Tetrahedron Vol. 45, No. 22, pp. 6987 to 6998, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00
Pergamon Press plc

THE ANOMERIC EFFECT OF THE CARBOETHOXY GROUP IN OXYGEN AND SULPHUR CONTAINING HETEROCYCLES

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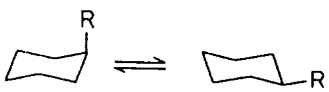
(*Received in Germany* 1 *March* 1989)

Abstract - The anomeric effect of the carboethoxy substituents and the ring oxygen in 1,3-dioxane- and 1,3-oxathiane-2-carboxylates has been estimated in low polar solvents by including empirical correlation factor α to be 4 kJ/mol. The conformational energies of the 2-carboethoxy substituent fit well the parabolic Zefirov dependence on the solvent dielectric constant in the 1,3-dioxane-2-carboxylates. Deviations herefrom in the case of the 1,3-oxathiane-2-carboxylates indicate a second conformational equilibrium involved which is the rotation of the COOR substituent about the exocyclic bond to the heterocyclic ring. Preferred rotamers have been assigned and discussed in terms of special $\pi_{CO}/3d_{(S)}$ orbital interactions.

INTRODUCTION

Lemieux and Chu[1-5] described the preference of the axial conformation of electronegative 2-substituents in tetrahydropyrans as anomeric effect; the conformational equilibrium of the corresponding cyclohexanes, however, is in favour of the equatorial arrangement 2. The anomeric effect has been observed also in many other heterocyclic systems and has been defined[6,7] generally as $\Delta G^o_{\underline{3}-\underline{4}} - \Delta G^o_{\underline{1}-\underline{2}}$:



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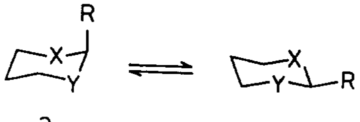


3 4

X = O,S
Y = O,S,CH_2

While much work has been dedicated to the study of substituents R like halogens, hydroxy, alkyloxy, aryloxy, alkylthio in especially tetrahydropyrans, much less effort has been devoted to the anomeric effect of the carboxylates. The preferred axial conformation of the 2-carbomethoxy group in 1,3,5-trithianes[8] and 1,3-dithianes[8-10] has been reported. However, methyl-oxane-2-carboxylate derivatives were found to prefer the equatorial conformation 4.[11,12] This phenomenon has been referred to a reverse anomeric effect in early reports.[11] More recent studies,[12] however, suggest that "there is little if any evidence for the earlier postulated reverse anomeric effect in this case, especially since, on steric reasons, one would expect the conformational energy of a carbomethoxy group at C-2 in tetrahydropyran to be somewhat larger than of the same substituent in cyclohexane".[12] In addition, Franck[13] stated a weak normal anomeric effect of 2.5 kJ/mol for the 2-carbomethoxy group in tetrahydropyran if using the equation: $\Delta G(\mathrm{THP}) = 1.53 \cdot \Delta G(\mathrm{cyclohexane}) + 0.02$

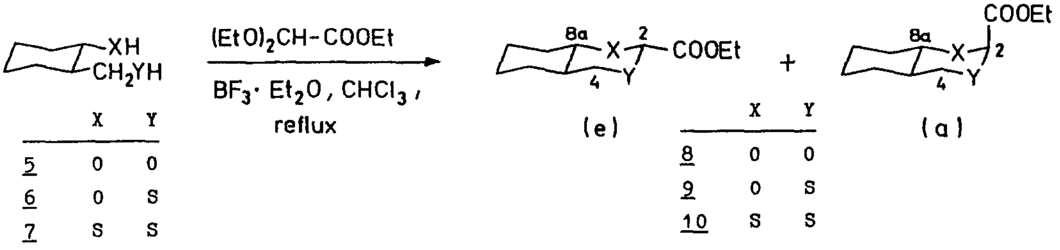
The sharp contrast in the conformational behaviour between the trithianes, dithianes and the tetrahydropyrans as well as the general confusion about the anomeric effect of a carboxylate group in tetrahydropyrans stimulated the present studies on a reverse or normal anomeric effect of the carboxylate group in different heterocycles.

