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Syntheses and conformational analyses of mono- and *trans*-1,4-dialkoxy substituted cyclohexanes—the steric substituent/skeleton interactions

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Abstract—Mono- and *trans*-1,4-dialkoxy substituted cyclohexanes (alkyl=Me, Et, *i*-Pr, *t*-Bu) were prepared using the solvomercuration–demercuration (SM–DM) procedure. The axial⇆axial and axial,axial⇆equatorial, equatorial conformational equilibria of the products were studied by low temperature ^{1}H and ^{13}C NMR spectroscopy in CD_2Cl_2. The structures and relative energies of the participating conformers were calculated at both the B3LYP (6-311G*//6-311+G*) and MP2 (6-311+G*//6-311G*) levels of theory. In the case of DFT, good correlations of ΔG^{o}_{calcd} versus ΔG^{o}_{exptl} were obtained. Both the structures and the energy differences of the conformers have been discussed with respect to established models of conformational analysis, viz. steric and hyperconjugative interactions. In addition, $^{1}J_{H,C}$ coupling constants were considered with respect to the hyperconjugation present.
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1. Introduction

There is a continuing interest in both the torsional barrier and the preferred staggered conformer of ethane. As the underlying causes, both hyperconjugation and steric hindrance have been preferred[1–3] but it seems that conventional steric repulsion is the principal reason for the conformation and molecular dynamics of this fundamental molecule.[4] We obtained similar results when studying the conformational equilibria of mono- and *trans*-1,4-disubstituted cyclohexanes with substituents of variable polarity and volume.[5–9] However, surprisingly special substituent influences proved to be active: (i) there was no influence on the position of the axial/equatorial, axial,axial/equatorial, equatorial conformational equilibria from 1,3-diaxial steric interactions,[6] which should destabilize the axial arrangements (in contradiction to the generally accepted model of substituent influences on cyclohexane,[10] but this result has since been proven to be true also by others);[11,12] (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 on (iii) their steric effects, but by destabilization of the equatorial conformer with increasing substituent volume. Actually, only ester groups as substituents in the mono- and *trans*-1,4-disubstituted cyclohexanes (–OCOR; R=Me, Et, *i*-Pr, *t*-Bu, CF_3, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, and CBr_3) were studied and the question arose if this strange steric effect (i.e., an increasing R volume increasingly favors the axial conformation) results from the interaction between the substituents and the cyclohexane skeleton, or is a consequence of interactions within the ester moieties of the cyclohexyl esters and the diesters studied. Both possible causes were investigated and it is the topic of this paper to report on the steric substituent/cyclohexane skeleton interactions. For this purpose, both mono- and the *trans*-1,4-dialkoxy substituted cyclohexanes **1**–**8** (cf. Scheme 1) were synthesized, their conformational equilibria studied and the results compared with the accompanying theoretical study at the ab initio MP2 and DFT levels of theory.

The conformational equilibrium of methoxycyclohexane **1** has been studied both experimentally[13–16] and theoretically by calculations at various levels.[11,17,18] The rotamer populations about the C–OMe bond were investigated by the ^{13}C chemical shifts of the methoxy and ring carbons and the $^{3}J_{H,C}$ coupling constants.[19] Although the conformational peculiarities of cyclohexanes have been reviewed,[10,20] not much is actually known about 1,4-disubstituted derivatives despite their behavior being of interest.[20–27]

Wiberg[28] ab initio MO calculated the conformational equilibria of *trans*-1,4-dihalocyclohexanes in solution and obtained results in good agreement with experimental measurements;[29–33] the conformational equilibria of the 1,4-dihalocyclohexanes could be predicted by simple addition[34] and deviations were considered to stem from the additional contribution of electrostatic effects.[28] Similar

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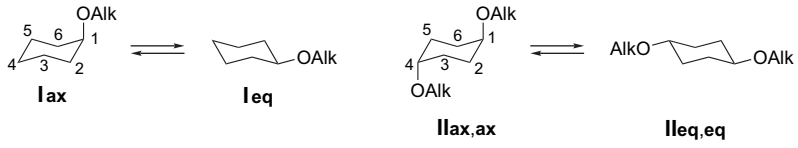


$$K = \frac{[\text{Ieq; IIeq,eq}]}{[\text{Iax; IIax,ax}]} \quad ; \quad -\Delta G^{\circ} = RT \ln K$$

Substituent	monosubstituted	trans-1,4-disubstituted
OMe	**1**	**5**
OEt	**2**	**6**
OiPr	**3**	**7**
OtBu	**4**	**8**

Scheme 1.

transannular interactions were found to be responsible for the preferred axial orientation of polar substituents in 4-substituted cyclohexanones.[35] On the other hand, dipole–dipole interactions between two polar substituents in cyclohexane proved to be negligible and inductive effects, due to the low polarizability of the intervening aliphatic ring, were also considered minimal.[36]

Thus, the relative activity of steric and hyperconjugative substituent effects (and in the case of 1,4-disubstituted analogs, also, the effect of transannular interactions) on the position of the conformational equilibria of substituted cyclohexanes is not yet completely understood;[37] the present paper tries to make further progress.

Of the disubstituted compounds examined here, *trans*-1,4-dimethoxy cyclohexane (**5**) has already been synthesized and studied with respect to both the conformational equilibrium and the barrier to ring interconversion[13a,38,39] whereby quantitative information on the population of the conformers was obtained ($-\Delta G^{o}$=1.4 kcal mol^{-1}).

2. Results and discussion

2.1. Synthesis of the compounds and NMR spectroscopic studies

The synthesis of cyclohexyl methyl ether (**1**) has been reported previously[7] and the cyclohexyl ethyl ether (**2**) was obtained by the Williamson ether synthesis.[40] The remaining mono-ethers (**3** and **4**) were synthesized by Brown's solvomercuration–demercuration (SM–DM) procedure.[41a,b] The disubstituted cyclohexyl ethers **5** and **6** were synthesized by the SM–DM procedure modified by Berger et al.[41c] The synthesis of the remaining 1,4-disubstituted cyclohexyl ethers, employing the same procedure, was not possible in case of **8**; Compound **7** was obtained in very low yield only. When using mercury trifluoroacetate instead of mercury acetate, however, **7** and **8** could be synthesized in high purity and good yield. The ethers, obtained as clear colorless liquids, except for **8**, which formed white crystals, were distilled in vacuo; the purity of the products was confirmed by ^{1}H, ^{13}C NMR, IR spectroscopy, and mass spectral analysis.

For determination of the equilibrium constants, K (cf. Scheme 1), the ^{1}H and ^{13}C NMR spectra of **1**–**8** were recorded in CD_2Cl_2 at low temperature wherein two sets of signals, one for each of the axial/diaxial and equatorial/diequatorial conformers, were obtained. The set of cyclohexane ring carbon atoms that were more shielded were assigned to the axial/diaxial conformers.[42] The equilibrium constants K (cf. Scheme 1) of the conformational equilibria were evaluated by careful integration of well-separated ^{1}H (H-1 and $OC_{\alpha}H_n$) and ^{13}C signals (depending on the *S*/*N*, up to five pairs of signals were evaluated; cf. Table S1 in Supplementary data) at 180 K, which subsequently provided the free energy differences ($\Delta G^{o}=-RT \ln K$). For the ^{13}C NMR, NOEs were suppressed by *inverse-gated decoupling* experiments and addition of Cr(acac)$_3$ to reduce T_1 relaxation; parallel inversion-recovery T_1 measurements proved the T_1 values of even quaternary carbon atoms to be <1 s; thus, pulse repetition times could be set to 5 s only. Cr(acac)$_3$, besides, proved to be of negligible influence on conformational equilibria.[42] In this manner, ^{1}H and ^{13}C analyses were comparable in determining the conformational equilibria.

