Electronic and Steric Substituent Influences on the Conformational Equilibria of Cyclohexyl Esters: The Anomeric Effect Is Not Anomalous!

Erich Kleinpeter,*[a] Ferdinando Taddei,*[b] and Philipp Wacker[a]

Abstract: The cyclohexyl esters of a series of carboxylic acids, RCO_2H, spanning a range of electronegativities and quotients of steric hindrance for the R substituent (R = Me, Et, *i*Pr, *t*Bu, CF_3, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, and CBr_3) were prepared. Their conformational equilibria in CD_2Cl_2 were examined by low-temperature ^1H NMR spectroscopy to study the axial or equatorial orientation of the ester functionality with respect to the adopted chair conformation of the cyclohexane ring. The ab initio and DFT geometry-optimized structures and relative free energies of the axial and equatorial conformers were also calculated at the HF/6-311G**, MP2/6-311G**, and B3LYP/6-31G** levels of theory, both in the gas phase and in solution. In the latter case, a self-consistent isodensity polarized continuum model was employed. Only by including electron correlation in the modeling calculations for the solvated molecules was it possible to obtain a reasonable correlation between $\Delta G^\circ_{\mathrm{calcd}}$ and $\Delta G^\circ_{\mathrm{exp}}$. Both the structures and the free energy differences of the axial and equatorial conformers were evaluated with respect to the factors normally influencing conformational preference, namely, 1,3-diaxial steric interactions in the axial conformer and hyperconjugation. It was assessed that hyperconjugative interactions, $\sigma_{\mathrm{C-C}}/\sigma_{\mathrm{C-H}}$ and $\sigma^*_{\mathrm{C-O}}$, together with a steric effect—the destabilization of the equatorial conformer with increasing bulk of the R group—were the determinant factors for the position of the conformational equilibria. Thus, because hyperconjugation is held responsible as the mitigating factor for the anomeric effect in 2-substituted, six-membered saturated heterocyclic rings, and since it is also similarly responsible, at least partly, in these monosubstituted cyclohexanes for a preferential shift towards the axial conformer, the question is therefore raised: can the anomeric effect really be construed as anomalous?

Keywords: ab initio calculations · conformation analysis · cyclohexanes · hyperconjugation · NMR spectroscopy

Introduction

It is generally accepted that the chair–chair conformational equilibrium of monosubstituted cyclohexanes with respect to the axial or equatorial disposition of the substituent (the *A* value) is primarily determined by the steric interactions between the axial substituent and the axial protons in the 3- and 5-positions.[1] In the case of oxygen as the first atom of the axial substituent, that is −OR, this amounts to steric interactions with the oxygen lone pairs.[2] An R group with electron-withdrawing properties leads to an increase in the population of the axial conformer, which is consistent with a decreased electron density on the oxygen atom and consequently a reduction in the nonbonded repulsions with the *syn*-axial hydrogen atoms in the axial conformation.[2] The presence of this repulsion, reflecting steric strain within the cyclohexane ring, is supported by the results of a survey of appropriate X-ray structures in the Cambridge Structural Data Base based on inclination angles (θ C3, C5, C1-OR) greater than 90°.[3] Seemingly enigmatically, the tendency of polar substituents, such as −OR, at the C2 position of tetrahydropyrans to occupy the axial position has been termed the anomeric effect.[4] The hyperconjugative origin of the anomeric effect has been recently stressed[5] and quantitatively modeled on the basis of ab initio calculations and the natural bond orbital (NBO) method.[6] The origin of this phenomenon is considered to be unfavorable dipole–dipole (electrostatic) interactions[7] that destabilize the equatorial conformer and the favorable hyperconjugation between the ring-oxygen lone-pair electrons and the antibonding C-OR orbital ($n_{\mathrm{O}} \rightarrow \sigma^*_{\mathrm{C-H}}$) stabilizing the axial conformer.[4] However, although the steric 1,3-diaxial interactions that destabilize the axial conformer are still present, it is not a simple matter to separate them from the electronic substituent effect. The original concept of the anomeric effect has also

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[a] Prof. Dr. E. Kleinpeter, P. Wacker
Institut für Organische Chemie und Strukturanalytik
Universität Potsdam
Am Neuen Palais 10, 14415 Potsdam (Germany)
Fax: (+49) 331-977-5064
E-mail: kp@chem.uni-potsdam.de

[b] Prof. F. Taddei
Dipartimento di Chimica
Universita degli Studi di Modena e Reggio Emilia

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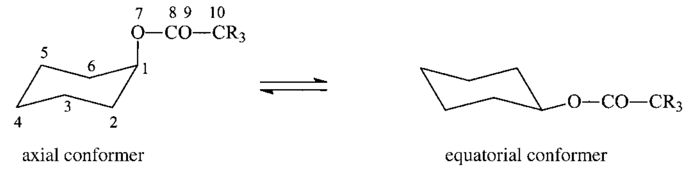
been extended[8] to various other substituents and six-membered saturated heterocycles. To take into account the different steric requirements of various substituents in different heterocycles in comparison to cyclohexane (and thereby characterize the anomeric effect as the difference of the *A* value of a certain substituent in monosubstituted cyclohexane and in the 2-position of a heterocycle), empirical correlation factors α for each particular heterocycle were introduced.[9, 10]



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

No.	CR3	No.	CR3	No.	CR3
1	Me	**5**	CF_3	**9**	CH_2Br
2	Et	**6**	CH_2Cl	**10**	$CHBr_2$
3	*i*Pr	**7**	$CHCl_2$	**11**	CBr_3
4	*t*Bu	**8**	CCl_3		

Scheme 1. Structure of the compounds **1**–**11** and the conformational equilibrium examined.

Previously,[11–13] we studied the influence of increasing the polarity of substituents on the conformational equilibria of cyclohexyl esters of acetic acid analogues with respect to the chair conformation of the cyclohexane ring (i.e., the ring substituents are $-O_2CR$) and assessed the observed increasing preference of the axial conformer with an increase in the polarity of the $-O_2CR$ substituent within the context of Bushweller's steric interaction model.[2] Other reports have corroborated[14, 15] our finding[11–13] that increasing electron withdrawal by the substituent in monosubstituted cyclohexanes leads to an increase in the amount of the axial conformer; however, Kirby and Williams ascertained[15] from simultaneous bond length variations that $\sigma_{C-H(axial)} \rightarrow \sigma^*_{C-OAr}$ hyperconjugation is the factor responsible for this observation.