In order to investigate conformational preferences of the carboethoxy group by the direct equilibration method, models have been chosen which bias the compounds in such a way that each isomer exists in one conformation essentially Therefore we selected the trans-1,3-diheterodecalin-2-carboxylates 8 and 9 since the trans-annulation ensures conformational homogenity. Studies on Dreiding models, however, have shown that the geometry of the parent ring systems ought to be disturbed to some degree. For this reason, we investigated also the anancomeric ethyl cis-4,6-dimethyl-1,3-dioxane-2-carboxylate (13) and the ethyl 6-methyl-1,3-oxathiane-2-carboxylate (14). The equilibration of the isomers was performed in different solvents using catalytic amounts of boron trifluoride etherate at 57 °C. After working up, the equilibrated samples were analyzed by ^{1}H NMR spectroscopy to obtain the equilibrium constants by peak area measurement of the corresponding 2-H signals and herefrom the free energy differences between the isomers.

RESULTS AND DISCUSSION

Preparation of the Compounds

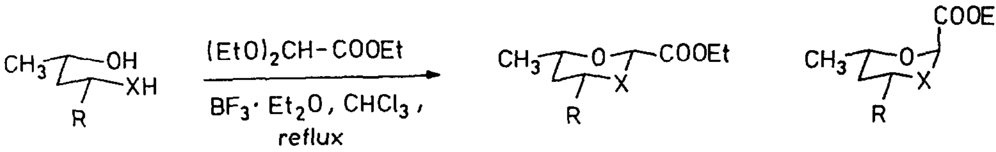
The bicyclic compounds 8, 9 and 10 have been synthesized by slow addition of equimolar amounts of ethyl diethoxyacetate[14] and trans-2-hydroxymethylcyclohexanol (5)[15,16] or trans-2-mercaptomethylcyclohexanol (6) or trans-2-mercaptomethylcyclohexanethiol (7) to a refluxing solution of boron trifluoride diethyletherate in chloroform:[17]



	X	Y
5	O	O
6	O	S
7	S	S

	X	Y
8	O	O
9	O	S
10	S	S

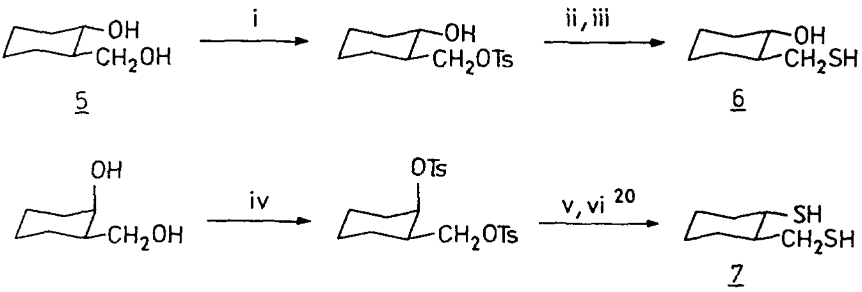
This way, we obtained mixtures of the stereoisomers (e) and (a) from which the pure isomers 8e, 9e, 10e and 10a were isolated. Compounds 13 and 14 were obtained similarly but starting with meso-pentane-2,4-diol (11) or 3-mercaptobutanol (12):[18,19]



	X	R
11	O	CH_3
12	S	H

	X	R
13	O	CH_3
14	S	H

Compounds 6 and 7, finally, have been prepared according to the following scheme:



i: Ts-Cl, pyridine, -15 °C; ii: $(NH_2)_2CS$, EtOH, reflux; iii: NaOH, H_2O, reflux; iv: Ts-Cl (2 equ.), pyridine, 0 - 20 °C; v: Na_2S_2, DMF, 80 °C, 67 h; vi: $LiAlH_4$, Et_2O.

Estimation of Conformational Effects

The magnitude of the anomeric effect is defined as difference of the conformational energies of a special substituent in the studied heterocycle and in cyclohexane.[6] There is, however, a well recognized difficulty: The steric requirements of the substituent in the heterocycle are different to those encountered in cyclohexane.[7] In order to overcome these difficulties we intend to introduce empiric correlation factors α, which correlate the apparent steric size of a substituent in a heterocycle with its size in cyclohexane on the basis of the ΔG^o-values for the methyl group:

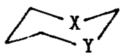
$$\alpha = \frac{\Delta G^o_{\text{Me (heterocycle)}}}{\Delta G^o_{\text{Me (cyclohexane)}}}$$

Thereupon a more precise evaluation of conformational effects[21] ($\Delta\Delta G^o$), e.g. the anomeric effect (AE) in heterocycles is expected according to the equation:

$$\Delta\Delta G^o = \Delta G^o_{\text{subst. (heterocycle)}} - \alpha\,\Delta G^o_{\text{subst. (cyclohexane)}} \qquad \text{(I)}$$

During this treatment, the methyl group has been used as a reference for two reasons: The methyl group is expected to possess minimal conformational effects and the corresponding ΔG^o-values are well known for many heterocycles.[12,18,22-24] Entropy differences, however, may be rather different in the case of the methyl group in comparison with other substituents because of no possibility to exclude the different rotational possibilities.[5,25,26]