In Table 1, both the ^{1}H and ^{13}C chemical shifts of the two conformers for **1**–**8** are presented. In addition, calculated (DFT and MP2) values are given which, in addition to general expectations,[42] provided the correct assignments. For the ^{1}H NMR, only the chemical shifts of H-1/H-4 and the protons of R substituents (H-10) are provided, as protons H-2, H-3, H-5, and H-6 furnished subspectra of higher order which, due to the poor state of homogeneity at the lower temperatures, were not amenable to simulation. Table 2 summarizes the conformational energy differences between the axial/diaxial and equatorial/diequatorial conformers of **1**–**8**. The values of **1** and **4** agree well with data reported previously. For **1**, Anteunis et al.[13a] in $CHFCl_2$ and Schneider and Hoppen[13b–d] in $CFCl_3$ determined $-\Delta G^{o}$ to be 0.89 and 0.75 kcal mol^{-1}, respectively, Robinson[14] and Eliel[15] both measured 0.6 kcal mol^{-1} whilst Mateos et al.[16] measured 0.64 kcal mol^{-1}. For **5**, Hammarstroem et al.[39] measured 1.4 kcal mol^{-1} (in $CHClF_2$); the value Fuchs et al.[43] measured for **4**, 0.75 kcal mol^{-1}, hardly deviates from that measured here. Two conclusions can readily be drawn from present conformational equilibria and are quite expectable: (i) with increasing volume of the alkoxy substituent(s), the equatorial/diequatorial conformers predominate ever

Table 1. Experimental (at 180 K in CD_2Cl_2) and calculated (DFT, MP2) ^1H and ^{13}C δ (ppm) of mono- and *trans*-1,4-dialkoxy cyclohexanes **1–8**

		H-4e	H-4a	H-3e, H-5e	H-3a, H-5a	H-2e, H-6e	H-2a, H-6a	H-1	OCαH	OCβH	C-4	C-3, C-5	C-2, C-6	C-1	OCα	OCβ
DFT																
1	ax	1.78	1.47	1.45	1.94	2.04	1.40	3.47	3.38	—	30.3	24.5	32.7	80.9	56.6	—
	eq	1.68	1.38	1.84	1.45	2.11	1.28	3.18	3.43	—	29.8	28.9	35.2	84.4	56.4	—
2	ax	1.81	1.49	1.48	1.97	2.08	1.42	3.65	3.53	1.33	30.4	24.7	33.4	80.2	67.2	17.5
	eq	1.7	1.40	1.85	1.47	2.15	1.36	3.37	3.64	1.28	29.8	28.9	35.8	83.3	67.0	17.5
3	ax	1.81	1.49	1.50	2.01	1.92	1.45	3.64	3.64	1.17	30.3	24.7	34.4	75.6	73.0	23.1
	eq	1.68	1.38	1.83	1.46	2.02	1.38	3.34	3.73	1.15	29.7	29.1	36.6	78.8	72.3	23.2
4	ax	1.8	1.46	1.51	2.06	1.76	1.51	3.75	—	1.22	30.2	24.6	37.0	70.6	78.1	28.3
	eq	1.66	1.34	1.80	1.50	1.89	1.48	3.37	—	1.2	29.3	29.4	39.3	74.1	78.0	28.5
MP2																
1	ax	1.84	1.51	1.49	2.02	2.10	1.46	3.55	3.32	—	31.2	24.5	34.2	81.4	58.2	—
	eq	1.74	1.38	1.89	1.45	2.19	1.33	3.14	3.35	—	30.6	29.4	36.8	85.9	58.3	—
2	ax	1.85	1.52	1.51	2.05	2.10	1.47	3.68	3.40	1.30	31.2	24.7	34.8	80.9	68.0	18.8
	eq	1.74	1.39	1.88	1.45	2.20	1.37	3.30	3.47	1.25	30.6	29.5	37.3	85.3	68.3	18.8
3	ax	1.84	1.49	1.53	2.11	1.93	1.46	3.61	3.53	1.18	31.0	25.0	35.4	76.7	74.3	25.0
	eq	1.72	1.38	1.88	1.44	2.04	1.40	3.20	3.59	1.14	30.6	29.8	38.2	81.2	73.8	25.0
4	ax	1.82	1.46	1.54	2.16	1.75	1.50	3.68	—	1.23	30.9	25.0	38.3	71.2	78.5	30.3
	eq	1.7	1.34	1.85	1.47	1.88	1.50	3.23	—	1.2	30.2	30.1	40.7	76.1	78.3	30.3
exptl																
5	ax	n.o.	n.o.	n.o.	n.o.	n.o.	n.o.	3.38	3.17	—	27.1	21.2	29.6	75.1	61.0	—
	eq	1.49	n.o.	1.65	n.o.	1.94	n.o.	2.96	3.22	—	26.4	25.0	32.4	79.6	55.7	—
6	ax	1.50–2.00[a]	1.27–1.50[a]	1.27–1.50[a]	1.50–2.00[a]	1.50–2.00[a]	1.27–1.50[a]	3.58	3.39	1.27–1.50[a]	26.4	20.8	29.9	73.6	66.6	15.8
	eq	1.58	1.02–1.25[a]	1.74	1.02–1.25[a]	2.02	1.02–1.25[a]	3.17	3.49	1.16	26.0	25.1	32.8	78.3	63.2	16.0
7	ax	n.o.	n.o.	n.o.	n.o.	n.o.	n.o.	3.68	3.62	n.o.	26.4	22.7	30.3	69.5	67.1	20.9
	eq	1.57	1.03–1.25[a]	1.72	1.03–1.25[a]	1.92	1.03–1.25[a]	3.24	3.75	1.1	29.9	25.2	33.4	74.6	67.5	22.8
8	ax	n.o.	n.o.	n.o.	n.o.	n.o.	n.o.	3.77	—	n.o.	n.o.	n.o.	n.o.	65.1	n.o.	n.o.
	eq	1.55	0.98–1.28[a]	1.69	0.98–1.28[a]	1.75	0.98–1.28[a]	3.3	—	1.16	25.6	25.7	35.8	70.3	73.5	28.2