In fact, workers have long been aware of the presence of hyperconjugation in substituted cyclohexanes ever since the elaboration of the Perlin effect[16] (where ${}^1J(C,H_{ax}) < {}^1J(C,H_{eq})$ in cyclohexane) and which has been corroborated by a natural bond orbital population (NBO) analysis based on high-level ab initio MO calculations on cyclohexanol derivatives.[17] Moreover, there was no evidence for 1,3-diaxial interactions between the axial −OR substituent and the axial protons in positions 3 and 5 as being a determinant factor for the equilibrium position.[17] The same result was obtained by Wiberg et al.[18] in a study of the conformational equilibria of monoalkyl-substituted cyclohexanes of varying steric bulk, and also employing high-level ab initio MO calculations. In both cases, the agreement between calculated and experimental ΔG° values was found to be excellent.[17, 18] The isotope effects of ${}^1H$ versus ${}^2D$ and ${}^{12}C$ versus ${}^{13}C$ were also in complete agreement.[19, 20]

Because this divergence in pinpointing the underlying cause for the equilibrium preference and the understanding of the substituent/cyclohexane ring interaction dependency on the substituent polarity is not yet fully understood,[21] we synthesized a variety of cyclohexyl esters (**1**–**11**, Scheme 1) to study and scrutinize the long-held belief that steric interactions in the axial conformer prevailed in determining the position of the conformational equilibrium (Scheme 1). The study consisted of an experimental component, whereby the conformational equilibria were studied by low-temperature NMR spectroscopy, and a theoretical component. The structures of the axial and equatorial conformers were calculated by both ab initio HF (at the HF/6-311G** and MP2/6-311G** levels of theory) and DFT calculations (at the B3LYP/6-31G** level of theory), both in the gas phase and in solution, and determined their free energy differences, ΔG°. In addition, NBO analysis at this level of theory was also used to understand the interaction mechanism. Initial results,[22] obtained for the cyclohexanol esters with $R = CH_3$, CF_3, and CCl_3 were encouraging as calculations correctly provided the sequence order, but not the amount, of the corresponding *A* values. This prompted the current expanded study.

Results and Discussion

Experimental studies: The esters **1**–**11** were prepared simply and efficiently by admixture of equimolar quantities of cyclohexanol and the corresponding carboxylic acid in toluene or chloroform (depending on the boiling points of the product esters) with the removal of any accumulated water by azeotropic distillation. Final distillation provided the esters **1**–**11** in reasonable purity, confirmed by ${}^1H$ and ${}^{13}C$ NMR spectroscopy and mass spectral analysis.

For the determination of the equilibrium constants *K* (Scheme 1), the ${}^1H$ and the ${}^{13}C$ NMR spectra of the esters were recorded in CD_2Cl_2 at low temperatures on Bruker NMR instruments (Avance 300 and 500); two sets of signals, one for each of the axial and equatorial conformers, were obtained and the set of cyclohexane carbon atoms that lay upfield were assigned to the axial conformers in each case on account of the steric compression effects they experience.[23] The equilibrium constants ($K = [\mathbf{1}_{eq}]/[\mathbf{1}_{ax}]$, etc.) of the conformational equilibria were evaluated by careful integration of the well-separated H1 signals in each case at 193 and 203 K (except in the case **5** ($R = CF_3$) where measurements were made at 183 and 193 K). These constants subsequently provided the free energy differences ($\Delta G^\circ = -RT\ln K$). The ${}^{13}C$ chemical shifts of the two conformers for **1**–**11** are presented in Table 1. For the ${}^1H$ NMR spectra, only the chemical shifts of H1 and the protons of the R substituent (H10) are given because protons H2–H6 furnished subspectra of higher order and severe overlap which, because of the poor state of homogeneity at the lower temperatures, were not amenable to simulation. The conformational energy

Table 1. Experimental ^{1}H and ^{13}C chemical shifts and ^1J(C,H) coupling constants for compounds **1**–**11** at 183 K (see Scheme 1 for structures and atom numbering).

Compd.	Conf.	^{13}C δ C1	C2/C6	C3/C5	C4	C8	C10	^{1}H δ H1	H10	^1J(C1,H1) [Hz]	^1J(C2,H2$_{ax}$) [Hz]	^1J(C2,H2$_{eq}$) [Hz]
1	ax	69.2	28.9	20.0	24.9	170.5	21.2	4.98	2.10	151.2	n.a.[a]	n.a.
	eq	72.2	31.2	23.8	24.4	170.3	21.2	4.62	2.10	145.8	127.7	130.5
2	ax	68.9	28.9	20.0	24.8	173.8	28.9	4.98	2.31	150.4	n.a.	n.a.
	eq	72.4	31.1	23.8	24.4	173.5	28.9	4.63	2.31	146.7	127.5	129.9
3	ax	68.8	29.0	20.2	25.0	176.5	33.6	4.96	2.50	151.9	n.a.	129.7
	eq	72.4	31.2	24.0	24.6	176.5	33.4	4.61	2.50	145.9	130.0	131.4
4	ax	68.7	29.1	20.3	25.1	177.5	38.4	4.88	–	150.3	126.9	131.2
	eq	72.3	31.2	24.1	24.7	177.5	38.0	4.51	–	145.4	127.8	129.6
5	ax	75.5	28.6	19.7	24.5	158.8	113.9	5.29	–	154.7	128.2	132.7
	eq	78.3	30.6	23.8	24.1	156.2	113.9	4.91	–	149.2	130.7	133.2
6	ax	71.9	28.9	20.0	24.8	166.5	41.8	4.99	4.15	151.3	n.a.	n.a.
	eq	75.1	31.1	23.9	24.3	166.3	41.8	4.62	4.10	147.0	128.0	131.1
7	ax	73.8	28.8	20.0	24.6	163.4	64.7	5.15	6.16	152.8	n.a.	132.5
	eq	76.9	30.9	24.0	24.4	163.4	64.5	4.78	6.01	148.0	129.4	131.8
8	ax	76.2	28.7	20.0	24.8	160.6	89.8	5.21	–	153.7	n.a.	n.a.
	eq	79.2	30.5	23.9	24.5	160.6	89.5	4.84	–	148.8	130.0	131.8
9	ax	71.8	28.8	20.0	24.8	166.3	27.9	5.08	4.03	151.7	128.8	131.9
	eq	75.1	31.0	23.9	24.3	166.1	27.9	4.72	3.99	148.7	128.8	131.6
10	ax	73.5	28.7	20.1	24.9	163.9	34.2	5.12	6.00	152.5	127.4	132.3
	eq	76.7	30.7	23.9	24.4	163.9	34.0	4.76	5.92	148.0	129.5	131.1
11	ax	76.1	28.5	20.0	24.7	160.7	30.9	5.19	–	153.0	126.2	128.4
	eq	79.0	30.3	23.7	24.2	160.7	30.7	4.83	–	148.1	130.4	132.5

[a] n.a. = Not available because the coupling pattern was too complex and because of an insufficient signal-to-noise ratio.

differences between the axial and equatorial conformers of **1**–**11** are summarized in Table 2. These values differ appreciably from those reported previously[11, 12] as they are dependent both on the method used and the solvent employed. However, the sequence order with respect to the polarity of the R substituent remains intact.

The ^1J(C,H) coupling constants were determined from standard HMQC spectra (without proton decoupling).

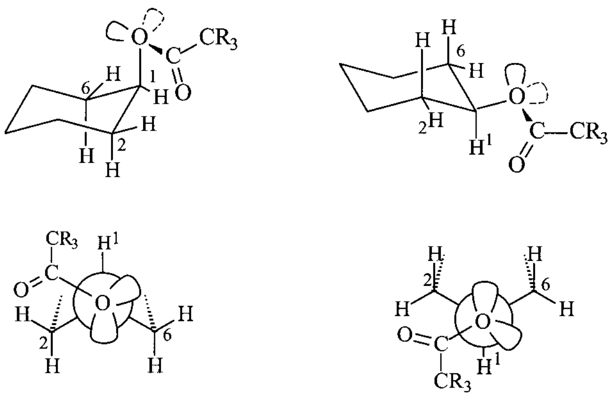
Table 2. Axial–equatorial conformational equilibria (K = [eq]/[ax]) and ΔG°_{exp} ($\Delta G^\circ_{exp} = -RT\ln K$) for compounds **1**–**11**.

