Accepted Manuscript

Synthesis and NMR spectroscopic conformational analysis of benzoic acid esters of mono- and 1,4-dihydroxycyclohexane, 4-hydroxycyclohexanone and the -ene analogue – The more polar the molecule the more stable the *axial* conformer

Erich Kleinpeter, Peter Werner, Torsten Linker

PII: S0040-4020(17)30401-5

DOI: 10.1016/j.tet.2017.04.029

Reference: TET 28630

To appear in: *Tetrahedron*

Received Date: 22 February 2017

Accepted Date: 12 April 2017

Please cite this article as: Kleinpeter E, Werner P, Linker T, Synthesis and NMR spectroscopic conformational analysis of benzoic acid esters of mono- and 1,4-dihydroxycyclohexane, 4-hydroxycyclohexanone and the -ene analogue – The more polar the molecule the more stable the *axial* conformer, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.04.029.

Synthesis and NMR spectroscopic conformational analysis of benzoic acid esters of mono- and 1,4-dihydroxycyclohexane, 4-hydroxycyclohexanone and the -ene analogue − the more polar the molecule the more stable the *axial conformer*

Erich Kleinpeter,* Peter Werner, Torsten Linker

Universität Potsdam, Institut für Chemie, Karl-Liebknecht-Str. 24-25, D-14476 Potsdam (Golm), Germany

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

A B S T R A C T

para-Substituted benzoic acid esters of cyclohexanol, 1,4-dihydroxycyclohexane, 4-hydroxy cyclohexanone and of the corresponding *exo*-methylene derivative were synthesized and the conformational equilibria of the cyclohexane skeleton studied by low temperature ^{1}H and ^{13}C NMR spectroscopy. The geometry optimized structures of the *axial/equatorial chair* conformers were computed at the DFT level of theory. Only one preferred conformation of the ester group was obtained for both the *axial* and the *equatorial* conformer, respectively. The content of the *axial* conformer increases with growing polarity of the 6-membered ring moiety; hereby, in addition, the effect of sp^2 hybridization/polarity of C(4)=O/C(4)=CH_2 on the present conformational equilibria is critically evaluated. Another dynamic process could be studied, for the first time in this kind of compounds.

Keywords: Conformational analysis; A-Values of COOAr on cyclohexane; Benzoic acid esters; Dynamic NMR; DFT calculations.

1. Introduction

Previously, the ester analogues (CR_3−CO−) of cyclohexanol, 1,4-dihydroxycyclohexane and 4-hydroxycyclohexanone [CR_3 = Me, Et, *i*-Pr, *t*-Bu, CH_2F, $CH_nCl(Br)_{n-1}$] have been synthesized and the conformational equilibria of the cyclohexane moiety determined by low temperature NMR spectroscopy.[1-3] The *axial/equatorial* position of the substituent −C(O)OCR_3 on the cyclohexyl moiety proved to be an interplay of *hyperconjugation* and *steric bulk* of the substituent.[1-3] In addition, the *polarity* of the cyclohexyl rest could be identified as another influence on present conformational equilibria which stabilizes the *axial* conformation of the CR_3 substituent by a certain amount.[3,4]

The corresponding substituted benzoic acid esters of cyclohexanol, 1,4-dihydroxycyclohexane and 4-hydroxycyclohexanone, respectively, have not been synthesized yet and studied adequately with respect to the conformational equilibria. In addition to the former studies,[1-5] the effect of substituents at the aromatic moiety can be investigated with regard to their effect on the conformation of the cyclohexane ring. First studies on the influence of *p*-substitution were relevant and the interplay of these electronic substituent effects with the polarity influence of the cyclohexyl rest could further clear up the topic. In addition, the aromatic substituent on cyclohexane could increase the coalescence temperature of the six-membered ring interconversion of the 4-hydroxycyclohexanone esters by transition state stabilization;[6] these compounds have barriers to six-membered ring interconversion of only 5 to 6 kcal/mol and cannot be readily studied by low temperature dynamic NMR spectroscopy.[3]

2. Results

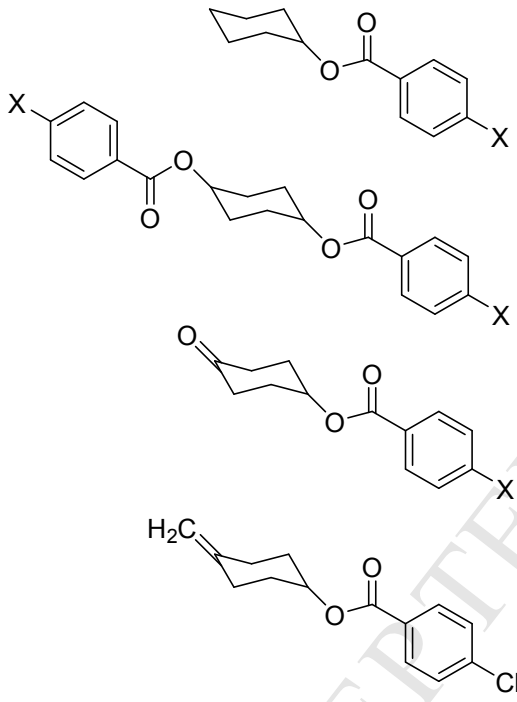
2.1 Syntheses

The cyclohexyl esters **1-7** and the diesters **8-9** (*cf.* Scheme 1) could be conventionally synthesized from cyclohexanol and 1,4-dihydroxycyclohexane, respectively, and the corresponding benzoic acid chlorides; all mono-esters **1-7** and the di-esters **8-9** were purified by column chromatography and could be isolated as analytically pure crystals (*cf.* Scheme 1). Di-esters **10-14** could not be isolated in analytically pure form.

The cyclohexanone esters **15-17** were synthesized from 1,4-dihydroxycyclohexane in high yield in two steps: Selective oxidation of one hydroxy group by Jones reagent afforded 4-hydroxycyclohexanone in 75 % yield.[7] This intermediate and the final esters **15-17** are quite

labile; thus, esterification with the various benzoic acid chlorides required mild conditions. After 4 hours reaction time in dichloromethane/pyridine at 45° C the crude mixtures were washed, the solvent removed and purified by column chromatography; three esters **15-17** could be isolated as analytically pure crystals in good yields (*cf.* **Scheme 1**). Cyclohexanone esters **18-21** could not be isolated in analytically pure form.

The synthesis of the *exo*-methylene ester **22** was accomplished by Wittig reaction[8] of the cyclohexanone ester **17** in 92% yield. Isolation of the analytically pure product on neutral aluminum oxide was important (*cf. Experimental section*), due to the instability of the alkene and possible binding to silica gel.



X = Br(**1**), Me(**2**), Cl(**3**), I(**4**)
NMe_2(**5**), NO_2(**6**), OMe(**7**)

X = Me(**8**), Cl (**9**), NO_2(**10**), Br(**11**)
I(**12**), NMe_2(**13**), OMe(**14**)

X = NO_2(**15**), Me(**16**), Cl(**17**), I(**18**)
NMe_2(**19**), Br(**20**), OMe(**21**)

22

Scheme 1. Compounds studied.

2.2 Theoretical calculations

The geometries of cyclohexyl mono- (**1−7**), di-esters (**8−14**), the cyclohexanone esters (**15–21**) and the corresponding *exo*-methylene analogue **22** were fully optimized using the *Gaussian09*[9] program employing ab initio calculations at the B3LYP/6-311G(d,p) level of theory.[10,11] The self-consisted reaction field (SCRF) method and the Integral Equation Formalism using Polarized Continuum Model (IEFPCM)[12] were used at the B3LYP/6-311G(d,p) level of theory to consider the solvent; chloroform was used in the calculations.

