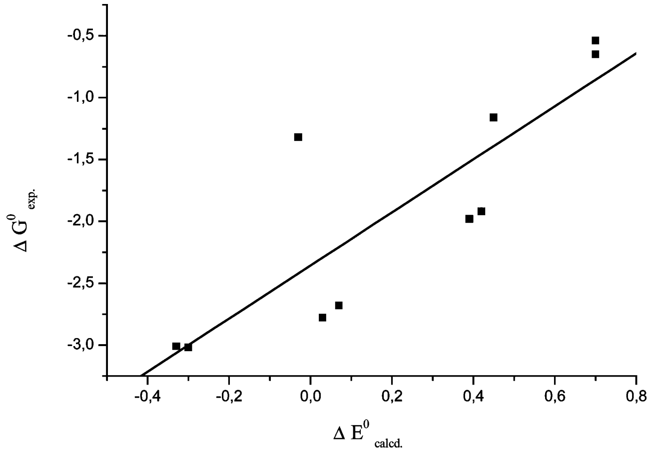


FIGURE 2. Plot of $\Delta E°_{calcd}$ (MP2/6-311+G*//MP2/6-311G*) vs $\Delta G°_{exptl}$ for compounds **1**−**11**.

The same can be said for the conformational distances H-1···O-9 in the two conformers which do not change significantly along the variation of the substituents in **1**−**11**. Also, when the

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[40] (a) de Oliveira, P. R.; Rittner, P. *Spectrochim. Acta, Part A* **2005**, *62*, 30. (b) de Oliveira, P. R.; Rittner, P. *J. Mol. Struct.* **2005**, *743*, 69.

geometries of the **1**−**11** conformers are compared with those of their monosubstituted analogues **Ia** and **Ib**, there are only very small differences to be found. Thus, the change in substitution of **1**−**11** does not result in considerable changes in either the geometry or the conformation of the cyclohexane ring for the two conformers. The same is also true for the monosubstituted analogues, and results are similar if corresponding members are compared across the two series. This is the major result of this theoretical study; the molecular structures of the two conformers participating in the conformational equilibria of **1**−**11** are very similar to each other and do not indicate immediately the substituent variation with respect to either polarity or volume.

Hyperconjugation. When studying the conformational equilibria of the monosubstituted analogues of **1**−**11**, viz., **Ia** vs **Ib**, hyperconjugation was identified as a significant contributor to the different stabilities of the two conformers **Ia** and **Ib**.[5,7] Hereby, the stereoelectronic interactions $\sigma_{C2-Hax}\rightarrow\sigma^*_{C1-O7}$ for the axial and $\sigma_{C2-C3}\rightarrow\sigma^*_{C1-O7}$ for the equatorial conformers were compared and found to be sufficiently stronger in the axial conformer, thus *hyperconjugation* could be employed for understanding *at least partly* the conformational equilibria of **Ia** vs **Ib**. Thus, the same stereoelectronic interactions were calculated for the 1,4-disubstituted cyclohexane derivatives **1**−**11** and were compared with the amount of hyperconjugation in the monosubstituted analogues. The results are presented in Table S3 of the Supporting Information. In the case of the disubstituted cyclohexanes, however, the diequatorial conformer will be additionally destabilized by the competitive ("anti-cooperative")[41] $\sigma_{C2-C3}\rightarrow\sigma^*_{C1-Oeq}$ hyperconjugation which renders the antiperiplanar arrangement of the two acceptor substituents to the same σ-bride unfavorable.[42]

The outcome of these calculations was unequivocal: if, in the disubstituted cyclohexyl derivatives **1**−**11**, the stereoelectronic interactions $\sigma_{C2-Hax}\rightarrow\sigma^*_{C1-O7}$ for the diaxial and $\sigma_{C2-C3}\rightarrow\sigma^*_{C1-O7}$ for the diequatorial conformers were compared, they were found again to be stronger in the diaxial conformer and *larger* than simple doubling of the monosubstituted conformational energy (cf. Table S3 of the Supporting Information). The difference, though small, is significant, ca. 0.3 kcal mol^{-1}, for nonpolar substituents and is 0.4−0.5 kcal mol^{-1} in the case of polar substituents.