Compd	K^{193}	$-\Delta G^\circ$ [kcal mol^{-1}]	K^{203}	$-\Delta G^\circ$ [kcal mol^{-1}]
1	7.4704	0.771	6.7145	0.678
2	9.5275	0.864	7.9572	0.836
3	6.1489	0.696	5.9011	0.716
4	2.9079	0.409	2.6448	0.392
5	5.7954[a]	0.639	5.3600[b]	0.644
6	6.1818	0.698	5.6146	0.696
7	4.1900	0.549	3.8675	0.545
8	2.7106	0.384	2.6056	0.386
9	5.9925	0.686	5.2484	0.668
10	3.8176	0.513	3.4987	0.505
11	2.3456	0.327	2.1963	0.317

[a] At 183 K. [b] At 193 K.

Computational studies: Ab initio MO calculations were performed with the GAUSSIAN 98 program package.[24] Different levels of theory were previously tested on three of the compounds (**1**, **3**, and **6**) and a number of sulfur analogues.[22] The results at the HF/6-311G**//HF/6-31G**, and MP2/6-311G**//HF/6-311G** theoretical levels proved to be the most reliable and were therefore used to calculate the energies of the axial and equatorial conformers of **1**–**11**, both in the gas phase and in solution. In addition, DFT calculations at the B3LYP/6-31G** level of theory were also performed. The Onsager reaction field theory was applied to calculate the solvent effect by self-consistent reaction field theory (SCRF). A self-consistent isodensity polarized continuum model (SCIPCM) was employed with the 6-311G** basis set in a solvent with a dielectric constant $\varepsilon = 2.6$. The solvent effect was estimated with the routines of the GAUSSIAN 98 program package.[24]

By means of internal rotation about the C1–O7 and O7–C8 bonds (rotation about the C8–C10 bond was not taken into consideration), a number of nondegenerate, but stable, conformers were assessed for each of the orientations of the ester group. This set of conformers was whittled down to the stage where only one conformer was found to be significant for each of the equatorial and axial orientations (Scheme 2). For example, for the equatorial conformation, a second con-



axial conformer equatorial conformer

Scheme 2. Preferred rotamers about C1–O7 and O7–C8 bonds for the axial and equatorial conformers of compounds **1**–**11**.

former, identified as a local minimum, was more than 3 kcal mol^{-1} higher in energy and was therefore not considered to contribute significantly to the population of the equatorial form. The two conformers, axial and equatorial, both adopted staggered orientations for the groups of C1 and O7 with, in each case, a lone pair of electrons on the oxygen atom orientated towards the cyclohexane ring (Scheme 2).[22] In both cases, the ester group was found to be in the *Z* configuration.[25]

The structural parameters of the molecular-relaxed geometries of the two conformations of **1**–**11** are summarized in Tables 3 and 4; the theoretical free energies of activation, $\Delta G^{\circ}_{\mathrm{calcd}}$, obtained by the different methods, both in the gas phase and in solution, are reported in Table 5. The electron

Table 3. Selected geometrical parameters for compounds **1**–**11** calculated at the B3LYP/6-31G** level of theory.

	Bond lengths [Å][a]									Angles [°]	
Compd	C1–C2	C1–C6	C1–O7	C2–C3	C5–C6	C2–H2$_{eq}$	C2–H2$_{ax}$	C6–H6$_{eq}$	C6–H6$_{ax}$	O7-C1-C4	θ[b]
equatorial conformers											
1	1.5301	1.5268	1.4544	1.5380	1.5377	1.0943	1.0983	1.0956	1.0980	147.56	157.660
2	1.5269	1.5302	1.4542	1.5377	1.5379	1.0956	1.0980	1.0943	1.0983	148.80	157.648
3	1.5301	1.5267	1.4542	1.5380	1.5379	1.0943	1.0984	1.0956	1.0980	148.86	157.699
4	1.5269	1.5300	1.4539	1.5376	1.5378	1.0957	1.0981	1.0943	1.0983	148.82	157.658
5	1.5284	1.5251	1.4658	1.5383	1.5380	1.0945	1.0977	1.0952	1.0976	148.60	157.464
6	1.5259	1.5293	1.4600	1.5378	1.5385	1.0952	1.0977	1.0945	1.0982	148.57	157.450
7	1.5286	1.5253	1.4640	1.5384	1.5383	1.0944	1.0977	1.0952	1.0974	148.51	157.391
8	1.5281	1.5249	1.4675	1.5385	1.5383	1.0944	1.0976	1.0951	1.0974	148.53	157.410
9	1.5260	1.5293	1.4588	1.5376	1.5380	1.0952	1.0979	1.0945	1.0981	148.75	157.593
10	1.5286	1.5254	1.4623	1.5383	1.5380	1.0944	1.0977	1.0952	1.0976	148.44	157.324
11	1.5283	1.5250	1.4653	1.5385	1.5380	1.0944	1.0975	1.0952	1.0974	148.43	157.323
axial conformers											
1	1.5331	1.5294	1.4608	1.5362	1.5371	1.0943	1.0987	1.0956	1.0983	102.58	93.377
2	1.5330	1.5294	1.4611	1.5363	1.5370	1.0943	1.0987	1.0956	1.0983	102.54	93.326
3	1.5329	1.5296	1.4607	1.5364	1.5371	1.0943	1.0987	1.0956	1.0983	102.38	93.190
4	1.5293	1.5334	1.4610	1.5372	1.5361	1.0956	1.0984	1.0938	1.0987	103.14	93.894
5	1.5312	1.5277	1.4728	1.5362	1.5373	1.0946	1.0984	1.0953	1.0980	101.71	92.460
6	1.5285	1.5321	1.4677	1.5371	1.5364	1.0955	1.0982	1.0945	1.0986	102.43	93.125
7	1.5318	1.5277	1.4716	1.5363	1.5369	1.0944	1.0985	1.0952	1.0982	102.39	93.087
8	1.5307	1.5275	1.4753	1.5365	1.5368	1.0946	1.0985	1.0951	1.0981	102.59	93.236
9	1.5285	1.5326	1.4652	1.5377	1.5365	1.0956	1.0980	1.0942	1.0985	100.88	91.767
10	1.5319	1.5281	1.4684	1.5367	1.5377	1.0946	1.0984	1.0953	1.0980	100.84	91.669
11	1.5310	1.5275	1.4720	1.5367	1.5376	1.0945	1.0984	1.0952	1.0980	100.83	91.643

[a] No changes in the following bond lengths for **1**–**11**: C1–H1, C3–H3$_{ax}$, C3–H3$_{eq}$, C5–H5$_{ax}$, and C5–H5$_{eq}$. [b] Angle between the axis of the bond C1–O7 and the plane defined by C3-C1-C5.

Table 4. Selected geometrical parameters (interatomic distances) for compounds **1**–**11** calculated at the B3LYP/6-31G** level of theory.