The chemical shifts were calculated using the gauge-including atomic orbital (GIAO) method;[12] at the B3LYP/6-311(d,p) level of theory,[13] by subtracting the shieldings of the protons and carbon atoms from tetramethylsilane (TMS) used as a reference and calculated at the same level of theory. The 3D structures were visualized using SYBYL7.3 molecular modelling software.[14]

In the molecules **1–7** internal rotation around the C(4)–O and C(=O)−CX_3 bonds (*cf.* **Scheme 1**) can generate stable conformations of different energy. A number of minima were located on the energy hypersurface and only two conformations each were found to be significant for describing the *equatorial* and the *axial* conformers, those labelled *syn* and *anti* in **Fig. 1**. The *anti* conformer proved to be more stable than the *syn* analogue by *ca.* 10 kcal/mol. The same is true for the di-esters **8−14**, the cyclohexanone esters **15−21** and the *exo*-methylene analogue **22**. Thus, only the preponderant *anti* conformations of both the *equatorial* (**a**) and the *axial* conformers (**c**) of **1–22** were considered further.

As measure for the quality of the computed structures of **1−22**, the proton chemical shifts of the latter compounds (*cf.* Experimental section) have been correlated with the corresponding computed δ-values; the regression coefficient of 0.99 proves an excellent correlation and hereby completely reliable structures to be discussed with respect to conformational items.

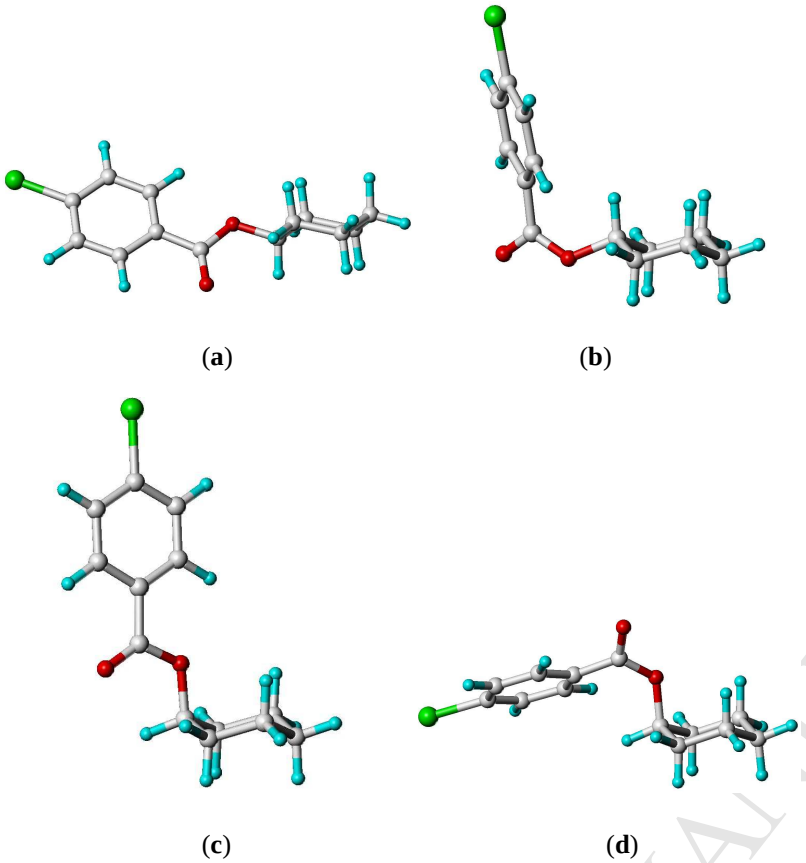


Figure 1. Preferred conformations *syn/anti* concerning C(4)–O and O–C(=O)CX_3 bonds of the *equatorial* (**a**,**b**) and *axial* (**c**,**d**) conformers of *p*-bromo-benzoic acid ester of cyclohexanol (**4**).

The relevant information concerning the conformational equilibria of **1**−**22** is the free energy difference between the corresponding *axial/equatorial* conformers (in case of **8**−**14** of the *axial,axial/equatorial,equatorial* conformers) in $CDCl_3$ as solvent; these values are collected in Table 1.

Table 1. Energy differences (kcal/mol) between *axial/equatorial* conformers of **1**−**7**, **15**−**21**, **22** and of the *axial,axial/equatorial,equatorial* conformers of **8**−**14** in $CDCl_3$ as solvent as computed at the DFT B3LYP/6−311G* level of theory.

mono-esters		di-esters		cyclohexanone esters		*exo*-methylene ester	
1	0.80	**8**	0.73	**15**	0.00	**22**	0.38
2	0.79	**9**	0.71	**16**	0.08		
3	0.78	**10**	0.74	**17**	0.03		
4	0.91	**11**	0.74	**18**	0.08		
5	0.79	**12**	1.02	**19**	0.09		
6	0.76	**13**	0.82	**20**	0.02		
7	0.83	**14**	0.78	**21**	0.02		

2.3 Dynamic NMR studies

To begin with mono- (**1**−**7**) and di-esters (**8**−**9**) the six-membered ring interconversion, which is fast at ambient temperature, could be readily frozen at lower temperatures; at 173 K the different signals of O-CH protons of the corresponding *axial/equatorial* conformers are completely resolved and sharp enough to be quantified. The two signals of *axial/equatorial* conformers could be differentiated by their signal widths due to the different size of $J_{ax,ax}$ (*ca.* 12 Hz) and $J_{eq,eq}$ and $J_{ax,eq}$ both *ca.* 3 Hz only; variable temperature spectra of O-CH protons for the mono-ester **3** and di-ester **9** are given in **Fig. 2** and **3**, respectively. In **Fig. 3** the corresponding ^{1}H NMR spectrum of the di-ester **9** at 173 K is remarkable. The readily assignable O-CH proton signals are clearly visible; because two isomers of the di-esters **8**−**9** are synthetically obtained, two sets of signals can be differentiated. The larger set (at 5.04 and 5.26 ppm) belongs to the *cis*-isomer − O-CH signals of the *axial* proton and the corresponding *equatorial* proton at the ratio of 1:1 − the smaller set (at 4.98 and 4.37 ppm, respectively) belongs to the *trans* isomer (with the **ax,ax** and **eq,eq** conformers in equilibrium). The ratio of the latter signals (as in case of the mono-esters) was measured and is the initial information, the equilibrium constant $-K$ = [**ax,ax**]/[**eq,eq**] for the calculation of present conformational equilibria ($-\Delta G° = RT \ln K$). The same procedure could be applied for the *exo*-methylene ester **22** but not for the cyclohexanone esters **15**−**17**.

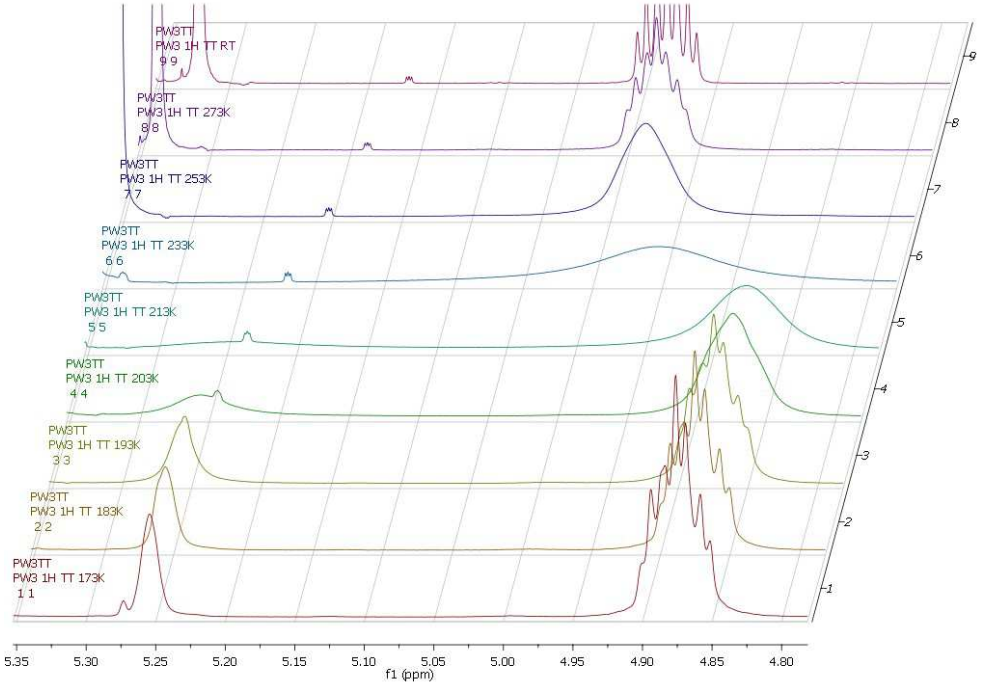


Figure 2. ^{1}H NMR Spectra of O-CH proton of the mono-ester **3** at various temperatures.