Table I. The equatorial-axial preferences and correlation factors α of the methyl group in some six-membered heterocycles and cyclohexane



				$-\Delta G^o_{CH_3}$(kJ/mol) (α)			
X	Y	Position: 2	3	4	5	6	Ref.
CH_2	CH_2			7.27 (1.0)			
O	CH_2	11.95 (1.64)	5.98 (0.82)	8.15 (1.12)	5.98 (0.82)	11.95 (1.64)	12
O	O	16.65 (2.29)	-	12.2 (1.68)	4.04 (0.56)	12.2 (1.68)	20
O	S	13.6 (1.87)	-	7.5 (1.03)	2.7 (0.37)	12.3 (1.69)	21
S	S	8.2 (1.13)	-	7.07 (0.97)	4.88 (0.67)	7.07 (0.97)	18

Conformational Preferences in Low Polar Solvents

The axial-equatorial free energy differences of some anancomeric ethyl 1,3-diheterocyclohexane-2-carboxylates obtained by means of chemical equilibration in different low polar solvents are summarized in Table II, together with the values for the conformational effects, calculated according to equation (I) and taking into account a $-\Delta G^o$-value of 5.0 kJ/mol for ethylcyclohexanecarboxylate.[27]

Table II. ΔG^o-values and the conformational effect of the carboethoxy group ($\Delta\Delta G^o$) in compounds 8, 9, 13 and 14 at 57 °C

X	Y	Comp.	Solvent (ε)[28]	K	ΔG^o_{exp}(kJ/mol)	ΔG^o_{calc}(kJ/mol)[a]	$\Delta\Delta G^o$(kJ/mol)[b]	
O	O	8	CCl_4 (2.17)	4.098	-3.9	-11.5	7.6	3.8[c]
			n-hexane (1.84)	4.049	-3.8	-11.5	7.7	
		13	CCl_4 (2.17)	4.032	-3.8	-11.5	7.7	4.0[c]
			n-heptane (1.87)	3.311	-3.3	-11.5	8.2	
O	S	9	CCl_4 (2.17)	1.852	-1.7	- 9.4	7.7	
			n-heptane (1.87)	1.00	0.0	- 9.4	9.4	
			n-hexane (1.84)	1.020	-0.05	- 9.4	9.35	
		14	CCl_4 (2.17)	1.546	-1.2	- 9.4	8.2	
			n-heptane (1.87)	1.00	0.0	- 9.4	9.4	

a: calculated according to $\Delta G^o_{calc} = \alpha(-5.0$ kJ/mol); b: calculated according to equation (I); c: conformational effect for the interaction between the carboethoxy group and a single heteroatom O or S.

First, in considering the ethyl 1,3-dioxane-2-carboxylates 8 and 13, the equatorial preference of the carboethoxy group is surprisingly low. The difference between the ΔG^o-values observed (-3.8 kJ/mol and -3.3 kJ/mol in hydrocarbon solvents) and the calculated value (-11.5 kJ/mol) must be due to specific interactions between the oxygen atoms and the carboethoxy group which force the carboethoxy group into the axial position. Thus, contrary to literature suggestions on the existence of a reverse anomeric[11] or weak normal anomeric effect,[12,13] in fact, there exists a strong anomeric effect of about 4.0 kJ/mol for the interaction per single oxygen and the carboethoxy group.

In the case of the 1,3-oxathiane derivatives 9 and 14 there is no equatorial preference of the carboethoxy group at all (ΔG^o = 0.0 kJ/mol in n-heptane); the conformational effect between a single sulfur atom and the carboethoxy group is estimated to be 9.4 - 4.0 = 5.4 kJ/mol. The conformational energy of the carbomethoxy group in methyl 1,3-dithiane-2-carboxylate had been determined by Juaristi (ΔG^o = 3.47 kJ/mol, CD_2Cl_2, -100 °C; ΔG^o = 3.85 kJ/mol, aceton-d_6, -90 °C)[10] and Hartmann (ΔG^o = 3.39 kJ/mol, $CHCl_3$, 23 °C).[9] From these data a conformational effect between the carbomethoxy group and a single sulfur atom of 4.5 - 4.75 kJ/mol may be calculated using equation (I). This is in rather good agreement with our value, taking into account that more polar solvents have been used by Juaristi and Hartmann. Such kind of strong conformational effects are only observeable in very low polar solvents like n-hexane or CCl_4, because of an unusual strong solvent dependence, which will be treated in detail now.