	Interatomic distances [Å]														
	O7–H2$_{eq}$	O7–H2$_{ax}$	O7–C2	O7–H6$_{eq}$	O7–H6$_{ax}$	O7–C6	O7–H3$_{eq}$	O7–H3$_{ax}$	O7–H5$_{eq}$	O7–H5$_{ax}$	O7–C1	O7–H1	O9–H2$_{eq}$	O9–H6$_{eq}$	C1–C10
equatorial conformers															
1	2.638	2.584	2.394	2.719	2.634	2.449	4.556	4.125	4.606	4.160	1.454	2.070	4.269	2.801	3.720
2	2.638	2.585	2.395	2.719	2.635	2.449	4.557	4.125	4.606	4.159	1.454	2.070	4.271	2.799	3.726
3	2.719	2.636	2.449	2.638	2.586	2.395	4.607	4.159	4.557	4.125	1.454	2.068	2.793	4.271	3.735
4	2.640	2,587	2.395	2.716	2.633	2.447	4.557	4.126	4.605	4.158	1.454	2.068	4.263	2.790	3.752
5	2.721	2.631	2.450	2.643	2.585	2.399	4.605	4.164	4.559	4.133	1.466	2.073	2.847	4.297	3.735
6	2.637	2.582	2.395	2.722	2.632	2.450	4.556	4.129	4.606	4.161	1.460	2.071	4.279	2.821	3.741
7	2.721	2.629	2.449	2.641	2.582	2.397	4.604	4.163	4.557	4.131	1.464	2.072	2.826	4.294	3.752
8	2.722	2.631	2.450	2.642	2.583	2.398	4.605	4.164	4.558	4.131	1.468	2.074	2.818	4.266	3.756
9	2.637	2.584	2.396	2.720	2.634	2.449	4.557	4.127	4.605	4.161	1.459	2.070	4.269	2.835	3.726
10	2.720	2.627	2.448	2.638	2.580	2.395	4.603	4.162	4.555	4.129	1.462	2.072	2.820	4.293	3.741
11	2.722	2.627	2.449	2.638	2.581	2.396	4.604	4.163	4.556	4.129	1.465	2.073	2.824	4.284	3.746
axial conformers															
1	2.678	3.378	2.451	2.588	3.334	2.394	4.016	2.746	3.962	2.699	1.461	2.068	2.768	4.273	3.726
2	2.677	3.378	2.450	2.590	3.335	2.394	4.014	2.743	3.962	2.699	1.461	2.069	2.765	4.274	3.733
3	2.677	3.377	2.449	2.591	3.335	2.394	4.012	2.741	3.959	2.693	1.461	2.069	2.773	4.270	3.741
4	2.584	3.333	2.394	2.680	3.380	2.456	3.970	2.712	4.029	2.766	1.461	2.067	4.304	2.683	3.758
5	2.680	3.377	2.448	2.594	3.337	2.396	3.997	2.718	3.956	2.692	1.473	2.073	2.801	4.312	3.740
6	2.588	3.334	2.394	2.679	3.378	2.452	3.959	2.695	4.016	2.748	1.468	2.071	4.282	2.789	3.754
7	2.682	3.379	2.454	2.585	3.335	2.395	4.019	2.754	3.957	2.693	1.472	2.071	2.775	4.305	3.758
8	2.676	3.378	2.452	2.588	3.337	2.398	4.019	2.756	3.966	2.707	1.475	2.072	2.822	4.290	3.763
9	2.593	3.332	2.388	2.689	3.376	2.447	3.937	2.665	3.983	2.694	1.465	2.073	4.342	2.718	3.729
10	2.681	3.374	2.443	2.592	3.333	2.390	3.980	2.692	3.939	2.668	1.468	2.074	2.781	4.317	3.743
11	2.687	3.377	2.447	2.587	3.332	2.388	3.985	2.699	3.936	2.664	1.472	2.074	2.752	4.325	3.750

Table 5. Comparison of experimental free energy differences, ΔG°_{exp}, with calculated[a] thermodynamic values, ΔG°_{calcd} or ΔE°_{calcd}, at various levels of theory for compounds **1**–**11**.

	ΔG°_{exp} [kcal mol^{-1}]	ΔG°_{calcd} or ΔE°_{calcd}[b, c] [kcal mol^{-1}] A	B	C	D	E	F
1	−0.771	−0.547	0.070	−0.626	0.001	0.294	−0.514
2	−0.865	−0.548	0.096	−0.699	−0.025	0.221	−0.507
3	−0.695	−0.579	0.061	−0.664	0.093	0.178	−0.523
4	−0.409	−0.739	0.121	−0.719	0.141	0.277	−0.654
5	−0.639	−0.286	0.370	−0.347	0.328	0.514	−0.407
6	−0.699	−0.542	0.421	−0.542	0.257	0.579	−0.403
7	−0.549	−0.348	0.436	−0.453	0.332	0.568	−0.442
8	−0.382	−0.323	0.317	−0.435	0.438	0.614	−0.429
9	−0.687	−0.479	0.420	–	–	0.577	0.350
10	−0.514	−0.451	0.450	–	–	0.584	0.231
11	−0.327	−0.511	0.492	–	–	0.626	0.455

[a] At 173.15 K. [b] A: HF/6-311G**//HF/6-311G**, GP; B: MP2/6-311G**//HF/6-311G**, GP; C: HF/6-311G**//HF/6-31G**, S; D: MP2/6-311G**//HF/6-311G**, S; E: MP2/6-311G**//HF/6-31G**, ΔE°; F: B3LYP/6-31G**, ΔE°. (Note: GP = gas phase, S = solution state). [c] Solution-state values were not calculated for the brominated compounds **9**–**11**.

populations of the atoms and lone pairs of the axial and equatorial conformers of the cyclohexane ring in compounds **1**–**11** were obtained by NBO analysis[26] and refer to the B3LYP/6-31G** molecular geometries. Both the hyperconjugative interactions of the C–H and C–C bonds of the cyclohexane moiety with the antibonding orbital of the C1–O7 bond and the electron population of the oxygen O7 lone pairs, which are both generally of interest with respect to the effects dominating the conformational equilibria of **1**–**11**, are presented in Table 6.

Relative energies of the equatorial and axial conformers: The free-energy differences of the monosubstituted cyclohexanes **1**–**11** exhibit a distinct trend: the more polar (−*I* effect) the R group, the more preferred is the axial conformer (Table 2). For example, with an increasing number of chlorine atoms the differences in energy between the two conformers are: CH_3 (−0.771 kcal mol$^{-1)}$) < CH_2Cl (−0.699 kcal mol$^{-1)}$) < $CHCl_2$ (−0.549 kcal mol$^{-1)}$) < CCl_3 (−0.382 kcal mol$^{-1)}$). Similarly with an increasing number of bromine atoms, the population of the axial conformer in the conformational equilibria increases, with the larger bromine atoms not limiting a greater shift towards the axial conformer. This result is in complete agreement with previously obtained measurements.[11–13] On the other hand, the effect of the alkyl substituents is also noticeable; however, the differences in ΔG° are not that remarkable: CH_2CH_3 (−0.865 kcal mol$^{-1)}$) < CH_3 (−0.771 kcal mol$^{-1)}$) < $CH(CH_3)_2$ (−0.695 kcal mol$^{-1)}$) < $C(CH_3)_3$ (−0.409 kcal mol$^{-1)}$).