		H-1, H-4	H-2e, H-3e, H-5e, H-6e	H-2e, H-3e, H-5e, H-6e	OCαH	OCβH	C-1, C-4	C-2, C-3, C-5, C-6	OCα	OCβ
B3LYP										
5	ax	3.44	1.74	1.83	3.38	—	81.0	26.8	56.5	—
	eq	3.22	2.10	1.30	3.42	—	83.8	33.1	56.8	—
6	ax	3.66	1.79	1.91	3.54	1.32	80.1	27.6	67.0	17.5
	eq	3.42	2.14	1.40	2.42	1.27	82.7	33.7	67.4	17.4
7	ax	3.64	1.65	1.97	3.66	1.17	76.1	28.8	73.2	23.1
	eq	3.37	1.99	1.41	3.68	1.16	78.5	34.7	73.0	23.2
8	ax	3.78	1.53	2.09	—	1.22	70.8	31.4	77.9	28.3
	eq	3.42	1.84	1.57	—	1.20	73.5	37.5	78.0	28.4
MP2										
5	ax	3.54	1.80	1.99	3.34	—	81.6	27.6	58.4	—
	eq	3.20	2.18	1.36	3.34	—	85.4	34.4	58.6	—
6	ax	3.68	1.81	2.03	3.43	1.30	81.1	28.3	68.2	18.8
	eq	3.35	2.17	1.40	2.30	1.25	84.9	35.0	68.6	18.8
7	ax	3.63	1.67	2.07	3.56	1.8	76.7	29.4	73.9	25.0
	eq	3.28	2.01	1.41	3.58	1.14	80.7	36.0	74.1	25.0
exptl										
5	ax	n.o.	n.o.	1.32	3.30	—	76.2	n.v.	55.8	—
	eq	3.15	2.08	1.15	3.33	—	78.6	29.8	56.3	—
6	ax	3.58	n.o.	n.o.	3.39	1.35	77.7	26.6	62.8	23.9
	eq	3.24	2.06	1.16	3.48	1.16	77.3	30.2	63.7	15.9
7	ax	3.84	n.o.	n.o.	3.64	1.28–1.78[a]	n.o.	24.4	n.o.	27.3
	eq	3.30	1.94	1.18	3.71	1.10	73.8	31.0	68.1	22.8
8	ax	—	—	—	—	—	—	—	—	—
	eq	3.32	1.73	1.24	—	1.15	69.4	33.7	73.7	28.0

n.o.: not obtained for technical reasons.

[a] Detailed assignments not possible due to signal overlap.

Table 2. Theoretical and experimental conformational energies (kcal mol^{-1}) of compounds **1–8**

Compd	B3LYP6-311G*//B3LYP 6-311G*			MP26-311+G*//MP26-311G*			exptl	
	$-\Delta E$	$-\Delta G^{o}$	$-\Delta E_{solv}$	$-\Delta E$	$-\Delta G^{o}$	$-\Delta E_{solv}$	$-\Delta G^{o}$ (^{1}H)	$-\Delta G^{o}$ (^{13}C)
1	0.19	0.49	0.62	−0.05	0.17	0.32	0.84[7]	—
2	0.30	0.40	0.56	−0.23	0.01	0.11	1.09	1.03
3	0.49	0.66	0.82	−0.01	0.09	0.51	1.09	1.10
4	0.57	1.11	0.94	−0.01	0.16	0.48	1.60	1.45
5	−0.26	0.27	0.50	−1.03	−0.61	−0.19	1.31	1.25
6	−0.10	0.10	0.53	−1.27	−0.82	−0.73	1.30	1.34
7	0.29	0.65	1.17	−0.84	—	—	1.63	1.67
8	0.59	0.70	1.61	−0.60	—	—	—	—

more (indeed, the diaxial conformer of **8** could not even be detected), and (ii) the substituent effect on the conformational equilibria is not additive. In the case of **5–8** they are up to 0.8 kcal mol^{-1} smaller than expected by simple addition of the $-\Delta G^{o}$ values of the monosubstituted analogs **1–4**.

Since *trans*-1,4-di-*tert*-butyl cyclohexane (**8**) was obtained as a white solid, crystals were grown and examined by single-crystal X-ray crystallography (data presented in Table S2 in Supplementary data). As expected, the molecule adopts the diequatorial conformation and the cyclohexane resides in a *chair* conformation with the *O*-*tert*-butyl substituents in *staggered* dispositions (cf. Fig. 1).

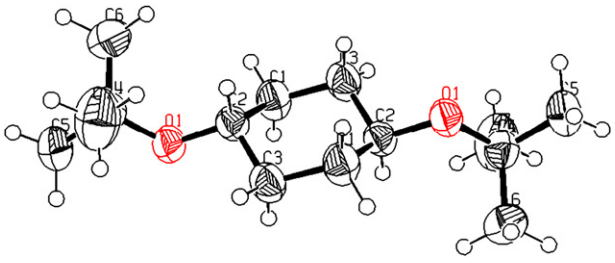


Figure 1. ORTEP structure of *trans*-1,4-di-*tert*-butyl cyclohexane **8**.

The acquisition of standard HMQC spectra without decoupling allowed evaluation of the $^{1}J_{H1,C1}$ coupling constants (cf. Table 3); because of the strongly biased conformational equilibria of **1–8**, the interesting $^{1}J_{H2ax,C2}$ coupling constants could be not obtained. The values of the $^{1}J_{H1,C1}$ couplings, however, are constant within the margin of error and thus incriminating information on any hyperconjugation present subject to substituent variation could be drawn.

Table 3. Experimental and calculated (DFT) $^{1}J_{H,C}$ coupling constants (Hz) of **1–8**

	$^{1}J_{H1,C1}$, exptl		$^{1}J_{H1,C1}$, calcd		$^{1}J_{H2,C2}$, calcd	
	ax	eq	ax	eq	ax	eq
1	143.7	137.7	136.3	132.4	121.9	125.7
2	143.5	137.7	136.4	132.4	121.8	125.7
3	142.1	137.9	136.0	132.0	121.2	126.2
4	143.8	136.1	134.6	130.9	120.5	126.6
5	142	141.6	136.8	133.2	125.5	125.4
6	143	142	136.8	133.2	125.2	125.4
7	n.o.	141.9	136.3	132.8	124.9	125.8
8	—	140.9	135.0	131.7	124.3	125.9

n.o., not obtained for technical reasons.

2.2. Computational studies

Ab initio MO and DFT calculations were performed using the Gaussian 98 program package.[44] Different levels of theory have previously been used to evaluate **1** and its sulfur analogue.[5] Results at the B3LYP (6-311G*//6-311+G*) and MP2 (6-311+G*//6-311G*) levels of theory proved to be the most reliable and were therefore used to calculate the energies of the fully relaxed structures for both the axial/diaxial and equatorial/diequatorial conformers of **1–8**. In addition, the solvent effect of dichloromethane was also considered whereby a self-consistent isodensity polarized continuum model (SCI-PCM)[45] using a dielectric constant ε=8.93 was employed. The results are summarized in Table 2 together with the experimentally determined values. In Table 4, some structural parameters of *trans*-1,4-di-*tert*-butyl cyclohexane (**8**) are compared with the X-ray data and strikingly corroborate the quality of the calculations.