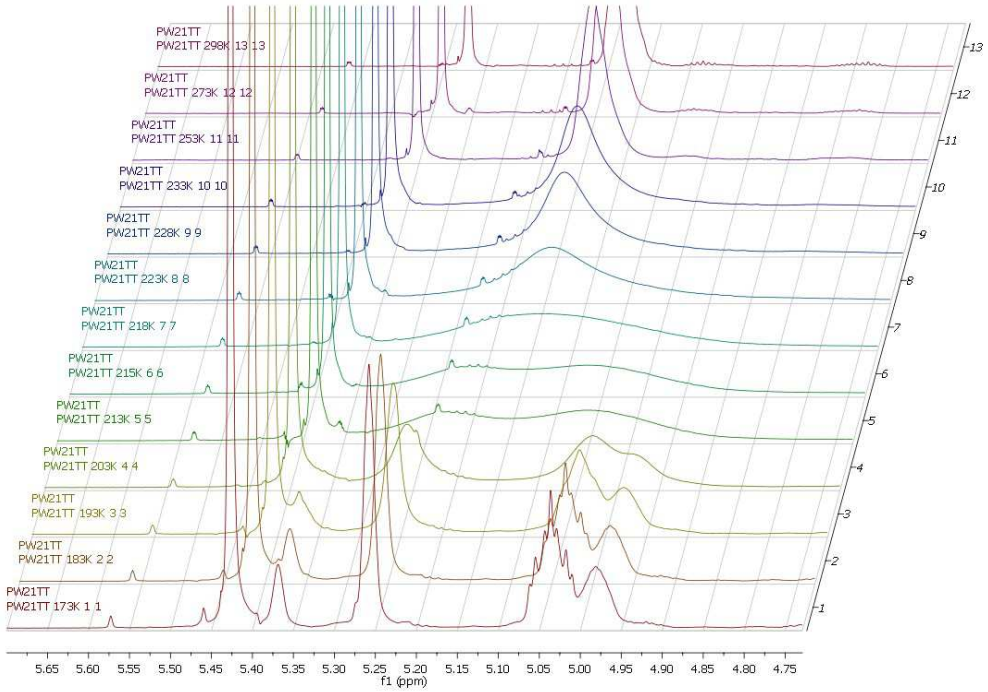


Figure 3. ^{1}H NMR Spectra of O-CH proton of the di-ester **9** at various temperatures.

In the latter case, the coalescence temperature of the six-membered ring interconversion T_c/K proves to be too low to be even studied with the local probe head, which is good enough down to 98 K,[3] even when studying the corresponding ^{13}C NMR spectra (in a freon mixture which is at 98 K still liquid for sufficient signal resolution).[3] In case of ^{13}C NMR spectra, due to the multiple elongation of the resonance range, sufficiently raised T_c/K values can be expected[6] (*cf.* Fig. 4), however, not high enough to be studied with the local dynamic NMR equipment.[3]

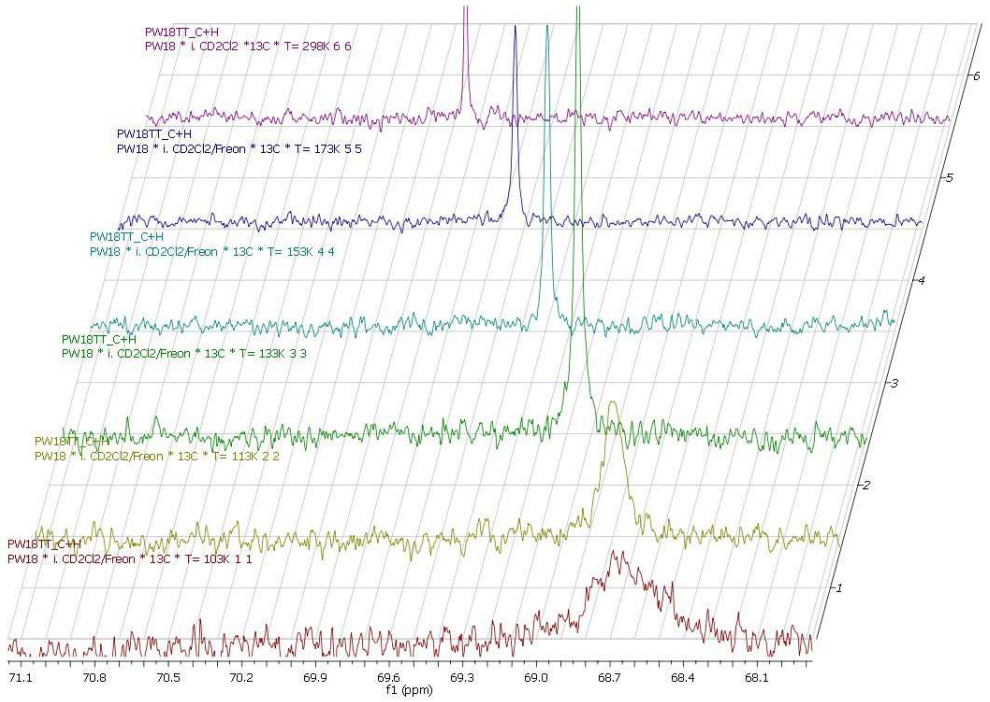


Figure 4. ^{13}C NMR Spectra of the O-CH carbon (at 68.6 ppm) of the cyclohexanone ester **17** at various temperatures.

Thus, direct information about the conformational equilibria of **15−17** is not available by dynamic NMR spectroscopy, at least with the present equipment. The ^{13}C signal of C(4)H proves to be very near to T_c/K (*cf.* **Fig. 4**), but not yet decoalesced to extract quantitatively the conformational equilibrium. However, indirect conformational information is accessible from the width of the O-CH proton signal at 1/12 signal height Δν(1/12)/Hz; in this position the remarkably different and discriminating vicinal H,H coupling constant are adequately respected and the data thus obtained sufficiently visualize the position of present conformational equilibria.[6] As references the values of the mono-ester **3** at 173 K were employed [Δν(1/12-*axial*) = 16 Hz and Δν(1/12-*equatorial*) = 30 Hz]; with the experimental value for cyclohexanone ester **17** at 273 K [Δ*ν*(1/12 = 19 Hz), *K* = 3.7 and −ΔG° = −0.71 kcal/mol] with heavy preference of the *axial* conformer and this in opposite to mono- and di-esters.

Finally, the ^{1}H NMR spectrum of the *exo*-methylene analogue **22** could be analyzed at 103 K: the equilibrium constant *K* = 2.17 from [0.647]/[0.297] and −ΔG° = 0.17 kcal/mol at 103 K, still preferring the *equatorial* conformer (*cf.* **Fig. 5**). The dynamic NMR results have been collected in Table 1.