Clearly, since polarity differences in the series **1**–**4** can be neglected, the increasing volume of the substituent also increases the population of the axial conformer, or, to state it alternatively, destabilizes the equatorial counterpart. This latter result, 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.

The total energy of the preferred conformers of the equatorial and axial conformers of compounds **1**–**11** was calculated with the 6-311G** basis set at the HF level of theory; for the DFT calculations, the 6-31G** basis set was used. The results, together with the free-energy differences, ΔG°, for the two conformers of **1**–**11** are presented in Table 5. Correction for the solvent effect, calculated according to the methods described in the Experimental Section, was applied to HF and MP2 calculations (data sets C and D in Table 5).

The correlation between the experimental ΔG° values for **1**–**11** with the theoretical values is only reasonable if the

Table 6. Hyperconjugative interactions [kcal mol^{-1}] of C–H and C–C bonds with the antibonding σ*(C1–O7) and occupancy by electrons of this orbital and of the O7 lone pairs[a] in compounds **1**–**11** from NBO analysis.

	Conf.	Donor orbital $\sigma(C2-H2_{eq})$	$\sigma(C2-H2_{ax})$	$\sigma(C6-H6_{eq})$	$\sigma(C6-H6_{ax})$	$\sigma(C2-C3)$	$\sigma(C5-C6)$	Σ of all σ	Σax − Σeq	Lone pair occupancy (O7)	σ*(C1–O7) occupancy
1	eq	0.345	0.699	0.445	0.709	3.677	3.384	9.259	2.955	1.8768	0.0431
	ax	0.692	5.387	0.817	4.978	0.162	0.178	12.214		1.8770	0.0489
2	eq	0.446	0.707	0.347	0.697	3.429	3.717	9.344	2.889	1.8769	0.0431
	ax	0.681	5.402	0.801	5.049	0.141	0.159	12.233		1.8768	0.0364
3	eq	0.343	0.687	0.443	0.700	3.683	3.404	9.260	2.944	1.8762	0.0432
	ax	0.692	5.366	0.807	4.988	0.169	0.182	12.204		1.8760	0.0489
4	eq	0.439	0.697	0.345	0.694	3.421	3.672	9.268	3.012	1.8762	0.0430
	ax	0.828	5.015	0.695	5.436	0.161	0.145	12.280		1.8760	0.0490
5	eq	0.362	0.736	0.452	0.744	3.916	3.647	9.857	3.053	1.8624	0.0470
	ax	0.718	5.663	0.845	5.283	0.196	0.205	12.910		1.8627	0.0533
6	eq	0.452	0.733	0.349	0.724	3.519	3.796	9.573	3.091	1.8680	0.0444
	ax	0.842	5.153	0.719	5.592	0.189	0.169	12.664		1.8663	0.0509
7	eq	0.359	0.736	0.453	0.745	3.897	3.622	9.812	3.122	1.8635	0.0449
	ax	0.453	0.745	0.359	5.263	0.171	0.194	12.934		1.8636	0.0513
8	eq	0.460	0.749	0.367	0.737	3.982	3.689	9.984	3.189	1.8642	0.0457
	ax	0.767	5.784	0.878	5.388	0.169	0.187	13.173		1.8642	0.0525
9	eq	0.454	0.705	0.352	0.697	3.599	3.839	9.646	3.301	1.9056	0.0313
	ax	0.827	5.282	0.651	5.802	0.204	0.181	12.947		1.9057	0.0376
10	eq	0.352	0.717	0.459	0.724	3.934	3.660	9.846	3.346	1.9016	0.0316
	ax	0.697	5.832	0.856	5.405	0.192	0.210	13.192		1.9022	0.0379
11	eq	0.360	0.742	0.464	0.749	3.945	3.638	9.898	3.060	1.8659	0.0451
	ax	0.692	5.676	0.863	5.146	0.193	0.218	12.788		1.8672	0.0518

[a] Averaged value of the two lone pairs.

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calculations take account of both electron correlation and the solvent effect. The best results were obtained by the use of the MP2/6-311G**//HF/6-311G** calculations (data set D in Table 5); the corresponding diagram is depicted in Figure 1. In this case, the correct order of the conformational energies as a function of the R substituent was obtained. In addition, there seem to be two linear dependencies, one for the more polar substituents R and another one (of lower ascent) for the alkyl substituents R, further corroborating the former view of a combined dependence of the long-range influence of the R substituent on the conformational equilibria of **1**–**11** based on both electronic and steric substituent effects. For this reason, the substituent–cyclohexane interaction has been studied in more detail on the basis of the experimental NMR spectra and the calculated results.

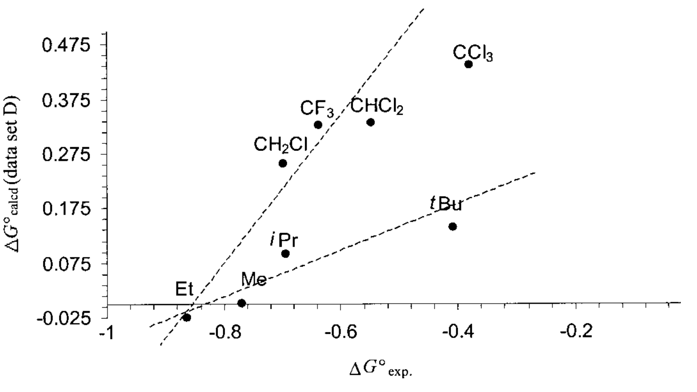

Figure 1. Plot of $\Delta G^{\circ}_{\text{calcd}}$ (MP2/6-311G**//HF/6-311G**,S) versus $\Delta G^{\circ}_{\text{exp}}$ for compounds **1**–**8**.

Molecular geometries: The structural parameters of the molecular-relaxed geometries of the axial and equatorial conformers of **1**–**11** by means of the B3LYP/6-31G** method are reported in detail in Tables 3 and 4 including bond lengths (Table 3), interatomic distances (Table 4), and the inclination angle θ (Table 3). These theoretical structural parameters, together with the experimental NMR parameters (^{13}C and ^{1}H chemical shifts and ^{1}J(C,H), see Table 1), are now discussed in light of the long-range substituent influence of the R group on the conformational equilibria of **1**–**11**.

First, the trend of the bond lengths and bond angles of monosubstituted cyclohexanes reported previously[1, 21] are also found for these compounds **1**–**11**, for example, the C1–O7 bonds are longer in the axial conformer than in the respective equatorial conformer. The same holds for the C1–H1 bond lengths, with the axial bonds being longer than those in the equatorial conformer and in agreement with the corresponding observed coupling constants, ^{1}J(C,H), (Table 1) and the well-described Perlin effect.[16]

Second, the electron densities at O7 and along the axial C–H bond fragments in the 3- and 5-positions in the axial conformers have been examined with respect to the steric bond polarization model, which is widely accepted for the conformational analysis of substituted cyclohexanes and heterocyclic analogues.[1, 2] For the calculated electron density at O7, the results were consistent with expectations (Table 7); electron-donating substituents (compounds **1**–**4**) increase the electron density at O7 whilst electron-withdrawing substituents (compounds **5**–**11**) reduce it. For these parameters, a fine correlation of q(O7) versus the inductive effect of the R group was obtained.