Table 4. Experimental and theoretically calculated geometries for the equatorial, equatorial conformer of compound **8**

	Bond lengths (Å)		
	X-ray	DFT	MP2
C_2–C_3	1.526	1.532	1.525
C_2–O_1	1.435	1.43	1.427
C_3–C_1	1.533	1.535	1.53
C_1–C_2	1.524	1.532	1.525
O_1–C_4	1.442	1.443	1.437
C_4–C_7	1.519	1.536	1.529
C_4–C_6	1.532	1.536	1.529
C_4–C_5	1.525	1.53	1.524
Bond angles (°)			
C_2–O_1–C_4	118.9	119.8	117.6
C_2–C_1–C_3	111.6	112.1	111.5
O_1–C_2–C_1	109.3	109.1	108.9
O_1–C_2–C_{3a}	109.4	109.1	108.9
C_1–C_2–C_{3a}	110.1	110.7	110.9
C_1–C_3–C_{2a}	111.4	112.1	111.5
O_1–C_4–C_5	103.2	103.3	103.3
O_1–C_4–C_6	110.4	111.1	111.0
O_1–C_4–C_7	111.7	111.1	111.0
C_5–C_4–C_6	109.4	110.0	110.0
C_5–C_4–C_7	111.5	110.0	110.0
C_6–C_4–C_7	110.4	111.0	111.3

Hyperconjugation was studied using the NBO option included in the Gaussian 98 package with B3LYP/6-311G* wave functions and B3LYP/6-311G* optimized molecular structures and following a protocol reported previously.[7–9] A number of interactions between filled NBO's and antibonding orbitals were considered as most representative

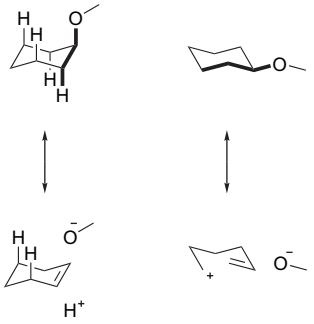
Table 5. Hyperconjugative stabilization energies E_{hyp} (kcal mol^{-1}) of the bonding/antibonding interactions between C_2–C_3/C_5–C_6 and C_2–$H_{2ax/eq}$/C_6–$H_{6ax/eq}$ orbitals with both bonding and antibonding orbitals of the C_1–O bond (DFT calculations) in **1–8** (cf. Scheme 2)

	1	**2**	**3**	**4**	**5**[a]	**6**[a]	**7**[a]	**8**[a]
Acceptor								
ax	10.79	10.79	10.86	10.95	10.87	10.91	10.96	11.08
eq	7.92	7.92	7.97	8.00	7.83	7.83	7.89	7.97
Donor								
ax	2.47	2.52	2.49	2.44	2.43	2.40	2.43	2.39
eq	3.31	3.26	3.28	3.32	3.29	3.27	3.26	3.28
Donor-LP								
ax	1.72	1.69	1.85	2.15	1.68	1.66	1.82	2.08
eq	1.91	1.87	2.01	2.44	1.90	1.89	2.03	2.42
Σ (donor, donor-LP, acceptor)								
ax	14.98	15.00	15.20	15.54	14.98	14.97	15.21	15.55
eq	13.14	13.05	13.26	13.76	13.02	12.99	13.18	13.67
$\Delta E_{HYP}=\Sigma E$(ax)$-\Sigma E$(eq)	1.84	1.95	1.94	1.78	1.96	1.98	2.03	1.88

[a] One substituent only studied.

for delocalization and retained for all the molecules studied. The interactions considered are those between the filled bonding and unfilled antibonding NBO's of the exocyclic C_1–O 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 energies of the two conformers resulting from hyperconjugation are presented in Table 5.

The most important hyperconjugative interactions for axial and equatorial conformers are represented by the Lewis bond/nonbonded structures depicted in Scheme 2 (only $\sigma_{C2-Hax} \rightarrow \sigma^*_{C1-O7}$ hyperconjugation for axial and $\sigma_{C2-C3} \rightarrow \sigma^*_{C1-O7}$ for the equatorial conformers are given; identical interactions are also active). In addition, the corresponding interactions between all orbitals in **1–8** were summed and are provided in Table 6.



Scheme 2.

Furthermore, interesting one-bond C, H coupling constants ($^1J_{H1,C1}$ and, for comparison, also $^1J_{H2,C2}$ values) were calculated at the DFT level of theory (cf. Table 3). Despite the experimental observations wherein the one-bond couplings remained constant within a margin of error, the calculated values revealed interesting tendencies, which will be discussed further on.

2.3. Relative stability of conformers of the mono- and *trans*-1,4-disubstituted cyclohexanes

With internal rotation about the C_1–O bond, non-degenerate but stable conformers could be assessed for various orientations of the alkoxy group. For each of **1–8**, one preferred conformer was obtained. In Figure 2 they are visualized for the monosubstituted cyclohexanes **1–4**; analogous orientations were found for **5–8** wherein *syn* and *anti* orientations of the two substituents proved to be of about the same energy. Only one other preferred conformer was obtained, which proved to be less stable (>3.2 kcal mol^{-1} for the equatorial and >8 kcal mol^{-1} for the axial conformer)[7] and hence was not studied further.

Table 6. Hyperconjugative stabilization energies E_{hyp} (kcal mol^{-1}) of the bonding/antibonding interactions between all orbitals with both bonding and antibonding orbitals of the C_1–O bond (DFT calculations) in **1–8**

	1	**2**	**3**	**4**	**5**[a]	**6**[a]	**7**[a]	**8**[a]
Acceptor								
ax	16.57	15.66	15.55	16.63	16.65	15.78	15.64	16.77
eq	14.28	13.40	13.30	14.33	14.16	13.26	13.20	14.28
Donor								
ax	3.98	4.80	4.88	4.28	3.93	4.74	4.82	4.21
eq	4.77	5.54	5.61	5.12	4.74	5.56	5.57	5.10
Donor-LP								
ax	34.48	33.02	32.19	34.20	34.30	32.78	31.97	34.09
eq	35.02	33.46	32.81	34.70	35.06	33.46	32.82	34.63
Σ (donor, donor-LP, acceptor)								
ax	55.03	53.48	52.62	55.11	54.88	53.30	52.43	55.07
eq	54.07	52.40	51.72	54.15	53.96	52.28	51.59	54.01
$\Delta E_{HYP}=\Sigma E$(ax)$-\Sigma E$(eq)	0.96	1.08	0.90	0.96	0.92	1.02	0.84	1.06

[a] One substituent only studied.

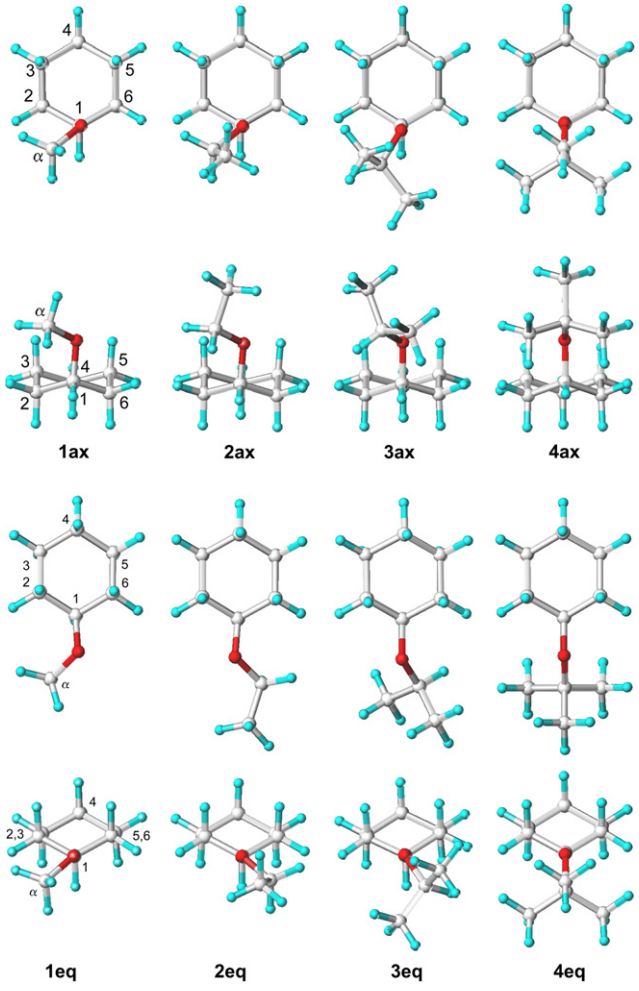


Figure 2. Preferred structures of both axial and equatorial conformers of **1**–**4**.