Solvent Dependence

The conformational energies, obtained by equilibration of the various compounds in more polar solvents, are given in Table III. According to most known cases, the population of the axial conformer decreases usually with increasing solvent polarity.[29,30]

Table III. Solvent effect on the axial-equatorial energy difference of the carboethoxy group in 8, 9, 13 and 14

X	Y	Solvent	ε	Comp.	K	ΔG^o(kJ/mol)	Comp.	K	ΔG^o(kJ/mol)
0	0	$CHCl=CCl_2$		8	5.952	-4.9	13	6.135	-5.0
		$CHCl_3$	4.16					4.878	-4.3
		CH_2Br_2	6.0		8.849	-6.0		5.714	-4.8
		CH_2ClCH_2Cl	8.65		10.204	-6.4		7.246	-5.4
0	S	$CHCl=CCl_2$		9	2.381	-2.4	14	2.387	-2.4
		$CHCl_2CHCl_2$	3.88		4.484	-4.1			
		$CHCl_3$	4.16		4.717	-4.2		4.292	-4.0
		CH_2Br_2	6.0					4.367	-4.0
		CH_2ClCH_2Cl	8.65		5.128	-4.5		4.762	-4.3

The solvent effects on the axial-equatorial equilibria were estimated by the extrapolation method, proposed by Zefirov,[29] which relates the free energy difference in solution to the dielectric constant (ε) of the solvent through a parabolic expression:

$$\Delta G^{o} = A + B\,(0.5 - X)^{1/2} \qquad X = (\varepsilon - 1)/(2\varepsilon + 1)$$

The plots of ΔG^{o} for the ethyl 1,3-oxathiane-2-carboxylates 9 and 14 vs. the square root expression is given in Figure I. Surprisingly, the plots do not provide the expected straight lines. The solvent dependence of ΔG^{o} is unusual strong. The ΔG^{o}-values of the equilibrium (9a) $\rightleftharpoons$ (9e) rise from -1.7 kJ/mol in CCl_4 (ε = 2.17 D) to 0.0 kJ/mol in n-hexane (ε = 1.84 D)!

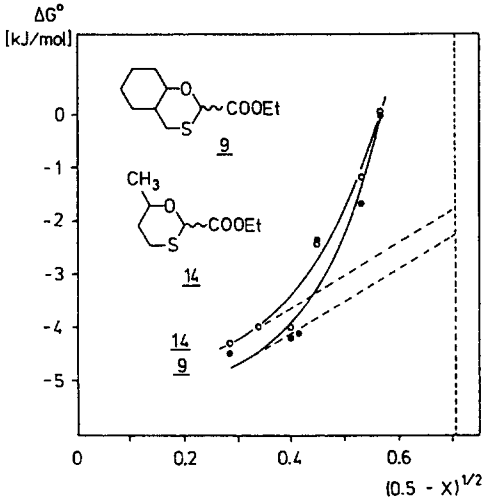


Figure I. Plots of the ΔG^{o}-values of the equilibria 9a $\rightleftharpoons$ 9e - black dots - and 14a $\rightleftharpoons$ 14e - white dots - against $(0.5\text{-}X)^{1/2}$ and extrapolation to vapour phase (broken lines).

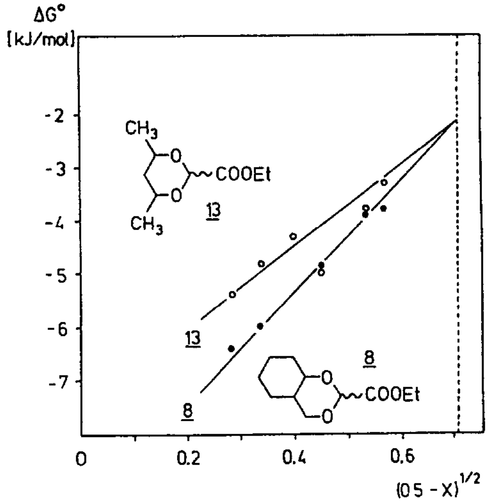


Figure II. Plots of the ΔG^{o}-values for the equilibria 8a $\rightleftharpoons$ 8e - black dots - and 13a $\rightleftharpoons$ 13e - white dots - against $(0.5\text{-}X)^{1/2}$ and extrapolation to vapour phase conditions by the PEM procedure.

This behaviour could be the result of at least two conformational equilibria. First, the axial-equatorial equilibrium 3 $\rightleftharpoons$ 4 whereby increasing solvent polarity stabilizes the equatorial conformer (isomer), because this is usually the more polar one due to the higher dipole moment. The second one, the exocyclic conformational equilibrium between the different rotamers around the C(2)-C=O bond, should be solvent dependend too, because any change in the rotamer distribution of the axial carboethoxy group should also influence the axial-equatorial equilibrium owing to different steric 1,3-diaxial repulsions in the rotamers possible.