Finally, the electron densities at H3$_{\text{ax}}$ and H5$_{\text{ax}}$ and at C3 and C5 correlate exceptionally well (Figure 2). As the electron density at C3 and C5 increases, the electron density

Table 7. Electronic properties (dipole moments and selected atomic charge densities) for compounds **1**–**11** calculated at the B3LYP/6-31G** level of theory.

	μ	Atomic charge densities, q [e]												
	[Debye]	C1	C3	C5	H2$_{\text{eq}}$	H2$_{\text{ax}}$	H6$_{\text{eq}}$	H6$_{\text{ax}}$	H3$_{\text{eq}}$	H3$_{\text{ax}}$	H5$_{\text{eq}}$	H5$_{\text{ax}}$	O7	O9
	equatorial conformers													
1	1.929	0.1697	– 0.1884	– 0.1887	0.0988	0.1002	0.1142	0.0956	0.0950	0.0953	0.0951	0.0984	– 0.4816	– 0.4732
2	1.801	0.1703	– 0.1884	– 0.1886	0.0988	0.1002	0.1140	0.0956	0.0950	0.0952	0.0950	0.0983	– 0.4947	– 0.4819
3	1.861	0.1702	– 0.1886	– 0.1883	0.1140	0.0955	0.0993	0.0997	0.0950	0.0984	0.0950	0.0953	– 0.4982	– 0.4860
4	1.897	0.1701	– 0.1882	– 0.1904	0.0993	0.0995	0.1143	0.0957	0.0951	0.0954	0.0951	0.0985	– 0.5008	– 0.4916
5	3.486	0.1557	– 0.1908	– 0.1911	0.1176	0.1065	0.1076	0.1090	0.1017	0.1010	0.1015	0.0982	– 0.4745	– 0.4519
6	2.253	0.1603	– 0.1904	– 0.1894	0.1081	0.1052	0.1142	0.0998	0.0988	0.0966	0.0978	0.0997	– 0.4605	– 0.4627
7	2.418	0.1546	– 0.1903	– 0.1912	0.1165	0.1078	0.1082	0.1095	0.1005	0.0998	0.1006	0.0972	– 0.4498	– 0.4522
8	3.499	0.1547	– 0.1911	– 0.1917	0.1189	0.1085	0.1094	0.1104	0.1011	0.1011	0.1019	0.0984	– 0.4537	– 0.4269
9	2.381	0.1611	– 0.1899	– 0.1894	0.1082	0.1035	0.1138	0.0986	0.0982	0.0968	0.0975	0.0998	– 0.4694	– 0.4623
10	2.249	0.1562	– 0.1905	– 0.1908	0.1165	0.1071	0.1078	0.1089	0.0999	0.0996	0.1000	0.0969	– 0.4586	– 0.4579
11	3.172	0.1555	– 0.1910	– 0.1915	0.1184	0.1079	0.1087	0.1097	0.1013	0.1007	0.1011	0.0979	– 0.4644	– 0.4391
	axial conformers													
1	1.983	0.1520	– 0.1781	– 0.1796	0.1149	0.0948	0.1008	0.0958	0.0907	0.0995	0.0895	0.1064	– 0.4744	– 0.4730
2	1.851	0.1523	– 0.1780	– 0.1797	0.1146	0.0946	0.1005	0.0956	0.0905	0.0998	0.0894	0.1066	– 0.4876	– 0.4817
3	1.892	0.1508	– 0.1786	– 0.1792	0.1148	0.0942	0.0999	0.0957	0.0905	0.1006	0.0892	0.1063	– 0.4905	– 0.4862
4	1.904	0.1554	– 0.1804	– 0.1807	0.1008	0.0961	0.1175	0.0942	0.0898	0.1057	0.0908	0.1017	– 04956	– 0.4918
5	3.229	0.1383	– 0.1820	– 0.1834	0.1185	0.1031	0.1096	0.1027	0.0965	0.1085	0.0954	0.1137	– 0.4679	– 0.4523
6	1.633	0.1424	– 0.1835	– 0.1836	0.1028	0.0989	0.1162	0.0983	0.0913	0.1170	0.0925	0.1145	– 0.4530	– 0.4656
7	2.069	0.1385	– 0.1841	– 0.1842	0.1179	0.1014	0.1104	0.1008	0.0946	0.1135	0.0939	0.1166	– 0.4441	– 0.4523
8	3.213	0.1359	– 0.1846	– 0.1846	0.1189	0.1037	0.1115	0.1030	0.0964	0.1133	0.0955	0.1159	– 0.4477	– 0.4270
9	1.912	0.1466	– 0.1817	– 0.1862	0.1016	0.0988	0.1190	0.0969	0.0906	0.1124	0.0913	0.1182	– 0.4630	– 0.4621
10	1.866	0.1389	– 0.1859	– 0.1840	0.1171	0.1002	0.1092	0.1000	0.0929	0.1160	0.0927	0.1169	– 0.4521	– 0.4576
11	2.821	0.1399	– 0.1863	– 0.1847	0.1199	0.1021	0.1105	0.1018	0.0945	0.1148	0.0940	0.1169	– 0.4585	– 0.4393

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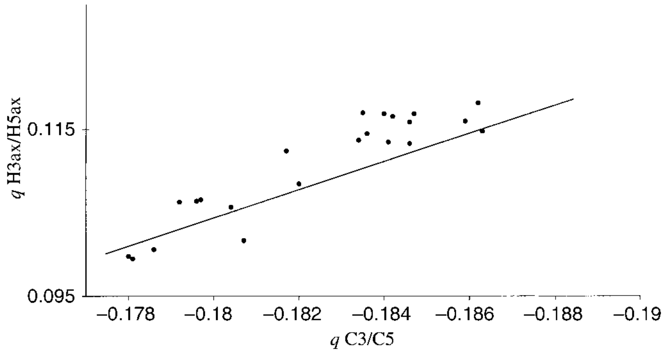
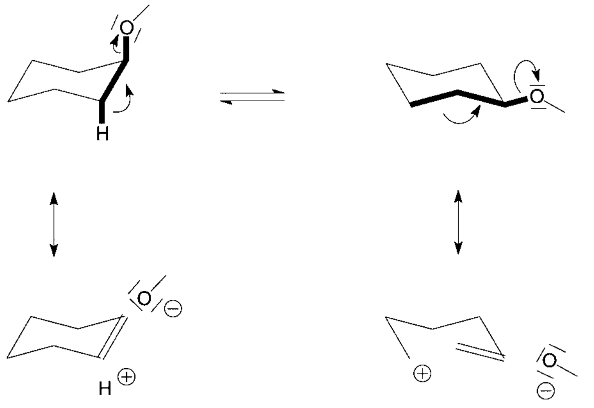


Figure 2. Plot of the $H3_{ax}$ ($H5_{ax}$) electron density, q, against the electron density of C3 (C5), respectively, for the axial conformers of compounds **1**–**11**.