While the preferred equatorial/diequatorial conformers were correctly calculated by both theoretical methods, only with DFT could the conformational energies of the participating conformers be reasonably reproduced. For all three parameters (cf. Table 2), the correlation coefficients obtained were fair (ΔE, thermodynamically uncorrected, R^2=0.73; ΔG, corrected, R^2=0.80; ΔE, with inclusion of the solvent, R^2=0.82). With MP2 no correlation was obtained. Thus, only the results of the DFT calculations were employed to study and discuss the experimentally obtained sequences. In the two series, the increasing volume of the alkoxy substituent(s) destabilizes the axial/diaxial conformers with respect to the equatorial/diequatorial analogs in complete agreement with general stereochemical rules, i.e., the axial/diaxial conformers are assessed to be less stable due to increased steric hindrance. In the case of *trans*-1,4-di-*tert*-butyl cyclohexane (**8**), the corresponding diaxial conformer could not even be detected in solution at low temperature, only the diequatorial conformation could be observed (corroborated by the X-ray structure analysis). As potential causes for the conformational changes, both hyperconjugation of the C–H/C–C orbitals of the cyclohexane skeleton with the bonding/antibonding orbital of the C_1–O bond(s)[5–9,46–48] and steric substituent effects,[5–10] and in case of the *trans*-1,4-disubstituted cyclohexanes **5**–**8** also additional electrostatic interactions[35,49,50] between the two C_1–O dipoles, have been considered.

2.4. Hyperconjugation

When studying the conformational equilibria of the corresponding mono- and *trans*-1,4-disubstituted cyclohexyl esters of the acetic acid analogs CX_3COOH (CX_3=Me, Et, *i*-Pr, *t*-Bu, CF_3, CH_2Cl, $CHCl_2$, CCl_3, CH_2Br, $CHBr_2$, CBr_3), hyperconjugation was identified as a significant contributor to the different stabilities of the two conformers *ax*/*ax*,*ax*, and *eq*/*eq*,*eq*.[9] In case of **1**–**8**, which are alkyl ethers of the former cyclohexyl esters,[9] the stereoelectronic interactions $\sigma_{C2-Hax} \rightarrow \sigma^*_{C1-O}$ for the axial and $\sigma_{C2-C3} \rightarrow \sigma^*_{C1-O}$ for the equatorial conformers as the main contributors to the hyperconjugation present (cf. Scheme 2) were compared and found to be sufficiently stronger in the axial conformer (cf. Table 5). Thus, hyperconjugation could be employed for understanding *at least partly* the corresponding conformational equilibria of these compounds. In addition to the above interactions, *all* of the interactions of the orbitals with σ^*_{C1-O} and σ_{C1-O} were considered and are presented in Table 6.

The results of these calculations were unequivocal: (i) when the stereoelectronic interactions of the bonding and antibonding C_2–C_3, C_5–C_6, C_2–H(ax,eq), and C_6–H(ax,eq) with the bonding and anti-bonding C_1–O orbitals for the axial/diaxial and equatorial/diequatorial conformers were compared, they were again found to be stronger in the axial/diaxial conformers (by ca. 1.8–2 kcal mol^{-1}). If all orbital interactions are considered the axial conformer is stabilized by ca. 1 kcal mol^{-1}. (ii) Further, this hyperconjugative stabilization proved to be slightly larger in the diaxial and diequatorial conformers than by simple doubling of the monosubstituted conformational energies (cf. Table 5). The difference, though, is small, and if considering all hyperconjugative interactions (cf. Table 6) it is even smaller. Thus, overall, hyperconjugative stabilization of the two conformers in mono- and disubstituted cyclohexanes by a single substituent is about the same. In addition (iii), there is no dependence on the different substituents in **1**–**4** and **5**–**8**, respectively; i.e., there are no substituent effect changes in the two series of compounds on hyperconjugative stabilization of the corresponding conformers. This result is corroborated by an attempted correlation of hyperconjugative stabilization energies versus $-\Delta G^o$, which could not be found.

Examinations of theoretical calculations and the NBO 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.[48] The same conclusions can be drawn from the theoretical calculations (cf. Table 3). Unfortunately, the hyperconjugation-indicating coupling constants, $^1J_{H2ax,C2}$, could not be measured in **1**–**8** for technical reasons.[8] On the other hand, the very recent calculations of $^1J_{H,C}$ coupling constants in saturated six-membered rings by Perrin et al.[51,52] showed that whilst $^1J_{H,C}$ coupling is dependent to a degree on hyperconjugation, it is much more dependent on polar interactions.

2.5. Steric substituent effects

Steric substituent effects were also found to be present. In Figure 3, experimental free energy differences of **1–8** are correlated to the volume of the alkoxy groups (in the case of **5–8**, doubled volumes were applied). Actually not one, but two correlations for the two sets of compounds were obtained. The excellent correlations strikingly corroborate the important role steric effects influencing the present conformational equilibria.

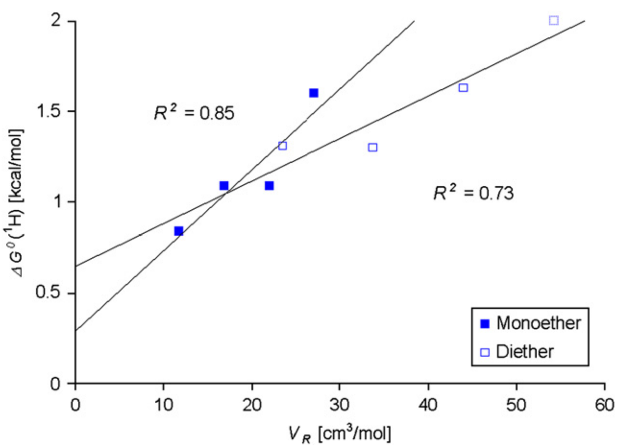


Figure 3. Correlation of experimental free energies of activation, $-\Delta G^o$ (kcal mol^{-1}), with the volumes V_R of the *O*-alkyl substituents.

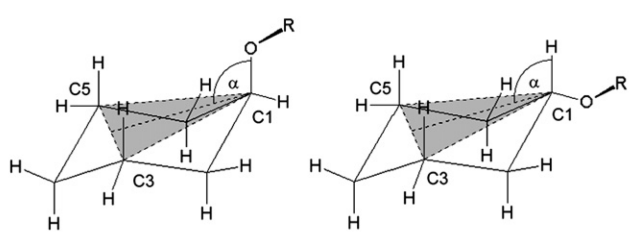


Figure 4. Visualization of the inclination angle α (Steiner and Saenger[26]).