Table 2. Conformational equilibria (−ΔG°/kcal/mol) of mono-esters (**1−7**), di-esters (**8, 9**) cyclohexanone ester **17** and the *exo*-methylene analogue **22**.

mono-esters		di-esters		cyclohexanone ester		*exo*-methylene ester	
1	0.58	**8**	0.23	**17**	−0.71	**22**	0.17
2	0.53	**9**	0.23				
3	0.53						
4	0.57						
5	0.58						
6	0.57						
7	0.47						

When carefully studying the dynamic ^{13}C NMR spectra of the cyclohexanone ester **17**, another dynamic process could observed unexpectedly (*cf.* **Fig. 6**). At 123 K the signals of the two *ortho/meta* CH carbon atoms of the aromatic moiety start to get broadened and are completely decoalesced at 103 K, the lowest temperature obtained. The basic dynamic process can be analyzed:

	T_c/K	$\Delta\nu$/Hz	k_c	$\Delta G_c^{\#}$/kcal/mol at T_c
(*ortho*) =CH−	118	90	200	5.4
(*meta*) =CH−	113	67.5	150	5.3

The ratio of the decoalesced signal is 1:1 in both cases and the free energy of activation was calculated to be 5.35 kcal/mol and can be only the restricted rotation about the OCO−C_{ipso} bond of the aromatic moiety. This kind of dynamic process was not observed yet and, obviously, proved to be a combined electronic/steric effect of the 4-aromatic moiety on cyclohexanone skeleton.

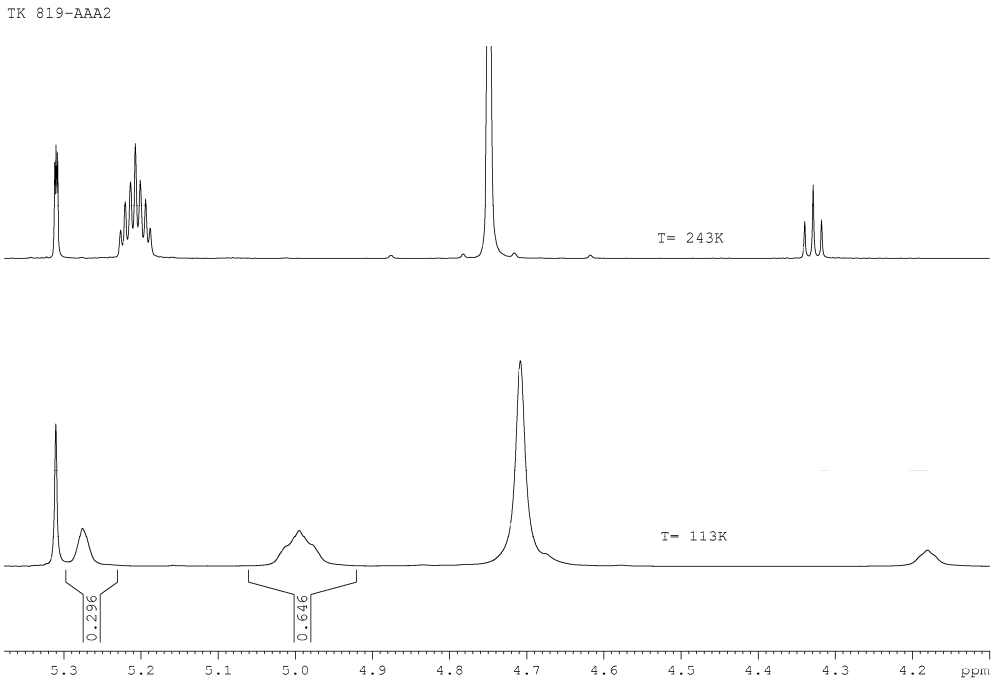


Figure 5. ^{1}H NMR Spectra of the O-CH proton of the *exo*-methylene analogue **22** of cyclohexanone ester **20** at 243 K (above) and at low temperature (112 K), respectively.

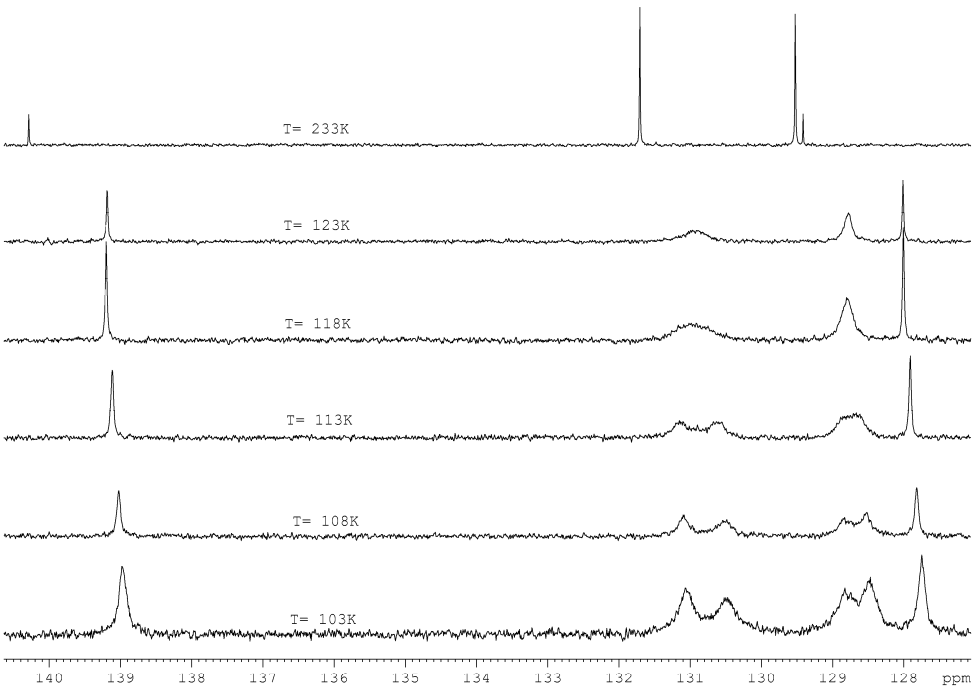


Figure 6. ^{13}C NMR Spectra of the O-CH carbon of the cyclohexanone ester **17** at various temperatures.

3. Discussion

The *axial* conformer in the mono-esters (and the *axial/axial* conformer in the di-esters) remarkably contributed to the conformational equilibrium but the *equatorial* (and *equatorial/equatorial* conformers in **8−14**) are preferred. There is no clear trend in the dependence of the position of the conformational equilibria (−ΔG°) on the substituent at the aromatic moiety, and this in both the experimental and the computed values, respectively (*cf.* **Tables 1** and **2**). The portion of the *axial* (*axial/axial*) conformers prove to be less in the mono-esters (−ΔG° *ca.* 0.5 to 0.6 kcal/mol) than in the di-esters (−ΔG° = 0.23 kcal/mol); this is experimentally observed but not confirmed by the computational results. The reason therefore is the second ester group in the di-ester molecules which increases the polarity of the cyclohexane moiety and hereby the content of the *axial* conformer.[3]

The preference of the *equatorial* conformer in **1−7** is impressively confirmed by the results of the X-ray analysis: from **1**, **6** and **7** crystals could be obtained which appear in *equatorial* conformation (*cf.* **Fig. 7**). The same can be concluded for the di-esters, however, adequate crystals for **8−14** could not be obtained. Differently behave the cyclohexanone esters; from the *p*-chloro ester **17** crystals could be provided and the X-ray analysis confirmed the different preferred conformation, the *axial* conformer, for this group of compounds; the solid state structure of **17** is included into **Fig. 7** as well.