Theoretical examinations (ab initio calculations and NBO/NCS analysis) of cyclohexane derivatives have afforded precise structural (bond lengths) and spectroscopic ($^1J_{H,C}$ NMR coupling constants) data to show the consequences of stereoelectronic hyperconjugative effects in these systems.[43] The corresponding, hyperconjugation-indicating coupling constants $^1J_{Hax,C2}$, however, could not be measured in **1**−**11** because of technical reasons.[5] On the other hand, the very recent calculations of $^1J_{H,C}$ coupling constants in saturated six-membered rings by Perrin et al.[44,45] determined that $^1J_{H,C}$ coupling not only is dependent on hyperconjugation but also is more dependent on polar interactions.[42]

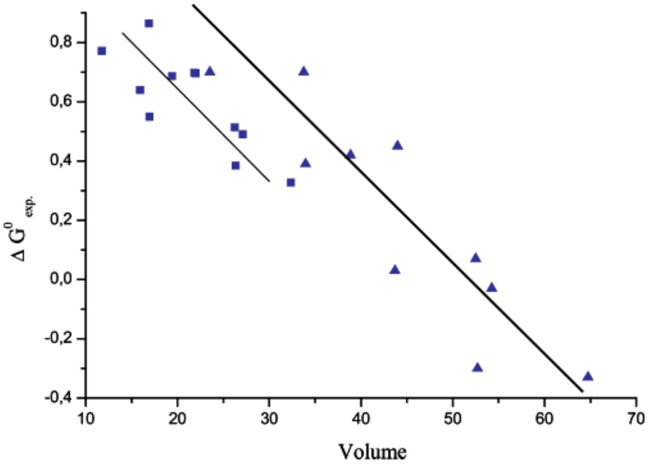

FIGURE 3. Plot of the volumes of the CX$_3$ substituents in compounds **1**−**11** vs $\Delta G°_{exptl}$. Linear regression provided two linear dependencies: for the monosubstituted cyclohexanes, $y = -0.025 + 1.12$ ($R^2 = 0.90$); for the 1,4-disubstituted cyclohexanes **1**−**11** (>), $y = -0.028 + 1.44$ ($R^2 = 0.81$).

However, in the present theoretical study, adequate structural changes are available (cf. Table 2) and the same conclusions as those derived from the energetic hyperconjugation study (cf. Table S3 of the Supporting Information) can be drawn, viz.: (i) The C_1-O_7 bond lengths in the diaxial conformers are longer (greater hyperconjugation) than those in the diequatorial conformers (e.g., 1.453 Å for the ax,ax but 1.445 Å for the eq,eq conformer if $CX_3 = CH_3$). (ii) This phenomenon is larger than in the monosubstituted analogues (e.g., $\Delta C_1-O_7 = 0.008$ Å in **1** but only 0.005 Å in the monosubstituted analogue; cf. Table 2) because greater hyperconjugation stabilizes the diaxial conformer (in equilibrium with diequatorial) with respect to the axial analogue (in equilibrium with equatorial). (iii) However, the additional effect of (ii) comes not from the diaxial conformer (hyperconjugation remains roughly constant in ax,ax and ax: $\Delta C_1-O_7 = \pm 0.001$ Å) but from the diequatorial conformer (decreased hyperconjugation in eq,eq with respect to eq: $\Delta C_1-O_7 = -0.002$ to -0.006 Å), altogether stabilizing the diaxial conformer in the present conformational equilibria. (iv) This effect is somewhat larger in **5**−**11**, the cyclohexanes substituted with polar CX$_3$ substituents. Thus, the main conclusion from this section is that hyperconjugation stabilizes the diaxial conformers in **1**−**11** by ca. 0.3−0.5 kcal mol^{-1} more effectively than the axial conformers in the monosubstituted analogues and that this influence on the conformational equilibria eq,eq vs ax,ax is somewhat higher in the case of polar substituents (**5**−**11**) in comparison to their nonpolar analogues (**1**−**4**).