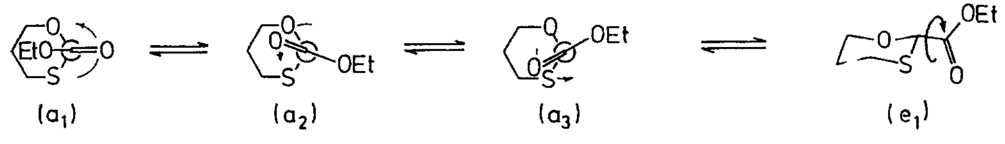
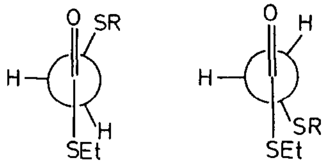


Figure III. Rotational conformers of the C(2)-C=O bond

For these reasons, the rotamers (a_2) and (a_3) should be favoured, but it is likely that not only steric reasons have to be considered. Olivato et al.[31] have shown recently that the interaction between the $\pi_{C=O}$ and $3d_{(S)}$ orbitals favours the "cis" rotamer over the "trans" rotamer in α-(alkylthio)-thioacetates. It has been mentioned also that the contribution of the "cis" rotamer decreases with increasing solvent polarity. In the light of these results, low polar solvents should increase the contribution of the rotational conformer (a_2); thereupon the effective size of the axial carboethoxy group decreases and the carboethoxy group favours the axial position to a greater extend in low polar solvents. This is in agreement with the behaviour observed.


"cis" "trans"

The plots of the ΔG^o-values of the axial-equatorial equilibria for the anancomeric 1,3-dioxane-2-carboxylates <u>8</u> and <u>13</u> vs. $(0.5 - X)^{1/2}$ are given in Figure II. Contrary to the sulphur containing heterocycles, these plots provide straight lines. This result is in accord with former explanations: In the case of 1,3-dioxane-2-carboxylates there are no special interactions between the heteroatom and the carboethoxy group - as in the case of ethyl 1,3-oxathiane-2-carboxylates - which cause the strong enhancement of the axial isomers in very low polar solvents.

Anomeric Effect

In the case of the 1,3-dioxane-2-carboxylates <u>8</u> and <u>13</u>, the plots of ΔG^o against $(0.5 - X)^{1/2}$ permit the extrapolation of $-\Delta G^o$ to vapour phase conditions ($\varepsilon = 1.0$).[29] This way, we have obtained an average $-\Delta G^o_{vap.}$-value of 2.1 kJ/mol from which the average vapour phase anomeric interaction AE_{COOEt} has been estimated using equation (I) to be 9.4 kJ/mol. The anomeric interaction between one oxygen and the carboethoxy group should therefore amount about 4.7 kJ/mol. The related extrapolation has been done for the ethyl 1,3-oxathiane-2-carboxylates <u>9</u> and <u>14</u> using the tangent at $(0.5 - X)^{1/2} = 0.3$ which gave the vapour phase anomeric interactions $AE_{COOEt} = 7.2$ and 7.7 kJ/mol, respectively. Therefrom we have calculated a vapour phase anomeric interaction between a single sulphur atom and the carboethoxy group of 2.5 and 3.0 kJ/mol, using $AE_{O/COOEt} = 4.7$ kJ/mol.

From these considerations, in contrast to previous reports, is to conclude on a strong anomeric interaction between oxygen and the carboethoxy group, which is obviously significantly stronger than the interaction between sulphur and the carboethoxy group. It appears likely, that the strong axial preference of the carbomethoxy group in 1,3-dithianes[7-9] as well as the low values for $-\Delta G^o_{COOEt}$, observed for 1,3-oxathianes in nonpolar solvents must be at least in part, due to the decrease in the effective size of the carboethoxy group as a result of the stabilization of the C=O-inside rotational conformer (a_2) by $\pi_{C=O} \rightarrow 3d_{(S)}$ orbital interactions.