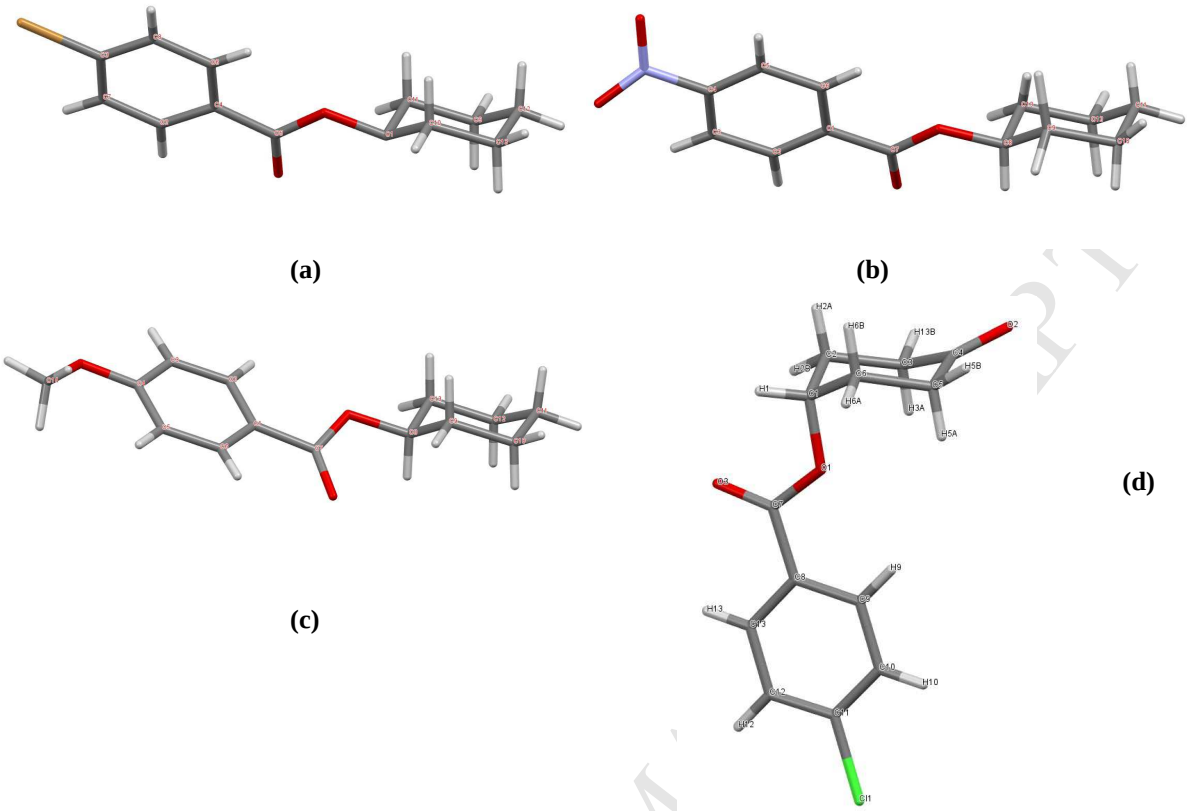


Figure 7. X-ray structures of the mono-ester **1**(a), **6**(b), **7**(c) and of the cyclohexanone ester **17** (d).

The immense increase of the *axial* conformer in the conformational equilibria of the cyclohexanone ester **15−21** (**17**: $-\Delta G° = -0.71$ kcal/mol; the computation results in about similar portions of *axial/equatoral* conformers at the conformational equilibrium) can have two reasons, (i) the increasing polarity of the cyclohexanone moiety due to the additional carbonyl group and (ii) the simultaneous sp^2 hybridization of C(4). The latter effect proves to be responsible for the flattening of the saturated six-membered ring chair conformation which is responsible for the ground state destabilization (with respect to the transition state) of the dynamic ring interconversion process lowering the coalescene temperature down to <100 K, the reason why this dynamic process could not be frozen in case of the studied cyclohexanone esters. The effect of the position on the corresponding conformational equilibria [heavily preferring the *axial* conformer (*vice infra*)], in similar compounds have been attributed to the polar influence of the cyclohexanone skeleton.[3] The same reason could be important for the position of the conformational equilibria of the present cyclohexanone esters **15−21**.

However, this effect on the position of the conformational equilibria of **15−21** can be understood as the combined influence of both sp^2 hybridization and the polarity of the

carbonyl group on the other hand. In order to separate the two effects, the *exo*-methylene analog **22** of the cyclohexanone ester **17** has been synthesized; X-ray compatible crystals could not be isolated but the liquid dynamic NMR study is really informative (*cf.* **Fig. 5** and **Table 2**): The portion of the *equatorial* conformer in **22** is lowered compared with the mono-esters, but far from that in the cyclohexanone esters. Thus, sp^2 hybridization of C(4) has some influence on the increase of the portion of the *axial* conformer: the corresponding effect proves to be ca. 0.3 to 0.4 kcal/mol but with the corresponding effect of the carbonyl group in **17** (> 1 kcal/mol) remains the (now cleanly separated) 0.6 to 0.7 kcal/mol impact which comes from the polarity influence of the carbonyl group.

The effect of sp^2 hybridization on the conformational equilibrium of the mono-esters is obviously of about the same size as the polarity effect of the second ester group in the corresponding di-esters (*cf.* **Table 2**).

4. Conclusions

The conformational equilibria of a collection of *para*-substituted benzoic acid esters of cyclohexanol, 1,4-dihydroxycyclohexane, 4-hydroxycyclohexanone **1**−**21** and of the *exo*-methylene analog **22** of the *para*-chloro ester of cyclohexanone **17** have been studied by quantum chemistry and characteristic examples of all four groups of compounds also experimentally by low temperature dynamic NMR spectroscopy. Free energy differences between *axial* and *equatorial* conformers [K = [**eq**]/[**ax**]; $-\Delta G° = RT \ln K$] have been determined: the *equatorial* conformer proved to be the preferred one in mono-esters (**1**−**7**) > di-esters (**8**−**14**) > *exo*-methylene ester (**22**), only in the cyclohexanone ester **15**−**21** the portion of the *axial* conformer increases to be the strongly preferred conformer:

(i) Substitution on the *para*-position of the aromatic moiety is without influence on the position of the conformational equilibrium.

(ii) The *axial,axial* conformer in the di-esters is 0.3 to 0.4 kcal/mol more stable than the *axial* conformer in the conformational equilibria of the mono-esters due to the increased polarity of the cyclohexyl moiety.

(iii) Similarly, the *axial* conformer in the *exo*-methylene ester is of about the same larger stability than the *axial,axial* conformer in the conformational equilibrium of the di-esters. Thus, the effect of C(4) sp^2 hybridization (mainly due to flattening of the cyclohexane skeleton) on the position of the conformational equilibrium of **22** agrees with the polarity effect of the ester-substituted cyclohexane skeleton in the diesters.

(iv) The reason for the high preference of the *axial* conformer in the cyclohexanone esters proves to be (in addition to C(4) sp^2 hybridization − *vide supra*) the polarity of the cyclohexanone moiety (*ca.* 0.9 kcal/mol).

(v) In addition to the elucidation of conformational properties of the present cyclohexane esters, in the cyclohexanone esters, the restricted rotation about the OCO−C_{ipso} bond of the aromatic moiety to be 5.35 kcal/mol (in **17**) could be identified. This usually free rotation gets restricted due to the combined electronic effect of the *para*-chloro substituent and the steric effect of the whole benzoic acid ester moiety.