Steric Substituent Effects. Steric substituent effects were also found to be in effect. In Figure 3, experimental free-energy differences of **1**−**11** (and of their monosubstituted analogues **Ia** $\rightleftharpoons$ **Ib**) are correlated to the volume of the CX$_3$ groups (in the case of **1**−**11**, doubled volumes were applied). Actually, not one but two correlations for the two sets of compounds were obtained. However, this is not really surprising, and as the two correlations are parallel, identical dependencies must be underlying. Because the span of volumes is much wider for the 1,4-disubstituted cyclohexyl derivatives **1**−**11**, the steric hindrance of the CX$_3$ volume destabilizing the diequatorial conformer has a more decisive influence on the position of the conformational equilibrium than in the monosubstituted analogues. The difference between the two dependencies amounts to approximately

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(41) Alabugin, I. V.; Manoharan, M.; Zeidan, T. A. *J. Am. Chem. Soc.* **2003**, *125*, 14014.

(42) Alabugin, I. V.; Manoharan, M. *J. Org. Chem.* **2004**, *69*, 9011.

(43) Martinez-Mayorga, K.; Juaristi, E.; Cuevas, G. *J. Org. Chem.* **2004**, *69*, 7266.

(44) Perrin, C. L.; Erdélyi, M. *J. Am. Chem. Soc.* **2005**, *127*, 6168.

(45) Cuevas, G.; Martínez-Mayorga, K.; Fernández-Alonso, M. del C.; Jiménez-Barbero, J.; Perrin, C. L.; Juaristi, E.; López-Mora, N. *Angew. Chem.* **2005**, *117*, 2412.

TABLE 3. ESI-MS

compd	ion	mass *m*/*z*	calcd mass
2	$[M + H]^+$	229.1421	229.1440
3	$[M + Na]^+$	279.1574	279.1572
4	$[M + H]^+$	285.2068	285.2066

TABLE 4. EI-MS (Negative Ion Mode)

compd	ion	mass *m*/*z*	calcd mass
5	$[M - F]^-$	289.0516	289.0499
6	$[M]^-$	268.0249	268.0269
8	$[M - Cl]^-$	368.9029	368.9022
9	$[M - Br]^-$	277.0068	277.0075
10	$[M - Br]^-$	432.8264	432.8286
11	$[M - Br]^-$	588.6503	588.6496

0.3−0.4 kcal mol^{-1}, similar to the energy difference in $\Delta G°$ due to hyperconjugation between the two groups of compounds, and thus it makes sense that the difference in hyperconjugation between identically substituted di- and monosubstituted cyclohexane derivatives is the reason for the two correlations.

The larger effect of the CX_3 groups with heavier halogens is consistent with the greater σ-acceptor ability of C−Cl and C−Br bonds compared with C−F bonds.[46] This effect may accentuate the steric bulk effect of the ester substituents in **1**−**11**.

Conclusions

Long-range substituent influences on the conformational equilibria of a number of 1,4-disubstituted cyclohexanes are based in part on electronic factors, hyperconjugation by way of $\sigma_{C2-Hax}\rightarrow\sigma^*_{C1-O7}$ and $\sigma_{C2-C3}\rightarrow\sigma^*_{C1-O7}$, but also in part on steric influences. Surprisingly, this is by destabilization of the diequatorial conformers with increasing volumes of the CX_3 substituents. The hyperconjugation $\sigma_{C2-Hax}\rightarrow\sigma^*_{C1-O7}$ in the diaxial conformer is more effective than the hyperconjugation $\sigma_{C2-C3}\rightarrow\sigma^*_{C1-O7}$ in the diequatorial counterpart, thereby leading to a preference of the former conformer with increasingly stronger stereoelectronic interactions between the $-OCOCX_3$ substituent and the cyclohexane skeleton. This stereoelectronic stabilization of the diaxial conformer is 0.3−0.5 kcal mol^{-1} higher in the 1,4-disubstituted cyclohexanes **1**−**11** in comparison with their monosubstituted analogues.[5] In addition, steric interactions, occurring throughout the whole molecule and not just by way of the 1,3-diaxial interaction model, further destabilize the diequatorial conformer with increasing bulk of the CX_3 group, and obviously, this too has a perpetuating effect on the conformational equilibria of **1**−**11**.

