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Polar substituent effect of the ester group on conformational equilibria of *O*-mono-substituted cyclohexanes—the para-substituent effect in cyclohexyl benzoates

Erich Kleinpeter *, Ute Bölke, Andrea Frank

Chemisches Institut, Universität Potsdam, Karl-Liebknecht-Straße 24-25, 14476 Potsdam (Golm), Germany

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ABSTRACT

Together with the nonsubstituted reference compound, *para*-methoxy- and *para*-nitro cyclohexyl benzoates have been synthesized and their conformational equilibria studied by low temperature NMR spectroscopy and theoretical DFT calculations. The free energy differences ΔG° between *axial* and *equatorial* conformers were examined with respect to polar substituent influences on the conformational equilibrium of *O*-mono-substituted cyclohexane.

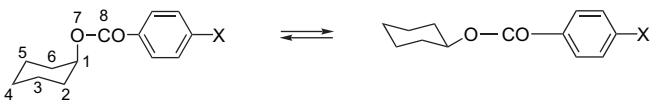
1. Introduction

The *equatorial* conformer in the conformational equilibria of *O*-mono-substituted cyclohexanes is preferred[1–8] by ΔG°=0.3 to 1.5 kcal mol^{-1}, but the *axial O*-substituents are almost unstrained (survey of X-ray structures)[9] and destabilizing *1,3-diaxial interactions* could not be identified in detailed theoretical studies.[4–8,10a] Thus, steric destabilization (so called *A*-values)[1] of the *axial* conformer in *O*-mono-substituted cyclohexanes, as the only source for the free energy differences between *axial* and *equatorial* conformers, can no longer be maintained. As the alternative mechanism, the increasing volume of an alkoxy substituent in **1** (*OR*=*OMe*, *OEt*, *Oi*-Pr, *Ot*-Bu) prove to destabilize the *axial* conformers due to steric hindrance within the –C^{2}(H$_2$)–C^{1}H(OAlkyl)–C^{6}(H$_2$)– segment.[8]

In opposite, the ester substituents in **2** (*OCOR*=*OCOMe*, *OCOEt*, *OCOi*-Pr, *OCOt*-Bu, $OCOCF_3$, $OCOCH_2Cl$, $OCOCHCl_2$, $OCOCCl_3$, $OCOCH_2Br$, $OCOCHBr_2$, $OCOCBr_3$) stabilize the corresponding *axial* conformers with increasing volume;[4–7] the reason for this substituent effect in the esters is not yet clear. It is the main objective of this paper to investigate if there is a polar component along with the steric stabilization of the *axial* conformers of the esters **2** with increasing volume.

2. Results and discussion

In order to study the polar substituent effect of ester substituents *OCOR* at cyclohexane on the conformational equilibrium under identical steric conditions, *para*-methoxy, *para*-nitro-, and the unsubstituted cyclohexyl benzoates **3a–c** (cf. Scheme 1) were synthesized, the conformational equilibria frozen at low temperature, and both the equilibrium constants *K* and the free energy differences ΔG° between the two conformers determined. The amounts of the *axial* conformer fall in the range of 18.2–19.3%. The



axial conformer equatorial conformer

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

3a (X = OMe), **3b** (X = H), **3c** (X = NO_2)

Scheme 1.

* Corresponding author. Tel.: +49 331 977 5210; fax: +49 331 977 5064.
E-mail address: kp@chem.uni-potsdam.de (E. Kleinpeter).

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Table 1
Axial/*equatorial* conformational equilibria ($K = [eq]/[ax]$) and free energy differences ($-\Delta G^\circ = RT\ln K$) for the cyclohexyl benzoates **3**

Compound	K[a]	$-\Delta G^\circ$	Reference
3a	4.503	0.545±0.02	This work
3b	4.225	0.521±0.01	This work
		0.50 (180 K)[b]	10
		0.49 (182 K)[c]	11
3c	4.181	0.518±0.01	This work

[a] At 183 K in CD_2Cl_2.
[b] Solvent $CFCl_3$.
[c] Solvent $CFCl_3/CDCl_3$.

results are given in Table 1. The unsubstituted cyclohexyl benzoate **3b** was synthesized and studied already previously;[10b–13] the best ΔG° values are included into Table 1. Differences in ΔG° are only minor, however, in order to measure the small differences in the series **3a–c**, the low temperature study of **3b** was repeated applying identical spectrometer and sample conditions (calibration, solvent, concentration, signal intensities of H-1 examined).