5. Experimental section

5.1 General

All solvents and commercially available chemicals were used as purchased or were purified. The synthesis for the cyclohexanone esters were performed under argon atmosphere with the use of standard Schlenk techniques. For the column chromatography silica gel (Kieselgel 60) or neutral aluminum oxide was used. TLC was performed on silica gel sheets (F 254). The NMR spectra were recorded with a Bruker spectrometer AVANCE 300. CD_2Cl_2 (≥ 99.5 %, ARMAR GmbH, Leipzig, Germany) and $CDCl_3$ (≥ 99.5 %, ARMAR GmbH, Leipzig, Germany) were used as solvent and TMS as internal standard, the chemical shifts, related to CH_2Cl_2 [δ (^{1}H) 5.31 ppm, δ (^{13}C) 53.7 ppm] and $CHCl_3$ [δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.0 ppm] are given in parts per million downfield to TMS. Low temperature ^{1}H and ^{13}C NMR spectra were performed on the Bruker AVANCE III 600 spectrometer in the solvent mixture of CD_2Cl_2 (≥ 99.5 %, ARMAR GmbH, Leipzig, Germany) : $CHFCl_2$: $CHCl_2F$ = 1 : 1 : 3 (the latter two from abcr GmbH, Karlsruhe, Germany). IR spectra were performed on a Perkin-Elmer 1600 FT-IR spectrometer (PerkinElmer LAS GmbH, Rodgau, Germany). For the elementary analysis an ELEMENTAR vario EL analysator (Elementar Analysensysteme GmbH, Langenselbold, Germany) was used. The X-ray analyses were performed on an Imaging Plate Diffraction System, IPDS-2 (Stoe & Cie GmbH, Darmstadt, Germany).

Ester	R	Yield (%)	
1	Br	67	mono-ester
2	CH_3	71	mono-ester
3	Cl	73	mono-ester
4	I	61	mono-ester
5	$N(CH_3)_2$	64	mono-ester
6	NO_2	83	mono-ester
7	OCH_3	71	mono-ester
8	CH_3	58	di-ester
9	Cl	61	di-ester
15	NO_2	70	cyclohexanone
16	CH_3	65	cyclohexanone
17	Cl	67	cyclohexanone
22	Cl	92	*exo*-methylene

5.2 Synthesis of mono-esters 1−7.

1.0 g of cyclohexanol (10 mmol) was dissolved in a mixture of 150 mL dried dichloromethane and 1.61 mL pyridine (20 mmol) at 25 °C in a 250 mL one-necked round-bottom flask, the corresponding acid chloride (1.1 equiv.) was added and the solution stirred and heated up to 45 °C. The reaction was performed under stirring and reflux for 4 hours at 45 °C. Subsequently, the reaction mixture was cooled down to room temperature and was extracted three times with a HCl/water solution (2.3 mL HCl (1 N), 100 mL deionized water). The organic phase was isolated, dried with sodium sulfate and filtered. The solvent was removed under vacuum and the esters purified by column chromatography (ethyl acetate/hexane 4:1); esters **1-3** and **5-7** were isolated as crystallized solids. Only ester **4** was isolated as a yellowish oil.

*5.2.1. Cyclohexyl-4-bromobenzoate (**1**)* R_f = 0.73 (hexane/ethyl acetate 10:1); ^{1}H NMR (300 MHz, CD_2Cl_2, ppm) δ = 7.90 (d, 2H, 11-H, 15-H), 7.56 (d, 2H, 12-H, 14-H), 5.01 (sept, 1H, 4-H), 1.89 (m, 2H, 3-H, 5-H), 1.74 (m, 2H, 3-H, 5-H), 1.59-1.29 (m, 6H, 1-H, 2-H, 6-H); ^{13}C-NMR (75 MHz, CD_2Cl_2, ppm) δ = 165.4 (C-8), 131.7 (C-12, C-14), 131.2 (C-11, C-15), 130.1 (C-10), 127.86 (C-13), 73.5 (C-4), 31.7 (C-3, C-5), 25.6 (C-1), 23.8 (C-2, C-6). MS (ESI): *m/z* calculated for $C_{13}H_{15}O_2Br$: $[M+H]^+$: 282.0255; found: 282.0245.

5.2.2. Cyclohexyl-4-methylbenzoate ***(2)*** $R_f = 0.71$ (hexane/ethyl acetate 10:1); ^{1}H-NMR (300 MHz, CD_2Cl_2, ppm) δ = 7.84 (d, 2H, 11-H, 15-H), 7.12 (d, 2H, 12-H, 14-H), 4.92 (sept, 1H, 4-H), 2.29 (s, 3H, 16-H), 1.82 (m, 2H, 3-H, 5-H), 1.65 (m, 2H, 3-H, 5-H), 1.51-1.21 (m, 6H, 1-H, 2-H, 6-H); ^{13}C-NMR (75 MHz, CD_2Cl_2, ppm) δ = 166.1 (C-8), 143.3 (C-12, C-14), 129.6 (C-11, C-15), 129.0 (C-10), 128.46 (C-13), 72.8 (C-4), 31.8 (C-3, C-5), 25.6 (C-3, C-5), 23.8 (C-1), 21.7 (C-16). MS (ESI): *m/z* calculated for $C_{14}H_{18}O_2$: $[M+H]^+$: 218.1307; found: 218.1309.

5.2.3. Cyclohexyl-4-chlorobenzoate ***(3)*** $R_f = 0.74$ (hexane/ethyl acetate 10:1);^{1}H-NMR (300 MHz, CD_2Cl_2, ppm) δ = 7.97 (d, 2H, 11-H, 15-H), 7.4 (d, 2H, 12-H, 14-H), 5.01 (sept, 1H, 4-H), 1.98 (m, 2H, 3-H, 5-H), 1.71 (m, 2H, 3-H, 5-H), 1.64-1.39 (m, 6H, 1-H, 2-H, 6-H); ^{13}C-NMR (75 MHz, CD_2Cl_2, ppm) δ = 165.3 (C-8), 139.24 (C-12, C-14), 131.1 (C-11, C-15), 129.7 (C-10), 128.75 (C-13), 73.57 (C-4), 31.7 (C-3, C-5), 25.6 (C-1), 23.82 (C-2, C-6). MS (ESI): *m/z* calculated for $C_{13}H_{15}O_2Cl$: $[M+H]^+$: 238.0761; found: 238.0765.

5.2.4. Cyclohexyl-4-iodobenzoate ***(4)*** $R_f = 0.65$ (hexane/ethyl acetate 10:1); ^{1}H-NMR (300 MHz, CD_2Cl_2, ppm) δ = 7.78 (d, 2H, 11-H, 15-H), 7.73 (d, 2H, 12-H, 14-H), 5.00 (sept, 1H, 4-H), 1.98 (m, 2H, 3-H, 5-H), 1.81 (m, 2H, 3-H, 5-H), 1.67-1.46 (m, 6H, 1-H, 2-H, 6-H); ^{13}C-NMR (75 MHz, CD_2Cl_2, ppm) δ = 165.5 (C-8), 137.72 (C-12, C-14), 131.1 (C-11, C-15), 130.6 (C-10), 100.43 (C-13), 73.5 (C-4), 31.7 (C-3, C-5), 25.6 (C-1), 23.7 (C-2, C-6). IR (film): ν = 2953, 2857, 1716, 1586, 1280, 1055, 753 cm^{-1}. elemental analysis calculated (%) for $C_{13}H_{15}O_2I$ (329.55): C 47.3, H 4.5; found: C 47.66, H 4.3. MS (ESI): *m/z* calculated for $C_{13}H_{15}O_2I$: $[M+H]^+$: 330.0117; found: 330.0110.

5.2.5. Cyclohexyl-4-(dimethylamino)benzoate ***(5)***; ^{1}H-NMR (300 MHz, CD_2Cl_2, ppm) δ = 7.85 (d, 2H, 11-H, 15-H), 6.57 (d, 2H, 12-H, 14-H), 4.90 (sept, 1H, 4-H), 2.96 (s, 6H, 16-H), 1.82 (m, 2H, 3-H, 5-H), 1.68 (m, 2H, 3-H, 5-H), 1.67-1.21 (m, 6H, 1-H, 2-H, 6-H); ^{13}C-NMR (75 MHz, CD_2Cl_2, ppm) δ = 166.6 (C-8), 153.4 (C-13), 131.35 (C-12, C-14), 118.1 (C-10), 110.9 (C-11, C-15), 128.75 (C-13), 72.1 (C-4), 40.2 (C-3, C-5), 31.9 (C-16), 25.8 (C-1), 23.9 (C-2, C-6). IR (solid): ν = 2932, 2855, 1688, 1601, 1314, 1179, 1037, 770 cm^{-1}. MS (ESI): *m/z* calculated for $C_{15}H_{21}O_2N$: $[M+H]^+$: 247.1572; found: 247.1562.