The evaluation of steric substituent influences on the conformational equilibria of substituted cyclohexanes by Steiner and Saenger[26] is based on the inclination angle (α) between the C_1–C_3–C_5 plane and the C_1–O bond in the axial conformer and the C_1–H_1 bond in the equatorial analogs (cf. Fig. 4). Rising inclination angles indicate increasing steric substituent influences. Cyclohexanes with axial *O*-substituents proved to be virtually strain-free.[26] Examination of the inclination angles in compounds **1–8** (cf. Table 4) suggests that the steric substituent effect even decreases with increasing volumes of the alkyl moieties (in the axial/diaxial conformers, α decreases by ca. 1°, in the equatorial/diequatorial conformers it remained almost constant). This conclusion contradicts the notion of the increasing steric hindrance with increasing volume of the alkoxy substituents.

Instead, as a measure of the steric substituent effect of the alkoxy substituents in **1–8**, both the spatial distances C_1–C_α and the bond angles C_1–O–C_α were employed (cf. Table 7). The supposition is that the increasing volume of an alkoxy group should both increase the C_1–C_α distance and widen the C_1–O–C_α bond angle. In Table 4, the continuous ascent of these two parameters in the two series **1**<**2**<**3**<**4** and **5**<**6**<**7**<**8** can be seen. In Figure 5, supporting this notion, the volumes of the alkyl groups at the ether oxygen correlate very well with the C_1–C_α distances. Accordingly, successful correlations for the bond angles C_1–O–C_α were also obtained.

The steric alkoxy substituent effect is larger in the axial/diaxial than in the equatorial/diequatorial conformers, and is revealed by correlating $-\Delta G^o$ values to the same parameters (cf. Fig. 6). Two almost parallel correlations are obtained, which prove that the same steric substituent influences in the conformational equilibria are present in both the mono- (**1–4**) and disubstituted (**5–8**) compounds.

This steric substituent effect due to the alkoxy substituents can be estimated simply from the $-\Delta G^o$ values of **1–4** to be ca. 1.9 kcal mol^{-1} (OMe), ca. 2.0 kcal mol^{-1} (OEt), ca.

Table 7. Steric substituent effects as determined by DFT calculations in mono- and *trans*-1,4-dialkoxy substituted cyclohexanes **1–8**

	Inclination angle α (°)	Torsion angle (°) H_1–C_1–O_7–C_α	Distance C_1–C_α (Å)	Bond length O–C_α (Å)	Bond length C_1–O (Å)	Bond angle C_1–O–C_α (°)
ax						
1	94.19	53.7	2.3953	1.4106	1.4314	114.88
2	94.26	54.2	2.4089	1.4180	1.4310	115.45
3	93.96	34.7	2.4299	1.4310	1.4338	116.03
4	92.91	0.0	2.4874	1.4428	1.4365	119.51
5	93.95	53.7	2.3955	1.4105	1.4328	114.81
6	94.13	54.4	2.4091	1.4177	1.4329	115.37
7	93.59	36.1	2.4301	1.4306	1.4357	115.95
8	92.85	0.1	2.4893	1.4420	1.4386	119.58
eq						
1	92.87	50.3	2.3937	1.4115	1.4258	115.05
2	92.83	51.8	2.4074	1.4187	1.4258	115.63
3	92.54	34.1	2.4300	1.4318	1.4278	116.38
4	93.02	0.0	2.4875	1.4426	1.4313	119.89
5	93.04	51.0	2.3924	1.4120	1.4247	115.01
6	92.88	52.4	2.4060	1.4193	1.4247	115.56
7	92.63	34.5	2.4290	1.4324	1.4267	116.33
8	92.98	0.0	2.4864	1.4432	1.4304	119.83

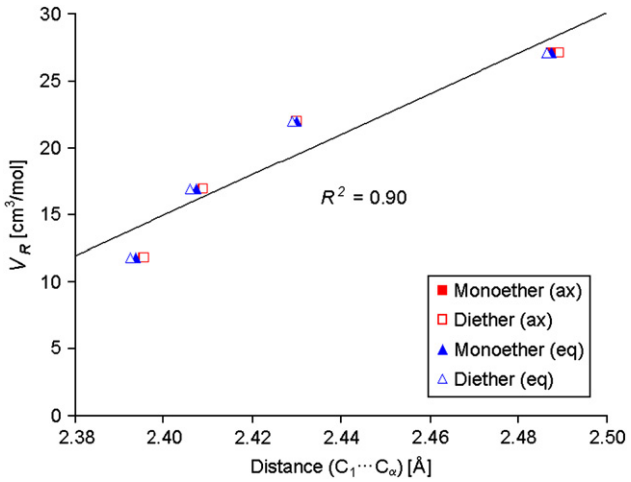


Figure 5. Correlation of the $C_1\cdots C_\alpha$ distances in **1–8** versus the volumes V_R of the *O*-alkyl substituents.

2.1 kcal mol^{-1} (O*i*-Pr), and ca. 2.6 kcal mol^{-1} (O*t*-Bu), taking ca. 1 kcal mol^{-1} hyperconjugative stabilization of the axial conformer (vide supra) additionally into account.

Since similar, almost identical and additive, hyperconjugative substituent effects are present in the mono- and disubstituted cyclohexanes, together with the result discussed above, it implies that both effects on the conformational equilibria of **1–4** can simply be added to determine the conformational equilibria of the disubstituted analogs **5–8**. However, the diequatorial conformers of **5–8** are less stabilized than expected. In other words, they are additionally destabilized by a third, additional effect which can only be represented by the polar interactions between the two C–O dipoles of the alkoxy substituents, obviously more effective in the diaxial than in the diequatorial conformation. It can be anticipated that the C–O_{alkyl} dipoles only change negligibly in **5–8** due to the modest alkyl variation. Thus, this *transannular electrostatic interaction effect*, which stabilizes the diaxial conformers with respect to their diequatorial counterparts can be expected to be between 0.5 and 0.7 kcal mol^{-1} (cf. Table 2).

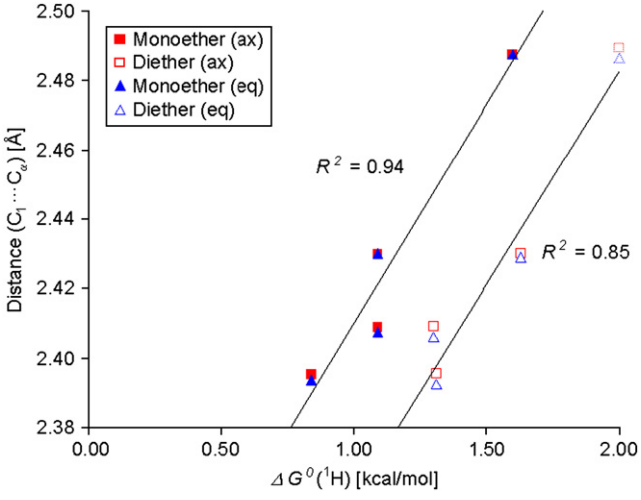


Figure 6. Correlation of experimental free energies of activation, $-\Delta G^{\circ}$ (kcal mol^{-1}), with the $C_1\cdots C_\alpha$ distances in **1–8**.