Scheme 3. Lewis bond/nonbonding structures of monosubstituted cyclohexane.

at the axial protons, $H3_{ax}$ and $H5_{ax}$, abates. Interestingly, the increased electron density at O7 does not polarize the axial C–H bonds in the 3- and 5-positions in the expected manner by decreasing the $H3_{ax}$ and $H5_{ax}$ electron density whilst concomitantly increasing the C3 and C5 electron densities and thereby destabilizing the axial conformer overall. However, the opposite is in fact happening: an increasing O7 electron density increases the polarization of the axial C3–H3 (C5–H5) bond and shifts electron density from C3 and C5 to the $H3_{ax}$ and $H5_{ax}$ protons, respectively. The correlations are without doubt fine and the bond polarization model (used also for the quantification of the γ effect in ^{13}C NMR spectroscopy[23]) is not active in the accepted manner in the conformational analysis of saturated six-membered ring systems. In addition, the axial C3(5)–H3(5) bond length in the axial conformers does not change in **1**–**11**; the same is also true for the inclination angle θ (see Table 4).

Hyperconjugation: According to the Perlin effect,[16] but also based on detailed ab initio quantum-chemical calculations, hyperconjugation should be active in cyclohexane and its monosubstituted derivatives.[27] This electronic interaction within the saturated six-membered ring skeleton was originally purported to be responsible for the anomeric effect of polar substituents in the 2-position of six-membered saturated heterocyclic compounds (e.g., in the 2-OH oxanes as donation of the ring-oxygen lone pair into the antibonding C–O orbital of the exocyclic C–O bond, $n_O \rightarrow \sigma^*_{C-O}$). In light of the studied compounds **1**–**11**, hyperconjugation can be best represented by the Lewis bond/nonbonded structures depicted in Scheme 3. Consequently, for the axial conformers, extended axial C2(6)–H2(6) and C1–O7 bond lengths and concomitantly reduced C1–C2 bond lengths are anticipated if hyperconjugation is present or increasing. In the corresponding equatorial conformer, the C2–C3 and C1–O7 bond lengths are expected to appropriately increase whilst the C1–C2 bond should shorten. In a comparison of the axial and equatorial conformers of compounds **1**–**11**, the C1–O7 and the C1–H1 bond lengths, and also the ^1J(C1,H1) coupling constants in the axial conformers were found to be larger than in the equatorial conformers. In the context of hyperconjugation, this means stronger hyperconjugation in the axial conformer in comparison to its equatorial counterpart.

To see if this effect also has an influence on the position of the conformational equilibria of **1**–**11**, subject to the different polarity of the R substituents, the characteristic bond lengths, axial C2(6)–H2(6), C2–C3, C2–C1, and C1–O7 in the two conformers have been appropriately compared. In addition, the electron populations of the atoms involved in the hyperconjugation mechanism have been calculated by NBO analysis[6] and are presented in Table 6. Both types of measurements provide promising indications for the presence of hyperconjugation in the compounds **1**–**11** for the following reasons:

1) There is a clear tendency that, with increasing polarity of the R substituent, the C1–C2 bond length shortens and the corresponding C1–O7 bond lengthens in both conformers. The corresponding effect on the lengths of the axial C2(6)–H2(6) bonds in the axial conformer and C2–C3 in the equatorial conformer is less sensitive. However, there is a clear tendency in the corresponding direct C,H coupling constants of the C(2,6)–H(2,6-axial) fragments (Table 1); with increasing population of the axial conformer also the ^1J(C-2,6)(H-2,6-axial) values decrease indicating less effective coupling on account of the increasing C–H bond length. In terms of hyperconjugation, this implies the presence of this electronic interaction in the two conformers and because the C1–O7 and C1–H1 bond lengths in the axial conformers were found to be longer than in the equatorial conformers (the ^1J(C1,H1) coupling constants also change appropriately), a stronger contribution by hyperconjugation occurs in the case of the axial conformer. In short, the higher the polarity of R, the higher the population of the axial conformer. This is complete agreement with the experimental results (Table 2).

2) Similar conclusions can be drawn from the occupation numbers of lone pair/antibonding orbitals involved in hyperconjugation: the total Σ of occupancies of all σ orbitals donating into the antibonding orbital of the C1–O7 bond (σ^*_{C1-O7}) by way of hyperconjugation proved to be remarkably higher in the axial conformer, indicating more extensive hyperconjugation in this conformer and corroborating also the former experimental results. In addition, the stronger hyperconjugation in the axial conformer correlates with the experimental free energy differences. This is depicted in Figure 3 which shows that increasing hyperconjugation sta-

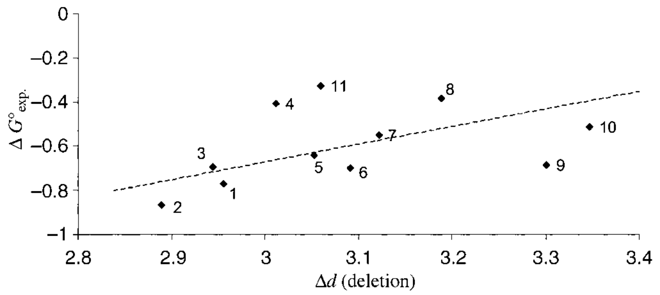


Figure 3. Plot of the calculated, stronger donation of the σ orbitals, Δ*d*, for the axial conformers of **1**–**11** against ΔG°_{exp}.

bilizes the axial conformer with respect to its equatorial counterpart.

Steric substituent effect: From the correlation of ΔG°_{exp} versus ΔG°_{calcd} given in Figure 1, it is clear that, besides the electronic long-range substituent effect of R in **1**–**11**, there should be another substituent effect present, probably of steric origin on account of the two dependencies indicated in Figure 1. Although the correlation coefficient is not very good, the tendency that there really is a steric effect is, nonetheless, evident. Thus, the volumes of the R groups in **1**–**11** have been tabulated (Table 8) and correlated with the conformational equilibria of **1**–**11** (Figure 4). It provides a rather good correlation ($r^2 = 0.78$), even better than the corresponding correlation of ΔG°_{exp} versus hyperconjugation given in Figure 3. The best correlation, however, was obtained if the least-squares treatment of a linear fit is conducted employing the two variables of R volume and hyperconjugation (Figure 5). The correlation coefficient improves considerably ($r^2 = 0.89$); the slope is close to 1 and the intercept close to 0, both of which are evidence for a close dependence [Eq. (1)].

$$\Delta G^\circ_{exp} = 0.8986\,\Delta G^\circ_{calcd} + 0.0474 \quad (1)$$

Table 8. Spatial volumes[a] of the R substituents in compounds **1**–**11**.

	R	V[cm^{3}mol^{-1}]		R	V[cm^{3}mol^{-1}]
1	Me	11.76	**7**	$CHCl_2$	21.85
2	Et[b]	16.88	**8**	CCl_3	26.36
3	*i*Pr[b]	22.00	**9**	CH_2Br	19.43
4	*t*Bu[b]	27.12	**10**	$CHBr_2$	26.26
5	CF_3	15.93	**11**	CBr_3	32.37
6	CH_2Cl	16.98			

[a] Reference [29]. [b] Calculated by employing van der Waals atomic radii and assuming spherical shapes for the atoms.