The *equatorial* preference (*A*-value)[1] of the benzoyloxy group in **3b** and in the analogs **3a**,**c** is corroborated by our results, however, it is seen clearly that the participation of the *equatorial* conformer is reduced by the electron-withdrawing *p*-nitro group and increased by the electron-donating *p*-methoxy group. This result is consistent with the data of other cylohexanol dervatives;[1,2] the authors noted a lower *A*-value for more polar substituents at oxygen but suggested that increased electron-withdrawal reduces the effective size of the oxygen lone pairs, and hence the 1,3-diaxial interactions as the key influence on *A*-values. As the alternative mechanism, hyperconjugation $\sigma_{C-H} \rightarrow \sigma^*_{C-OR}$ was discussed and proved to be the contributing electronic interaction[13] considering that *axial O*-substituents are almost unstrained (survey of X-ray structures)[9] and that destabilizing *1,3-diaxial interactions* could not be identified.[4–8,10] In addition, the existence of hyperconjugation already in cyclohexane was proved theoretically[14] and the *anomeric effect* in carbohydrates, which is dominated by hyperconjugation along the $n_O \rightarrow \sigma^*_{C-OR}$ interaction, proved to be a general physical-organic phenomenon and is not related only to *O*R substituents in 2-position of saturated six-membered heterocyclic ring systems.[4]

Additionally, the corresponding *axial* and *equatorial* conformers of the benzoates **3a–c** were theoretically calculated at the DFT B3LYP/6-311G(d) level of theory[15] applying the Gaussian 03 program package.[16] Preferred conformers were obtained as global minimum structures for the two conformations; the energetically next coming local minimum structures proved to be >3 kcal mol^{-1} less stable and, therefore, were not considered. The two preferred conformers of the *para*-methoxy benzoate **3a** are visualized in Figure 1.

Generally, the benzoate moieties *O*-C(O)–C_6H_5 and *O*-C(O)–C_6H_4–X(*p*) are planar in staggered positions at the cyclohexane skeleton [torsional angles H-1–C-1–O-7–C-8: **3a**: 34.6° (*ax*), 34.1° (*eq*); **3b**: 33.6° (*ax*), 30.7 (*eq*); **3c**: 34.4 (*ax*), 33.3 (*eq*)]. Changes in the geometry, when comparing **3a–c**, are only negligible as are the differences in energy between the corresponding *axial* and *equatorial* conformers. They prefer the *equatorial* conformer by ΔG°=0.7–0.8 kcal mol^{-1}, which is near to the experimentally obtained values (cf. Table 1), however, differences between **3a–c** are not realized.

Opposite to hyperconjugative stabilization energies E_{hyp}, which were calculated employing the NBO option included in the Gaussian 03 program package[16] at the same level of theory following a protocol reported previously.[5–8] The interactions between *all* filled NBO's and antibonding orbitals in **3a–c** were considered, summed up and are given in Table 2a. 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

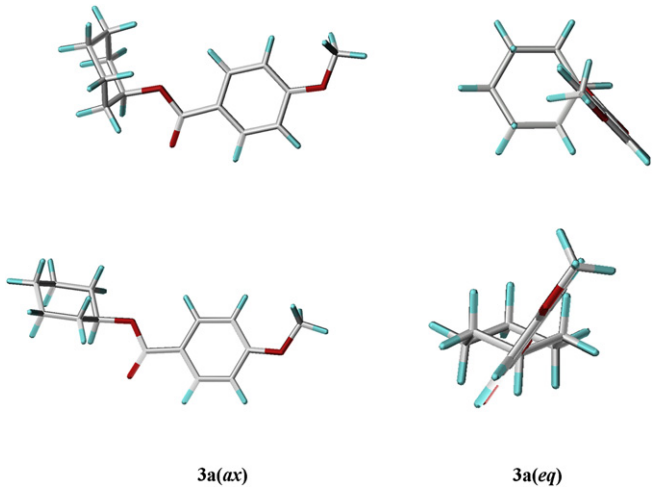
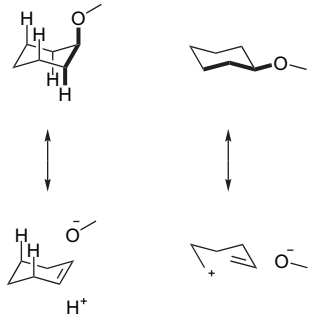


Figure 1. Preferred *axial* and *equatorial* conformers of *p*-methoxy-benzoate **3a**.