Table IV. Evaluation of the anomeric effect of the carboethoxy group

X	Y	Comp.	$\Delta G^o_{vap.}$ [a] (kJ/mol)	$\Delta G^o_{calc.}$ [b] (kJ/mol)	AE_{COOEt} [c] (kJ/mol)	$AE_{X/COOEt}$ [d] (kJ/mol)	$\Delta\Delta G^o_{sol.}$ [e] (kJ/mol)	(Solvent)
O	O	8	-2.1	-11.5	9.4	4.7	7.7	(n-hexane)
O	O	13	-2.1	-11.5	9.4	4.7	8.2	(n-heptane)
O	S	9	-2.2	-9.4	7.2	4.7/2.5	9.4	(n-heptane)
O	S	14	-1.7	-9.4	7.7	4.7/3.0	9.4	(n-heptane)

a: graphically extrapolated from Figures I and II to $(0.5 - X)^{1/2} = 0.707$; b: α(-5.0 kJ/mol); c: anomeric effect of the carboethoxy group in the considered heterocycle under vapour phase conditions, calculated according to equation (I); d: value for the anomeric interaction between a single heteroatom X or Y and COOEt; e: see Table II.

Rotational Conformation of the Carboethoxy Group

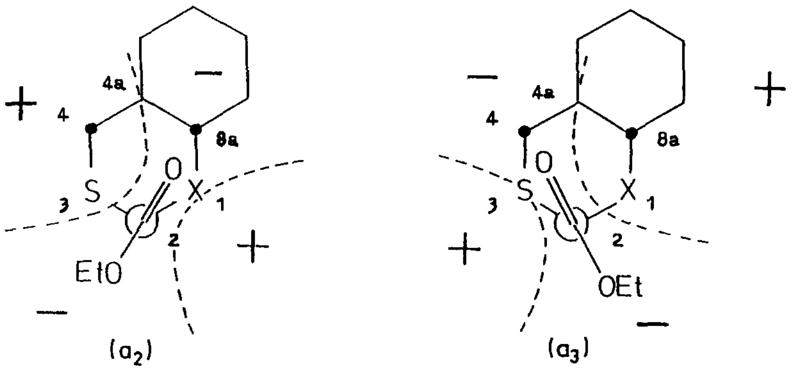
In the ^1H NMR spectra of the 1,3-oxathiane-2-carboxylates, the chemical shifts of the axial protons 8a-H and $4\text{-}H_{ax}$ have been found strongly solvent dependent. Table V lists the chemical shifts of the protons $4\text{-}H_{equ}$, $4\text{-}H_{ax}$ and 8a-H for the two isomeric ethyl 1-oxa-3-thiadecalin-2-carboxylates 9a and 9e in different solvents.

Table V. Chemical shifts of the 2-H, $4\text{-}H_{equ}$, $4\text{-}H_{ax}$ and 8a-H protons of the ethyl trans-1-oxa-3-thiadecalin-2-carboxylates in different solvents at 23 °C (ppm)

Solvent	(ε)	δ 2-H			δ $4\text{-}H_{equ}$			δ $4\text{-}H_{ax}$			δ 8a-H		
		9a	9e	$\Delta\delta^a$	9a	9e	$\Delta\delta$	9a	9e	$\Delta\delta$	9a	9e	$\Delta\delta$
C_6D_{12}	(2.0)	4.96	5.30	-0.34	2.50	2.51	-0.01	2.68	2.94	-0.26	4.40	3.01	+1.39
CCl_4	(2.2)	4.96	5.24	-0.28	2.28	2.56	-0.28	2.67	2.83	-0.16	4.27	3.10	+1.17
$CDCl_3$	(4.8)	5.18	5.46	-0.28	2.37	2.65	-0.28	2.81	2.89	-0.08	4.19	3.21	+0.98
CD_2Cl_2	(8.9)	5.14	5.44	-0.30	2.36	2.63	-0.27	2.82	2.82	0.00	4.12	3.21	+0.91
CD_3COCD_3	(20.7)	5.18	5.53	-0.35	2.41	2.65	-0.24	2.85	2.81	+0.04	-	3.30	-
CD_3CN	(37.5)	5.19	5.50	-0.31	2.39	2.61	-0.22	-^{b}	-	-	4.03	3.23	+0.80

a: $\Delta\delta = \delta(a) - \delta(e)$; b: not observeable due to serious signal overlapping.

There is an unusual strong difference between the chemical shifts of the 8a-H protons in the axial and the equatorial isomer. In the axial isomer 9a the 8a-H proton is deshielded ($\Delta\delta$ = 1.39 ppm in C_6D_{12}) while the axial 4-H proton is more shielded in this isomer. In the light of these results, it seems likely that in the axial isomer a rotamer is preferred with the carbonyl group in a nearly eclipsed conformation with the C(2)-O(1)-bond (see Figure IV, conformer (a_2)). Only then the deshielding part of the anisotropy cone[32] is directed towards the 8a-H proton, while the $4\text{-}H_{ax}$ proton gets positioned in the shielded area. Additionally, this preferred rotamer should allow the best through space



(a₂) (a₃)

Figure IV. Diamagnetic shielding (+) and deshielding (−) regions of the carbonyl group in the rotamers (a_2) and (a_3) of the compounds 9a (X = O) and 10a (X = S)

interaction between the π-orbital of the C=O group, behaving as electron donor, and one of the empty 3d-orbitals at the sulphur atom, behaving as electron acceptor. The solvent dependence of these $\Delta\delta$-values observed is in good agreement with the results, obtained by the equilibration studies, indicating the rotamer (a_2) to be the more preferred one in low polar solvents.