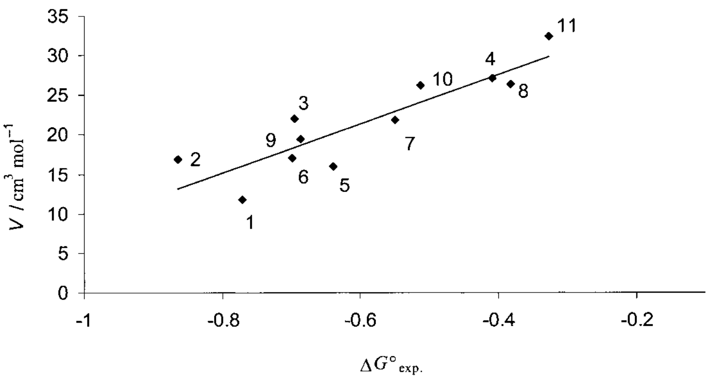


Figure 4. Plot of the volumes of the CR_3 substituents in compounds **1**–**11** against ΔG°_{exp}. Linear regression analysis ($r^2 = 0.78$) provides an equation, $y = ax + b$ with values of 31.17 (±5.53) for *a* and 40.06 (±3.41) for *b*.

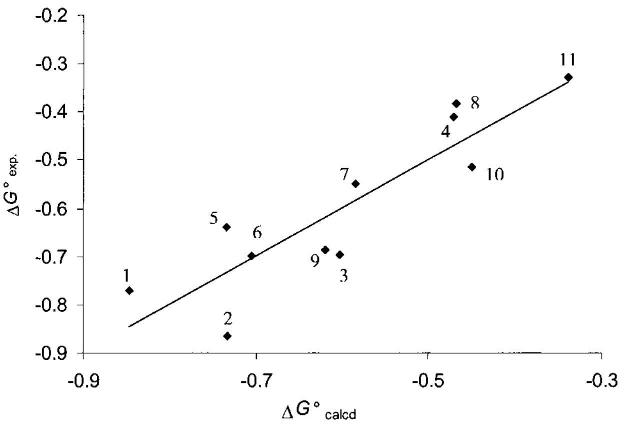


Figure 5. Plot of ΔG°_{exp} against ΔG°_{calcd} after taking account of the volume *V* of the CR_3 substituents and the hyperconjugation Δ*d*, for compounds **1**–**11** against $\Delta G^\circ_{calcd} = 0.125\,\Delta d + 0.024\,V - 1.499$. Linear regression analysis ($r^2 = 0.80$) provides an equation, $y = ax + b$ with, values of 0.899 (±0.154) for *a* and 0.047 (±0.113) for *b*.

The stabilization of the axial conformer by the hyperconjugative effect of the $OC(O)CR_3$ substituent is evident, yet it only has a partial influence on the relative stability ΔG° as a function of R. The dependence of ΔG° on the volume of the CR_3 group is present and should be caused by steric interactions involving the cyclohexane ring and the whole $OC(O)CR_3$ group. Nevertheless, how this effect intervenes to destabilize the equatorial conformer is a point that needs further insight. Although bond polarization via nonbonding 1,3-diaxial interactions as a cause can be discarded (vide supra), conversely, the reversed-substituent effect has to be considered. Thus, the characteristic bond lengths C1–O7 and spatial distances (internuclear distances between substituent atoms and the protons and carbon atoms of the cyclohexane ring, see Table 4) have been examined to illuminate the steric effects present in the two conformers of **1**–**11**. First, there is no clear trend amongst any of the distances examined, except the C1–O7 bond lengths and the spatial distances H1–O7 and H1–O9, and this occurs in both conformers. Furthermore, the increase of the bond lengths and spatial distances is very similar in the two conformers with the same R substituent. The inclination angle θ in the *equatorial* and *axial* conformers was found to be rather independent of the volume of CR_3 (Table 4). This should mean that the steric interaction of the $OC(O)CR_3$ substituent does not modify the geometry of the cyclohexane ring, while it is influential in changing the relative energy of *axial* and *equatorial* conformers. The fact that the modifications of the geometrical features of the cyclohexane ring in the series of compounds with different R are rather small should be assumed as further evidence that hyperconjugation only partly changes the relative stability of *axial/*

equatorial conformers as a funcion of R, since more significant geometric distortions should have otherwise been expected.[28] When the size of the CR_3 group increases as a function of R, more probably, it is able to provoke deformations within the ester group itself. In fact, the calculated C10–C1 distances (Table 4) always have a greater value in the *axial* conformer than in the *equatorial* analogue and this interatomic distance increases with increasing bulk of CR_3. This is particularly evident within the series of the alkyl substituents, since the C10–C1 distance increases in the order Me < Et < *i*Pr < *t*Bu. Furthermore, we performed the natural steric analysis within the framework of the NBO model with the facilities of the NBO5.0 program.[6] From the pairwise additive estimate of steric exchange energy and referring to the difference between the two conformers of each R-substituted molecule, it turns out that the steric effect is always greater in the *equatorial* conformer. For example, for the alkyl groups, the contribution ΔE to the relative destabilization of the two conformers are: Me 0.47, Et 0.73, *i*Pr 0.77, *t*Bu 1.12 $\mathrm{kcal\,mol^{-1}}$ (B3LYP/6-31G** wavefunctions). The steric effect should thus also influence the molecular stabilization of the two conformers as a result of intramolecular hydrogen bonding since the relative orientation of O9 and the hydrogen atoms H1, $H2_{eq}$/$H6_{eq}$ changes as a function of the spatial requirements of the CR_3 group.

Conclusion

The long-range substituent influences on the conformational equilibria of a number of monosubstituted cyclohexanes are partly based on electronic factors—hyperconjugation by way of $\sigma_{C2-H2ax} \rightarrow \sigma^*_{C1-O7}$ and $\sigma_{C2-C3} \rightarrow \sigma^*_{C1-O7}$—but also partly on steric influences—ironically, by destabilization of the equatorial conformer with increasing volume of the R substituent. The hyperconjugation $\sigma_{C2-H2ax} \rightarrow \sigma^*_{C1-O7}$ in the axial conformer is more effective than hyperconjugation $\sigma_{C2-C3} \rightarrow \sigma^*_{C1-O7}$ in the equatorial counterpart, thereby leading to a preference of the former conformer with increasingly stronger electronic interactions between the $-O_2CR$ substituent and the cyclohexane skeleton. The linear fit obtained employing the two variables of R, hyperconjugation and R volume, is excellent. Significantly, there is no hint of the existence of sterically destabilizing 1,3-diaxial nonbonding interactions in the axial conformers. Steric interactions, occurring in the whole molecule, estimated also from the NBO method, destabilize the *equatorial* conformer and the increasing bulk of the CR_3 group is one relevant component of the global effect.

Because this electronic interaction found here is similarly responsible for the stabilization of the axial conformer in the case of 2-substituted, six-membered saturated heterocyclic compounds (i.e. the *anomeric* effect), the question therefore arises: can the *anomeric* effect really be construed as anomalous or rather, is it a general physical-organic phenomenon? The mass of previous theoretical work and the results of this study clearly indicate that the answer is “No”.

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