Table 2
Hyperconjugative stabilization energies E_{hyp} (kcal mol^{-1}) of the bonding/antibonding interactions (**a**) between *all* orbitals with both bonding and antibonding orbitals of the C_1–O bond and (**b**) 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* in **3a–c** (cf. Scheme 2)

(a)	**3a**(*ax*)	**3b**(*ax*)	**3c**(*ax*)
Acceptor	17.68	17.88	18.33
Donor	5.55	5.56	5.78
Donor-LP	66.26	67.16	68.86
Sum	89.49	90.60	92.97
	3a(*eq*)	**3b**(*eq*)	**3c**(*eq*)
Acceptor	15.06	15.22	15.54
Donor	6.15	6.21	6.32
Donor-LP	66.67	67.49	69.24
Sum	87.88	88.92	91.10
ΔE_{hyp}=(*ax*−*eq*)	*1.61*	*1.68*	*1.87*
(b)	**3a**(*ax*)	**3b**(*ax*)	**3c**(*ax*)
Acceptor	12.27	12.37	12.72
Donor	2.69	2.68	2.64
Donor-LP	10.58	10.26	9.91
Sum	25.54	25.31	25.27
	3a(*eq*)	**3b**(*eq*)	**3c**(*eq*)
Acceptor	9.70	9.77	10.00
Donor	3.40	3.40	3.34
Donor-LP	10.69	10.31	10.06
Sum	23.79	23.48	23.40
ΔE_{hyp}=(*ax*−*eq*)	*1.75*	*1.83*	*1.87*

$\sigma_{C2-C3} \rightarrow \sigma^*_{C1-O7}$ for the *equatorial* conformers are given; identical interactions are also active). Thus, only the interactions 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–



Scheme 2.

C-6 bonds for the substituent at C-1 were considered; the corresponding stabilization energies of the two conformers, and thus the results are given in Table 2b.

First and as expected, the stabilization via $\sigma_{C2-Hax} \rightarrow \sigma^*_{C1-O7}$ hyperconjugation for the *axial* conformers proves to be 1.68–1.87 kcal mol^{-1} stronger than $\sigma_{C2-C3} \rightarrow \sigma^*_{C1-O7}$ hyperconjugation in the corresponding *equatorial* conformers, and second, hereby the results of the low temperature NMR study (cf. Table 1) are confirmed. In the *p*-nitro benzoate **3c** with the *O*R substituent of strongest electron-withdrawing power, the hyperconjugative stabilization of the *axial* conformer proves to be strongest, in the *p*-methoxy benzoate **3a** (electron releasing substituent) this stabilization is lowest and **3a**, as the reference, occupies the middle position. This row of stabilization is obtained if *all* (cf. Table 2a) and if only the $\sigma_{C2-Hax} \rightarrow \sigma^*_{C1-O7}/\sigma_{C2-C3} \rightarrow \sigma^*_{C1-O7}$ hyperconjugation (cf. Table 2b) are considered; obviously, hyperconjugative stabilization of the *axial* conformers with respect to the *equatorial* analogs in **3a**–**c** increases with stronger electron-withdrawal of the *O*R substituents as suggested previously.[17]