3. Conclusions

A variety of mono- and *trans*-1,4-dialkoxy substituted cyclohexanes **1–8** (alkyl=Me, Et, *i*-Pr, *t*-Bu) have been synthesized and their axial⇋equatorial and axial, axial⇋equatorial, equatorial conformational equilibria studied. Depending on the volume of the alkoxy substituents, the equatorial and diequatorial conformers were increasingly preferred with respect to the corresponding axial and diaxial conformers and in harmony with the results of theoretical calculations at various levels of theory (DFT, MP2). Although hyperconjugation stabilizes the axial and diaxial conformers with respect to the equatorial and diequatorial analogs, this effect is constant along the present substitution pattern and additive when comparing **1–4** and **5–8**, respectively. An increasing volume of an alkoxy substituent, however, increasingly destabilizes axial and diaxial conformers due to steric hindrance within the –$C^2(H_2)$–C^1H(OAlkyl)–$C^6(H_2)$– segments(s) and is thus responsible for the steric substituent influences. Though the substituent effects on the conformational equilibria of the monosubstituted cyclohexanes **1–4** should be additive in determining the corresponding equilibria in **5–8**, in reality they are not. Differences of 0.5–0.7 kcal mol^{-1} were determined and have been assigned to transannular *electrostatic interactions between the C–O dipoles*, which additionally stabilize the diaxial conformers in **5–8** with respect to their diequatorial analogs, as has been suggested previously.[28,35,49,50]

4. Experimental section

4.1. Syntheses

Purchased chemicals were used without further purification. The cyclohexyl ethers **1–8** were characterized by ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectroscopy (APT, H,H-COSY, HMQC, HMBC), FTIR spectroscopy, and ESI-Q-TOF mass spectrometry.

4.1.1. Cyclohexyl methyl ether (1). Compound **1** was available from a previous preparation[7] by the Williamson ether synthesis.[40]

4.1.2. Cyclohexyl ethyl ether (2). Elementary sodium (0.165 mol, 3.8 g) was first dispersed under toluene after which the toluene was replaced by anhydrous ether (50 mL). A solution of cyclohexanol (0.165 mol, 16.5 g) in 50 mL anhydrous ether was then added and the solution left to stir. After 3 h, ethyl iodide (0.170 mol, 28.9 g) was added dropwise and the solution left to stir for another 3 h. The ether was then evaporated and the residue distilled to yield 3 g (15%) of a clear colorless liquid, bp 100 °C (22 mbar); HRMS $[M+H]^+$ calcd for $C_8H_{17}O$ 129.1275, found 129.1279; ^{1}H NMR δ (ppm) 1.13–1.26 (m, 5H, H-2ax–H-6ax), 1.17 (t, 3H, J=7.0 Hz, CH_3), 1.52 (m, 1H, H-4eq), 1.71 (m, 2H, H-3eq, H-5eq), 1.92 (m, 2H, H-2eq, H-6eq), 3.20 (m, 1H, H-1), 3.48 (q, 2H, J=7.0 Hz, OCH_2); ^{13}C NMR δ (ppm) 15.7 (CH_3), 24.3 (C-3, C-5), 25.8 (C-4), 32.4 (C-2, C-6), 62.9 (OCH_2), 77.3 (C-1); IR ν (cm^{-1}) 2932, 1449, 1371 (CH_3, CH_2), 1111 (CH_2–O–CH_2), 976, 895.

4.1.3. Synthesis of cyclohexyl ethers 3 and 4. Compounds **3** and **4** were synthesized by Brown's solvomercuration–demercuration procedure.[41] To $Hg(OCOCF_3)_2$ (25 mmol, 10.7 g) dissolved in 30 mL of the corresponding anhydrous alcohol, cyclohexene (25 mmol, 2.05 g) was added dropwise under rapid stirring. After stirring the mixture for 15 min, 25 mL of 3 M KOH solution was added to the reaction mixture whilst cooling in an ice bath. After 2 min, 25 mL of 0.5 M $NaBH_4$ solution in 3 M KOH solution was added causing the precipitation of colloidal black mercury. The reaction product was extracted with hexane (3×20 mL) after which the organic phase was washed with distilled water (15×60 mL) and then dried with anhydrous Na_2SO_4. The hexane was then removed and the products distilled in vacuo.

4.1.4. Cyclohexyl *iso*-propyl ether (3). Yield 3 g (61%) of a clear, colorless liquid, bp 120–124 °C (23 mbar); HRMS $[M+H]^+$ calcd for $C_9H_{19}O$ 143.1436, found 143.1439; ^1H NMR δ (ppm) 1.15–1.27 (m, 5H, H-2ax, H-6ax), 1.12 (d, 6H, J=6.2 Hz, CH_3), 1.51 (m, 1H, H-4eq), 1.71 (m, 2H, H-3eq, H-5eq), 1.85 (m, 2H, H-2eq, H-6eq), 3.25 (m, 1H, H-1), 3.48 (sp, 1H, J=6.2 Hz, OCH_2); ^{13}C NMR δ (ppm) 22.9 (CH_3), 24.5 (C-3, C-5), 25.8 (C-4), 33.2 (C-2, C-6), 68.1 (OCH_2), 74.8 (C-1); IR ν (cm^{-1}) 2932, 1450, 1376 (CH_3, CH_2), 1157, 1125, 1083 (CH_2–O–CH_2), 1042, 1013, 916.

4.1.5. Cyclohexyl *tert*-butyl ether (4). Yield 1.31 g (33%) of a clear, colorless liquid, bp 79–81 °C (38 mbar); HRMS $[M+H]^+$ calcd for $C_{10}H_{21}O$ 157.1592, found 157.1595; ^1H NMR δ (ppm) 1.05–1.27 (m, 5H, H-2ax–H-6ax), 1.15 (s, 9H, CH_3), 1.53 (m, 1H, H-4eq), 1.71 (m, 4H, H-2eq, H-3eq, H-5eq, H-6eq), 3.33 (m, 1H, H-1); ^{13}C NMR δ (ppm) 24.5 (C-3, C-5), 25.2 (C-4), 28.5 (CH_3), 35.6 (C-2, C-6), 70.2 (C-1), 73.0 (OCH_2); IR ν (cm^{-1}) 2933, 1449, 1361 (CH_3, CH_2), 1199, 1076 (CH_2–O–CH_2), 1042, 1023, 1004, 885.

4.1.6. Synthesis of cyclohexyl ethers 5–8. Dialkoxy cyclohexyl ethers **5–8** were synthesized by a procedure analogous to the above. To $Hg(OCOCH_3)_2$ (0.12 mmol, 38.2 g) [in the case of **7** and **8**, $Hg(OCOCF_3)_2$ was used in place of $Hg(OCOCH_3)_2$] dissolved in the appropriate alcohol (800 mL), cyclohexadi-1,4-ene (0.05 mol, 4 g) was added whilst stirring. After 7 days, during which time any mercury salts that had precipitated were removed, the solution was poured into 0.5 M NaCl solution (500 mL). The precipitated mercury salt was filtered by suction and washed carefully with 20 mL of water, ethanol, and then ether. The precipitate was dispensed into a 0.5 M KOH solution (250 mL) at 0 °C whilst vigorously stirring the reaction mixture. During continuous cooling, 1 M $NaBH_4$ solution in 0.5 M KOH was then added and stirring continued for further 20 min. At completion, the reaction mixture was extracted with CH_2Cl_2 (3×50 mL) and the organic phase dried over anhydrous Na_2SO_4 followed by removal of the solvent.