*5.2.6. Cyclohexyl-4-nitrobenzoate (**6**)* R_f = 0.69 (hexane/ethyl acetate 10:1); ^{1}H-NMR (300 MHz, CD_2Cl_2, ppm) δ = 8.28 (d, 2H, 11-H, 15-H), 8.20 (d, 2H, 12-H, 14-H), 5.06 (sept, 1H, 4-H), 2.02 (m, 2H, 3-H, 5-H), 1.87 (m, 2H, 3-H, 5-H), 1.67-1.47 (m, 6H, 1-H, 2-H, 6-H); ^{13}C-NMR (75 MHz, CD_2Cl_2, ppm) δ = 164.2 (C-8), 149.5 (C-10), 136.5 (C-12, C-14), 130.8 (C-13), 123.6 (C-11, C-15), 74.6 (C-4), 31.7 (C-3, C-5), 25.5 (C-1), 23.8 (C-2, C-6). MS (ESI): *m/z* calculated for $C_{13}H_{15}O_4N$: $[M+H]^+$: 249.1001; found: 249.1004.

*5.2.7. Cyclohexyl-4-methoxybenzoate (**7**)* R_f = 0.56 (hexane/ethyl acetate 10:1); ^{1}H-NMR (300 MHz, CD_2Cl_2, ppm) δ = 7.99 (d, 2H, 11-H, 15-H), 6.89 (d, 2H, 12-H, 14-H), 4.98 (sept, 1H, 4-H), 3.83 (s, 3H, 16-H), 1.91 (m, 2H, 3-H, 5-H), 1.83 (m, 2H, 3-H, 5-H), 1.65-1.39 (m, 6H, 1-H, 2-H, 6-H); ^{13}C-NMR (75 MHz, CD_2Cl_2, ppm) δ = 165.8 (C-8), 163.3 (C-10), 131.6 (C-12, C-14), 123.6 (C-13), 113.6 (C-11, C-15), 72.7 (C-4), 55.5 (C-16), 31.8 (C-3, C-5), 25.6 (C-1), 23.8 (C-2, C-6). MS (ESI): *m/z* calculated for $C_{14}H_{18}O_3$: $[M+H]^+$: 234.1256; found: 234.1248.

5.3. Synthesis of di-esters 8−15.

1.74 g of 1,4-cyclohexanediol (15 mmol) was dissolved in 100 mL of dried dichloromethane at room temperature in a 250 mL one-necked round-bottom flask. 4.8 mL pyridine (60 mmol) and the corresponding acid chloride (2.2 equiv) were added and dissolved. The reaction mixture was stirred and heated up to 45 °C. The reaction was performed under stirring and reflux for 4 hours at 45 °C. Afterwards, the solution was cooled down to room temperature and extracted three times with a HCl/water solution (2.3 mL HCl (1 N), 100 mL deionized water). The mixture was dried by adding sodium sulfate and filtering afterwards. The solvent was removed under vacuum and the esters purified by column chromatography (methyl-*tert*-butyl ether/hexane 2:5); both the cis- and the trans-diesters as mixtures were obtained (*cf.* Fig. 3). Only the esters **8-9** could be isolated as crystalline solids.

*5.3.1. Cyclohexane-1,4-diyl bis(4-methylbenzoate) (**8**)*; ^{1}H-NMR (300 MHz, CD_2Cl_2, ppm) δ = 7.98 (d, 4H, 11-H, 15-H, 21-H, 25-H), 7.26 (d, 4H, 12-H, 14-H, 22-H, 24-H), 5.11 (sept, 2H, 1-H, 4-H), 2.4 (s, 6H, 16-H, 26-H), 2.16-1.6 (m, 8H, 2-H, 3-H, 4-H, 6-H); ^{13}C-NMR (75 MHz, CD_2Cl_2, ppm) δ = 166.4 (C-8, C-18), 144.2 (C-13, C-23), 131.1 (C-10, C-20), 130.1 (C-11, C-15, C-21, C-25), 129.6 (C-12, C-14, C22, C-24), 71.6 (C-1, C-4), 28,3 (C-2,C-3, C-5, C-6), 21,9 (C-16, C-26). IR (solid): ν = 2954, 2926, 2855, 1719, 1360, 1270, 1102, 754 cm^{-1}. MS (ESI): *m/z* calculated for $C_{22}H_{24}O_4$: $[M+H]^+$: 352.1675; found: 352.1654.

*5.3.2. Cyclohexane-1,4-diyl bis(4-chlorobenzoate) (**9**)*; ^{1}H-NMR (300 MHz, CD_2Cl_2, ppm) δ = 7.93 (d, 4H, 11-H, 15-H, 21-H, 25-H), 7.35 (d, 4H, 12-H, 14-H, 22-H, 24-H), 5.07 (sept, 2H, 1-H, 4-H), 2.1-1.5 (m, 8H, 2-H, 3-H, 4-H, 6-H); ^{13}C-NMR (75 MHz, CD_2Cl_2, ppm) δ = 165.3 (C-8, C-18), 139.6 (C-13, C-23), 131.1 (C-11, C-15, C-21, C-25), 129.3 (C-10, C-20), 129.2 (C-12, C-14, C22, C-24), 71.8 (C-1, C-4), 28.0 (C-2,C-3, C-5, C-6). IR (solid): ν = 3056, 2945, 2869, 1704, 1612, 1273, 1034, 752 cm^{-1}. MS (ESI): *m/z* calculated for $C_{20}H_{18}O_4Cl_2$: $[M+H]^+$: 392.0582; found: 392.0561.

5.4. Synthesis of cyclohexanone esters 15−21.

In a precursor step, 1.5 mL of 4-hydroxylcyclohexanone (15 mmol) were synthesized[7] and dissolved directly under argon atmosphere in 150 mL dried dichloromethane in a 250 mL one-necked round-bottom flask**.** Afterwards, 2.4 mL of pyridine (30 mmol) and the corresponding acid chloride (1.1 equiv) were added. The reaction mixture was stirred and heated up to 45 °C. The esterification was performed under stirring for 4 hours at 45 °C. After cooling down to room temperature the solution was extracted three times with a HCl/water solution (2.3 mL HCl (1 N), 100 mL deionized water). The organic phase was dried over sodium sulfate and filtered. The solvent was removed under vacuum and the esters purified by column chromatography (methyl-*tert*-butyl ether/hexane 8:1). Only the cyclohexanone esters **15-17** could be isolated as crystalline solids.

*5.4.1. 4-Oxo-cyclohexyl 4-nitrobenzoate (**15**)* R_f = 0.77 (hexane/dichlormethane 1:4); ^{1}H-NMR (300 MHz, CD_2Cl_2, ppm) δ = 8.25 (d, 2H, 11-H, 15-H), 8.15 (d, 2H, 12-H, 14-H), 5.41 (sept, 1H, 4-H), 2.55 (m, 2H, 2-H, 6-H), 2.4 (m, 2H, 3-H, 5-H), 2.31-2.16 (m, 4H, 3-H, 5-H, 2-H, 6-H); ^{13}C-NMR (75 MHz, CD_2Cl_2, ppm) δ = 209.2 (C-1), 164.1 (C-8), 150.9 (C-13), 135.7 (C-10), 130.7 (C-11, C-15), 123.7 (C-12, C-14), 70.5 (C-4), 37.2 (C-2, C-6), 30.4 (C-3, C-5). IR (solid): ν = 3107, 2956, 1720, 1524, 1274, 1119, 874 cm^{-1}. elemental analysis calculated (%) for $C_{13}H_{13}O_5N$ (262.91): C 59.3, H 4.9, N 5.3; found: C 59.4, H 4.96, N 5.1. MS (ESI): *m/z* calculated for $C_{13}H_{13}O_5N$: $[M+H]^+$: 263.0794; found: 263.0780.