3. Conclusions

To conclude, (i) the difference in $\sigma_{C2-Hax} \rightarrow \sigma^*_{C1-O7}/\sigma_{C2-C3} \rightarrow \sigma^*_{C1-O7}$ hyperconjugation obviously determines the differences in the conformational equilibria of the cyclohexyl benzoates **3a**–**c** as suggested previously for the corresponding phenoxycyclohexanes.[13] (ii) The electronic (polar) substituent effect of the ester group on the position of the conformational equilibria of *O*-monosubstituted cyclohexanes proves to be in agreement with the general model: the more polar substituent stabilizes increasingly the *axial* conformer with respect to its *equatorial* analogue. (iii) Returning to the starting point of this study, the polar substituent effect, besides the volume of the ester substituents, which destabilizes progressively the *equatorial* conformer, fits in with the accepted models of stereochemical analysis. (iv) The source of the progressive steric destabilization of the *equatorial* conformer of *O*-mono-substituted cyclohexanes by the ester substituents **2** (*O*COR=*O*COMe, *O*COEt, *O*CO*i*-Pr, *O*CO*t*-Bu, *O*COCF$_3$, *O*COCH$_2$Cl, *O*COCHCl$_2$, *O*COCCl$_3$, *O*COCH$_2$Br, *O*COCHBr$_2$, *O*COCBr$_3$)[4–7] is not yet clear and will be the topic of further related studies.

4. Experimental section

4.1. Syntheses

The cyclohexyl benzoates **3a**–**c** have been synthesized from molar quantities of cyclohexanol and the corresponding benzoic acids (*p*)X-C$_6$H$_4$–COOH (R=OMe, H, NO$_2$) by removing the water continuously from the reaction mixture by means of azeotropic distillation with toluene or chloroform, dependent on the boiling points of the esters. The reaction products were extracted with dichloromethane, the organic phase neutralized with NHCO$_3$, dried, and the solvent redistilled. Yellow oily liquids were obtained, which were cleaned by column chromatography [Kieselgel 60, solvent: *n*-hexane/ethyl acetate (3:1)] and characterized by NMR spectroscopy and HRMS.

*4.1.1. p-Methoxy-cyclohexyl benzoate (**3a**)*

Yellow oil; yield 73%; HRMS [M+H]$^+$: C$_{14}$H$_{19}$O$_3$ (235.1326, calcd 235.1334); ^{1}H NMR (δ/ppm, CDCl$_3$): 1.396 (m, 1H, H-4*ax*), 1.452 (m, 2H, H-3*ax*), 1.560 (m, 1H, H-4*eq*), 1.601 (m, 2H, H-2*ax*), 1.773 (m, 2H, H-3*eq*), 1.927 (m, 2H, H-2*eq*), 3.854 (s, 3H, OCH$_3$), 4.997 (quintet, 1H, H-1), 6.911 (dt, 2H, *m*-H), 8.002 (dd, 2H, *o*-H); ^{13}C NMR (δ/ppm, CDCl$_3$): 167.1 (C-7), 164.55 (*p*-C), 132.9 (*m*-C), 124.9 (*i*-C), 114.8 (*o*-C), 74.0 (C-1), 56.75 (OMe), 33.1 (C-2), 27.0 (C-4), 26.6 (C-3).

*4.1.2. Cyclohexyl benzoate (**3b**)*

Yellow oil; yield 58%; HRMS [M+H]$^+$: C$_{13}$H$_{17}$O$_2$ (205.1232, calcd 205.1229); ^{1}H NMR (δ/ppm, CDCl$_3$): 1.32 (m, 1H, H-4*ax*), 1.40 (m, 2H, H-3*ax*), 1.55 (m, 1H, H-4*eq*), 1.59 (m, 2H, H-2*ax*), 1.77 (m, 2H, H-3*eq*), 1.93 (m, 2H, H-2*eq*), 5.034 (quintet, 1H, H-1), 7.425 (dt, 2H, *m*-H), 7.52 (t, 1H, *p*-H), 8.045 (dd, 2H, *o*-H); ^{13}C NMR (δ/ppm, CDCl$_3$): 166.95 (C-7), 133.6 (*p*-C), 132.4 (*i*-C), 130.5 (*o*-C), 129.2 (*m*-C), 74.0 (C-1), 32.6 (C-2), 32.4 (C-3), 26.5 (C-4).