Experimental Section

General Procedure for the Synthesis of Compounds 1 and 5−10. A mixture of *cis*- and *trans*-1,4-cyclohexanediol (1.16 g, 10 mmol) and the corresponding carboxylic acid (21 mmol) was dissolved in 50 mL of toluene followed by the addition of *p*-toluene sulfonic acid (1 mg). The resulting solution was heated under reflux for 8 h with an attached Dean−Stark trap. After cooling, the mixture was extracted with 10 mL of a saturated sodium hydrogen carbonate solution and, afterward, with water (10 mL). The resulting organic phase was then dried over sodium sulfate. The white solid obtained after removal of the toluene in vacuo was purified by column chromatography (silica; ethyl acetate−*n*-hexane, 1:3). The structure and purity of the compounds were determined by ^1H and ^{13}C NMR spectroscopy (see Table 5) and accurate mass measurements by ESI-MS or EI-MS (see Tables 3 and 4; compounds **1** and **7** excluded).

TABLE 5. Selected ^1H and ^{13}C NMR Chemical Shifts (ppm) for Compounds 1−11

	^{13}C δ (ppm)				^1H δ (ppm)			
compd	C-1	C-2	C-8	C-10	H-1	H-2eq	H-2ax	H-10
1	69.9	27.2	170.4	21.2	4.78	1.97	1.53	2.04
2	69.7	27.9	173.8	27.3	4.80	1.95	1.56	2.30
3	70.3	27.6	176.5	34.1	4.84	1.94	1.55	2.53
4	70.0	27.1	177.9	38.9	4.85	1.91	1.58	
5	74.2	26.6	156.8	114.5	5.12	2.07	1.79	
6	72.6	27.1	166.6	41.1	4.97	2.01	1.62	4.05
7	73.6	26.0	163.8	64.5	5.05	2.03	1.76	5.95
8	75.4	25.2	161.2	89.2	5.18	2.11	1.91	
9	72.4	26.0	166.5	26.9	4.92	1.99	1.66	3.84
10	73.5	25.8	164.1	32.8	5.00	2.05	1.79	5.82
11	75.5	25.0	161.4	29.7	5.20	2.13	1.92	

General Procedure for the Synthesis of Compounds 2−4 and 11. A mixture of *cis*- and *trans*-1,4-cyclohexanediol (1.16 g, 10 mmol) and pyridine (21 mmol) was dissolved in 50 mL of dried diethyl ether followed by the slow addition of the corresponding carboxylic acid (21 mmol) at 0 °C (cooling strongly recommended). The mixture was stirred at room temperature for 10 h and then extracted using 10 mL of each of the following solvents: saturated sodium hydrogen carbonate solution, water, hydrochloric acid (0.1 M), and finally, water again. The resulting organic phase was then dried over sodium sulfate. After removal of the diethyl ether, the diesters were obtained as white solids which were purified by column chromatography (silica; ethyl acetate−*n*-hexane, 1:3). The structure and purity of the compounds were determined by ^1H and ^{13}C NMR spectroscopy (see Table 5) and accurate mass measurements by ESI-MS or EI-MS (see Tables 3 and 4).

Acknowledgment. The authors gratefully acknowledge very useful references of one of the referees regarding the additional presence of anticooperative hyperconjugative interactions of antiperiplanar substituents in the trans-1,4-disubstituted cyclohexanes and language correction of the manuscript by Dr. Karel K. Klika.

Supporting Information Available: Experimental ^1H and ^{13}C NMR chemical shifts, $^1J_{C,H}$ coupling constants, ab initio calculated conformational equilibria of **1**−**11** (and also of all **Ia** vs **Ib**), the corresponding hyperconjugation effects, and the coordinates and absolute energies at the MP2/6-311G* level of theory for compounds **1**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0600858

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[46] Alabugin, I. V.; Zeidan, T. A. *J. Am. Chem. Soc.* **2002**, *124*, 3175.