The chemical shifts of the 4-H_{equ}, 4-H_{ax} and 8a-H protons in the compounds 8 and 10 and those of the 4-H and 6-H protons in the compounds 13 and 14 are summarized in Table VI. The chemical shift differences, obtained for the ethyl 6-methyl-1,3-oxathiane-2-carboxylate (14) agree very well with those of the bicyclic compound 9. Contrary to this the anisotropy effect of the C=O group upon the axial protons in the 1,3-dioxane-2-carboxylates 8 and 13 is low ($\Delta\delta$ = 0.09 - 0.24 ppm) due to the rather small contribution of the C=O-inside rotamers in these cases.

The down field shift of the axial protons 4-H_{ax} and 8a-H in the 1,3-dithiadecalin-2-carboxylate (10a) are of the same order of magnitude, since the carbonyl group has two nearly equally populated C=O-inside rotamers (a_2) and (a_3). The proton 8a-H in 10a exhibits a smaller deshielding than the same proton in the corresponding 1,3-oxathiadecalin-2-carboxylate (9a) because it may be located inside or outside the anisotropic cone (see Figure IV).

Table VI. Chemical shifts of the 4-H_{equ}, 4-H_{ax}, 8a-H and 2-H protons in 8 and 10 and of the 2-H, 4-H and 6-H protons in 13 and 14, ppm

				δ2-H		δ4-H_{equ}			δ4-H_{ax}			δ8a-H/δ6-H	
Comp.	X	Y	Solvent	(a)	(e)	(a)	(e)	$\Delta\delta^a$	(a)	(e)	Δδ	(a)	(e)	Δδ
8	O	O	$CDCl_3$	5.31	4.99	3.84	4.03	-0.27	3.66	3.42	+0.24	3.42	3.33	+0.09
13	O	O	$CDCl_3$	5.33	4.99	-^{b}	-	-	4.01	3.81	+0.20	4.01	3.81	+0.20
14	O	S	$CDCl_3$	5.18	5.36	2.61	2.75	-0.14	3.01	2.99	+0.02	4.52	3.52	+1.00
10	S	S	$CDCl_3$	4.09	5.00	2.40	-	-0.14	3.24	-	+0.58	3.37	-	+0.7
10	S	S	$(CD_3)_2CO$	4.23	5.16	2.31	2.68	-0.37	3.17	2.79	+0.38	3.29	2.85	+0.44

a: $\Delta\delta$ = δ(a) - δ(e); b: not determined due to serious signal overlapping.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker WP 200 NMR spectrometer at 200 MHz. ^{13}C NMR spectra were recorded on a Bruker AC 80 NMR spectrometer at 20.15 MHz and on the Bruker WP 200 at 50.33 MHz; the instruments were operating in pulsed Fourier transform mode and locked on the deuterium signal of the solvent. Samples were prepared as 5 - 10% solutions with tetramethylsilane as internal reference. Solutions in CCl_4 were locked on external acetone-d_6.

Equilibrations

The equilibrations were carried out at 57 °C for 10 days in sealed ampoules containing 3 ml solvent, 50 mg of the substrate in question and 3 drops boron trifluoride diethyletherate as a catalyst. Before the analysis, the equilibrations were quenched by addition of K_2CO_3 solution. The resulting mixtures were extracted twice with ether and the latter was evaporated afterwards. Then the samples were dissolved in $CDCl_3$ and ^{1}H NMR spectra were recorded. Hereby, the well separated absorptions of the tertiary protons in position 2 (2-H) of the resulting cis/trans isomers have been integrated very carefully. The equilibrations were repeated several times. If both stereoisomers in question were available, the equilibrations were started using samples including initially either the one or the other isomeric form. Otherwise cis or trans enriched samples were used.