*4.1.3. p-Nitro-cyclohexyl benzoate (**3c**)*

Yellow oil; yield 60%; HRMS [M+H]$^+$: C$_{13}$H$_{18}$NO$_2$ (220.1347, calcd 220.1338); ^{1}H NMR (δ/ppm, CDCl$_3$): 1.34 (m, 1H, H-4), 1.41 (m, 2H, H-3*ax*), 1.53 (m, 1H, H-4*eq*), 1.60 (m, 2H, H-2*ax*), 1.74 (m, 2H, H-3*eq*), 1.95 (m, 2H, H-2*eq*), 5.07 (quintet, 1H, H-1), 8.21 (dt, 2H, *m*-H), 8.285 (dd, 2H, *m*,*p*-H); ^{13}C NMR (δ/ppm, CDCl$_3$): 169.25 (C-7), 155.7 (*p*-C), 141.8 (*o*-C), 128.7 (*i*-C), 101.9 (*m*-C), 79.6 (C-1), 36.7 (C-4), 30.8 (C-2), 29.45 (C-3).

4.2. NMR measurements

For the determination of the equilibrium constants *K* (cf. Scheme 1), the ^{1}H and the ^{13}C NMR spectra of esters studied were recorded in CD$_2$Cl$_2$ at low temperature; two sets of signals according to the *axial*/*equatorial* conformers were obtained and the set of the cyclohexane carbon atoms usually at higher field assigned to **3a**–**c**(*ax*) (due to the more crowded character).[18] With respect to the equilibrium constants *K* of the conformational equilibria, the ^{1}H NMR spectra were examined and the well separated H-1 signals in the two conformers carefully integrated. The quotients [*eq*]/[*ax*]=*K* at 183 K were measured and the free energy differences of the two conformers ($-\Delta G^\circ = RT\ln K$) were calculated.

In Table 3, both the ^{1}H and the ^{13}C chemical shifts of the conformers **3a**–**c**(*ax*/*eq*) at 183 K are given.

4.3. Theoretical calculations

The ab-initio MO calculations were all done with the Gaussian 03 program package at the DFT B3LYP/6-311G(d) level of theory.[15] Due to internal rotation about C(1)–O(7) and O(7)–C(8) bonds [the C(8)–C(10) bond was not adequately considered] the studied cyclohexane derivatives can generate stable conformers of different energy; finally, only two conformers were found to be significant for the *equatorial* and the *axial* conformations, respectively. The two conformers occupy *staggered* conformations having one oxygen lone

Table 3
^{1}H (a) and ^{13}C chemical shifts (b) of benzoates **3** at 183 K

Compound	**3a**		**3b**		**3c**	
	ax	*eq*	*ax*	*eq*	*ax*	*eq*
(a) ^{1}H-chemical shifts						
H-1	4.485	5.22	4.89	5.26	4.93	5.32
H-2/H-6	1.72	2.045	1.735	2.06	1.72	2.10
H-3/H-5	1.395	1.93	1.41	1.945	1.43	1.85
H-4	1.16	1.555	1.16	1.57	1.20	1.66
o-H	8.04		8.11		8.36	
m-H	6.97		7.505		8.265	
p-H	3.87[a]		7.63		—	
(b) ^{13}C-chemical shifts						
C-1	69.4	73.0	69.8	73.4	71.6	74.5
C-2/C-6	29.2	31.4	29.2	31.3	29.05	31.2
C-3/C-5	20.3	24.2	20.3	24.0	20.25	23.9
C4	25.05	24.6	25.0	24.55	24.9	24.4
C-8	164.9		165.1		163.45	
i-C	122.1		131.0		135.4	
o-C	112.8		128.7		130.05	
m-C	130.75		127.9		123.05	
p-C	162.2 (55.2)[a]		132.45		149.2	

[a] OMe proton and carbon atom.

pair oriented toward the cyclohexane ring (cf. Fig. 1); the ester group proved to be in both cases in *Z* configuration. In both the *axial* and the *equatorial* conformations, a second conformer was identified as local minimum, but being more than 3 kcal mol^{-1} higher in energy and does not contribute significantly to the population of both forms.

The electron populations of atoms and lone pairs in the cyclohexane conformers **3a–c**(*ax*/*eq*) were obtained from the natural bond population analysis (NBO)[19] and refer to the B3LYP/6-311G(d) molecular geometries.

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