4.1.7. *trans*-1,4-Dimethoxy cyclohexane (5). Yield 3.11 g (43%) of a clear, colorless liquid, bp 74–76 °C (26 mbar); ^1H NMR δ (ppm) 1.27 (m, 4H, H-2ax, H-3ax, H-5ax, H-6ax), 1.99 (m, 4H, H-2eq, H-3eq, H-5eq, H-6eq), 3.17 (m, 2H, H-1, H-4), 3.30 (s, 6H, CH_3); ^{13}C NMR δ (ppm) 29.0 (C-2, C-3, C-5, C-6), 56.3 (OCH_3), 78.4 (C-1, C-4); IR ν (cm^{-1}) 2937, 1454, 1378 (CH_3, CH_2), 1199, 1103 (CH_2–O–CH_2), 1031, 982, 914.

4.1.8. *trans*-1,4-Diethoxy cyclohexane (6). Yield 5.35 g (62%) of a clear, colorless liquid, bp 103–107 °C (38 mbar); HRMS $[M+H]^+$ calcd for $C_{10}H_{21}O_2$ 173.1542, found 173.1543; ^1H NMR δ (ppm) 1.17 (t, 6H, J=7.0 Hz, CH_3), 1.26 (m, 4H, H-2ax, H-3ax, H-5ax, H-6ax), 2.00 (m, 4H, H-2eq, H-3eq, H-5eq, H-6eq), 3.24 (m, 2H, H-1, H-4), 3.48 (Q, 4H, J=7.0 Hz, OCH_2); ^{13}C NMR δ (ppm) 15.7 (CH_3), 29.7 (C-2, C-3, C-5, C-6), 63.4 (OCH_2), 76.7 (C-1, C-4); IR ν (cm^{-1}) 2936, 1447, 1374 (CH_3, CH_2), 1108 (CH_2–O–CH_2), 1035, 991, 957, 882.

4.1.9. *trans*-1,4-Di-*iso*-propyl cyclohexane (7). Yield 1.93 g (70%) of a clear, colorless liquid, bp 110–115 °C (36 mbar); HRMS $[M+Na]^+$ calcd for $C_{12}H_{24}O_2Na$ 223.1698, found 223.1698; ^1H NMR δ (ppm) 1.09 (d, 12H, J=6.0 Hz, CH_3), 1.22 (m, 4H, H-2ax, H-3ax, H-5ax, H-6ax), 1.89 (m, 4H, H-2eq, H-3eq, H-5eq, H-6eq), 3.28 (m, 2H, H-1, H-4), 3.48 (sp, 2H, J=6.0 Hz, OCH_2); ^{13}C NMR δ (ppm) 22.9 (CH_3), 30.7 (C-2, C-3, C-5, C-6), 68.6 (OCH_2), 74.3 (C-1, C-4); IR ν (cm^{-1}) 2970, 1453, 1377 (CH_3, CH_2), 1126, 1088 (CH_2–O–CH_2), 1035, 982, 914.

4.1.10. *trans*-1,4-Di-*tert*-butyl cyclohexane (8). Yield 6.35 g (70%), white crystals, mp 91–98 °C; HRMS $[M+Na]^+$ calcd for $C_{14}H_{28}O_2Na$ 251.1987, found 251.1999; ^1H NMR δ (ppm) 1.16 (s, 18H, CH_3), 1.32 (m, 4H, H-2ax, H-3ax, H-5ax, H-6ax), 1.76 (m, 4H, H-2eq, H-3eq, H-5eq, H-6eq), 3.31 (m, 2H, H-1, H-4); ^{13}C NMR δ (ppm) 28.8 (CH_3), 34.1 (C-2, C-3, C-5, C-6), 70.0 (C-1, C-4), 73.6 (OCH_2); IR ν (cm^{-1}) 2972, 1456, 1362 (CH_3, CH_2), 1195, 1079 (CH_2–O–CH_2), 978, 896.

4.2. NMR measurements

^1H and ^{13}C NMR spectra were recorded on Bruker Avance 500 and 300 NMR spectrometers using 5 mm probes operating at 500 and 300 MHz for ^1H, respectively, and 125 and 75 MHz for ^{13}C, respectively. For all measurements, $CDCl_3$ (for lower temperatures CD_2Cl_2) was employed as the solvent using TMS as an internal reference (=0 ppm for both nuclei). Signal assignment was performed at 298 K and utilized standard Bruker pulse sequences (^1H, ^{13}C, COSY, HMQC, and HMBC); digital resolution in 2D heteronuclear experiment 0.1 Hz.

For ^1H NMR spectra, the digital resolution was set to 16 data points Hz^{-1} and for ^{13}C spectra, to 1.6 data points Hz^{-1}. For 2D NOESY experiments, an optimal value for the mixing time τ_m was assessed as 400 ms. To avoid confusion arising from spin diffusion, 2D ROESY spectra were also recorded for comparison and also utilized mixing times of 400 ms. For both NOESY and ROESY experiments as well as the T_1 measurements, paramagnetic oxygen was displaced from the NMR solutions by ultrasonification for 30 min under argon prior to measurement. T_1 values were measured using the inversion recovery pulse sequence with a total of 16 different delay times. T_1 values were calculated using standard Bruker software and are reported with an uncertainty of 50 ms. Vicinal ^1H–^1H coupling constants were measured using the JRESQF pulse sequence where the spectral widths were

set to 4125 and 40 Hz for the f_2 and f_1 dimensions, respectively, with digital resolutions of 4 and 0.2 Hz in f_2 and f_1, respectively.

4.3. Theoretical calculations

Ab initio calculations were carried out with the GAUSSIAN 98 program[44] using the 6-311G** basis set at the B3LYP and MP2 levels of theory. Geometry optimization of all configurations were performed without constraints. The SCI-PCM (Self-Consistent Reaction Field/Self-Consistent Isodensity Polarized Continuum Model)[45] method was used to consider the solvent effect; the dielectric constant of ε=8.93 was applied.

Hyperconjugation was studied using the NBO option included in the Gaussian 98 package with B3LYP/6-311G* wave functions and B3LYP/6-311G* optimized molecular structures and following a protocol reported previously.[7–9]

Chemical shift calculations were performed using the GIAO approach. The values of the coupling constants were calculated with the Amsterdam Density Functional (ADF)[53] program. The VWN+BLYP (Vosko–Wilk–Nusiar+Becke–Lee–Yang–Parr) generalized gradient approximation (GGA) was used to determine the unperturbed molecular orbitals. All calculations were performed using a core double zeta, valence triple zeta, and double polarized basis (TZ2P) implemented in the ADF program. The spin–spin coupling constants were calculated using Fermi-contact interactions including the spin-dipolar (FC–SD), the paramagnetic spin-orbit (PSO), and the diamagnetic spin-orbit (DSO) contributions.

The quantum chemical calculation was processed on SGI Octane (R 12000) computers and a Linux cluster computer at Potsdam University.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.06.094.

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