*5.4.2. 4-Oxo-cyclohexyl 4-methylbenzoate (**16**)* R_f = 0.61 (hexane/MTBE 2:5); ^{1}H-NMR (300 MHz, CD_2Cl_2, ppm) δ = 7.87 (d, 2H, 11-H, 15-H), 7.18 (d, 2H, 12-H, 14-H), 5.34 (sept, 1H, 4-H), 2.58 (m, 2H, 3-H, 5-H), 2.34 (m, 2H, 2-H, 6-H), 2.3-2.0 (m, 4H, 3-H, 5-H, 2-H, 6-H);

^{13}C-NMR (75 MHz, CD_2Cl_2, ppm) δ = 210.1 (C-1), 166.1 (C-8), 144.2 (C-13), 130.5 (C-12, C-14), 129.5 (C-11, C-15), 127.8 (C-10), 69.1 (C-4), 37.6 (C-2, C-6), 30.9 (C-3, C-5), 21.2 (C-16). IR (solid): ν = 2953, 2898, 1715, 1612, 1275, 1152, 754 cm^{-1}. MS (ESI): *m/z* calculated for $C_{14}H_{16}O_3$: $[M+H]^+$: 232.1099; found: 232.1103.

*5.4.3. 4-Oxo-cyclohexyl 4-chlorobenzoate (**17**)* R_f = 0.88 (hexane/MTBE 2:5); ^{1}H-NMR (300 MHz, CD_2Cl_2, ppm) δ = 7.92 (d, 2H, 11-H, 15-H), 7.37 (d, 2H, 12-H, 14-H), 5.31 (sept, 1H, 4-H), 2.49 (m, 2H, 3-H, 5-H), 2.31 (m, 2H, 2-H, 6-H), 2.2-2.0 (m, 4H, 3-H, 5-H, 2-H, 6-H); ^{13}C-NMR (75 MHz, CD_2Cl_2, ppm) δ = 208.9 (C-1) 164.8 (C-8), 139.3 (C-13), 130.9 (C-12, C-14), 129.3 (C-10), 128.95 (C-11, C-15), 69.6 (C-4), 37.2 (C-2, C-6), 30.4 (C-3, C-5). IR (solid): ν = 2953, 2853, 1716, 1592, 1268, 1118, 909 cm^{-1}. MS (ESI): *m/z* calculated for $C_{13}H_{13}O_3Cl$: $[M+H]^+$: 252.0553; found: 252.0557.

5.5. Synthesis of the *exo*-methylene analog 22.

In analogy to ethyl *exo*-methylene cyclohexane,[15] a 2M solution of butyl lithium in hexane (5 mL, 10.0 mmol) was mixed with 100 mL of anhydrous diethyl ether under nitrogen atmosphere at room temperature. Solid triphenylmethylphosphonium bromide (3.60 g, 10.0 mmol) was added in small portions within 30 min at this temperature and the mixture was stirred for 4 h. A solution of cyclohexanone ester **17** (2.52 g, 10.0 mmol) in 10 mL of anhydrous diethyl ether was added within 2 min and the mixture was stirred for additional 20 h. The mixture was poured onto 100 mL of water, extracted with pentane (3 x 100 mL), and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified on 50 g of neutral aluminum oxide to afford 2.90 (92%) of the *exo*-methylene analog **22** as a colorless liquid in analytically pure form.

*5.5.1. 4-Methylene-cyclohexyl 4-chlorobenzoate (**22**)* R_f = 0.17 on aluminum oxide (pentane); ^{1}H NMR (600 MHz, $CDCl_3$ ppm) δ = 7.96 (d, 2H, 11-H, 15-H), 7.38 (d, 2H, 12-H, 14-H), 5.17 (sept, 1H, 4-H), 4.70 (s, 2H, 9-H), 2.40 (m, 2H, 2-H, 6-H), 2.19 (m, 2H, 2-H, 6-H), 1.98 (m, 2H, 3-H, 5-H), 1.76 (m, 2H, 3-H, 5-H); ^{13}C NMR (150 MHz, $CDCl_3$, ppm) δ = 165.1 (C-8), 147.1 (C-1), 139.3 (C-13), 131.0 (C-11, C-15), 129.3 (C-10), 128.7 (C-12, C-14), 108.5 (C-9), 72.2 (C-4), 32.3 (C-2, C-6), 31.4 (C-3, C-5). IR (film): ν = 2979, 1714, 1594, 1269, 1086, 893 cm^{-1}. elemental analysis calculated (%) for $C_{14}H_{15}ClO_2$ (250.72): C 67.07, H 6.03; found: C 66.82, H 6.29.

Acknowledgements

We thank Tobias Krüger for the synthesis, Dr. Matthias Heydenreich und Angela Krtitschka for the NMR spectroscopic study, and Dr. Andreas Koch for the computation of the conformational equilibrium of the *exo*-methylene analog **22**.

References and notes

1. Kleinpeter, E.; Taddei, F.; Wacker, Ph. *Chem., A Eur. J.* **2003**, *9*, 1360.
2. Kleinpeter, E.; Rolla, N.; Koch, A.; Taddei, F. *J. Org. Chem.* **2006**, *71*, 4393.
3. Kleinpeter, E.; Heydenreich, M.; Koch, A.; Linker, T. *Tetrahedron* **2012**, *68*, 2363.
4. Kleinpeter, E.; Thielemann, J. *Tetrahedron* **2007**, *63*, 9071.
5. Kleinpeter, E.; Bölke, U.; Frank, A. *Tetrahedron* **2008**, *64*, 10014.
6. Kleinpeter, E. *Adv. Heterocycl. Chem.* **2004**, *86*, 41 − Conformational analysis of Saturated Heterocyclic Six-Membered Rings.
7. Seo, J. W.; Comninos, J. S.; Chi, D. Y.; Kim, D. W.; Carlson, K. E.; Katzenellenbogen, J. A. *J. Med. Chem.* **2006**, *49*, 2496; (b) *4-Hydroxycylo-hexanone* in *Org. Prep. Proced. Int.* **1969**, *1*, 127.
8. Wittig, G.; Schoell, U. *Organic Syntheses Coll, Vol. 5* **1973**, 751.
9. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, T. A.; Peralta, Jr. J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision A.02*, Gaussian, Inc., Wallingford CT, **2009**.
10 Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.
11. Hehre, J. W.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. Ab Initio Molecular Orbital Theory; Wiley & Sons: New York, NY, **1986**.
12. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
13. Becke, A. D.; Density-functional thermochemistry. III. The role of exact exchange, J. Chem. Phys. 1993, 98, 5648; Lee, C.; Yang, W.; Parr, R. G.; Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, *Phys. Rev. B* **1988**, *37*, 785.
14. SYBYL7.3, Tripos Inc., 1699 South Hanley Road, St. Louis, Missouri 63144, USA, 2007.
15. Roth, W. R.; Unger, C. *Liebigs Ann.* **1995**, 1361.

Graphical Abstract:

Synthesis and NMR spectroscopic conformational analysis of benzoic acid esters of mono- and 1,4-dihydroxycyclohexane, 4-hydroxycyclohexanone and the -ene analogue−the more polar the molecule the more stable the *axial conformer*

Erich Kleinpeter,* Peter Werner, Torsten Linker