Substituted Ethyl 1,3-diheterocyclohexane-2-carboxylates 8 - 10, 12 and 14 - General Procedure

0.01 mol (1.76 g) ethyl diethoxyacetate[14] and 0.01 mol of the appropriate diol 5 or 11, the dithiol 7 or 3-hydroxymercaptan 6, 12, dissolved in 5 ml $CHCl_3$, were added dropwise to a refluxing solution of 0.02 mol (2.82 g) boron trifluoride diethyletherate in 5 ml $CHCl_3$. The resulting solutions were refluxed for 30 m., cooled and were washed successively with 20 ml water, 20 ml 20% aqu. K_2CO_3 solution and finally again with 20 ml water. After drying over Na_2SO_4, the solutions were filtered and concentrated at reduced pressure. The products were purified by Kugelrohr distillation and/or recrystallization. The physical properties of the freshly synthesized compounds are given below. ^{13}C NMR spectral data are collected in Table VII.

8e: b.p. 95 °C (0.02 mm Hg); m.p. 33 °C (n-hexane); 9e: b.p. 110 °C (0.05 mm Hg); m.p. 86 °C (n-hexane); 10: b.p. 130 °C (0.1 mm Hg); 10e: m.p. 86 °C (n-hexane); 10a: m.p. 62 - 64 °C; 13 b.p. 80 °C (0.1 mm Hg); 14: b.p. 125 - 130 °C (12 mm Hg).

Table VII. ^{13}C NMR signal assignments in compounds 8 - 10, 13 and 14 ($CDCl_3$, ppm)

Compound	8e	9e	9a	10e	10a	13e	13a	14e	14a
C=O	165.88	167.42	169.68	167.46	170.44	165.81	168.29	167.37	169.43
CH_2O	61.79	61.97	61.24	62.37	61.49	61.37	60.95	61.85	61.22
CH_3	13.96	14.08	14.08	14.04	14.08	13.71	13.88	14.05	14.05
C(2)	96.97	84.24	76.89	50.56	42.72	96.33	93.25	80.21	72.94
C(4)	71.85	33.96	32.68	37.16	33.93	73.05	67.58	28.45	24.00
C(4a)/C(5)[a]	40.64	40.42	41.20	42.07	40.45	39.76	39.85	32.05	32.05

Table VII continued

Compound	8e	9e	9a	10e	10a	13e	13a	14e	14a
C(8a)/C(6)[a]	82.12	79.67	72.48	48.70	42.07	73.05	67.58	76.46	68.79
	31.11	32.25	31.79	33.44	32.23				
C(5)-C(8)/	25.87	31.41	29.35	32.28	31.57				
CH_3[a]	24.77	25.71	25.48	26.30	26.63	21.02	31.34	22.04	21.84
	24.44	24.87	24.74	26.30	26.56				

a: compounds 13 and 14

trans-2-(p-Toluenesulfonyloxymethyl)-cyclohexanol

A solution of 0.05 mol (6.5 g) 5[15,16] in 30 ml dry pyridine was added dropwise to a stirred solution of 0.05 mol (9.65 g) p-toluenesulfonyl chloride in 20 ml dry pyridine at -10 °C. Stirring was continued for 8 hrs. at this temperature. After standing at 0 °C for 48 hrs. the reaction was quenched by means of a mixture of 200 g ice and 100 ml conc. hydrochloric acid. Extraction with ether and usual working up afforded the crude product, which was recrystallized from n-heptane/ethyl acetate: white crystals. m.p. 75 °C; yield 49%; IR (CCl_4, cm^{-1}): 3500, 2920, 2840, 1600, 1495, 1365, 1185, 1175, 1095, 1065, 1035, 940; ^1H NMR ($CDCl_3$, ppm) 7.18 - 8.80 (m, 4H, H-arom.), 4.10 (d, 2H, J = 4.5 Hz, OCH_2), 3.26 (1H, OH), 2.65 (m, 1H, CHOH), 2.36 (s, 3H, CH_3), 0.8 - 2.0 (m, 9H).

trans-2-Mercaptomethylcyclohexanol 6

According to the standard procedure,[33] 0.02 mol (6.4 g) trans-2-(p-toluenesulfonyloxymethyl)-cyclohexanol was treated with 0.022 mol (1.7 g) thiourea to give the thiuronium salt. After the alkaline hydrolysis of the latter with 200 ml 2n NaOH solution, the desired 6 was obtained in 80% yield, b.p. 127 °C/ 12 mm Hg.

cis-2-(p-Toluenesulfonyloxymethyl)-cyclohexane-2-(p-toluenesulfonate)

A solution of 0.17 mol (32.4 g) p-toluenesulfonyl chloride in 50 ml dry pyridine was added to a solution of 0.08 mol (10.5 g) cis-2-hydroxymethylcyclohexanol[16] in 30 ml dry pyridine at 0 - 5 °C. The resulting mixture was stirred at 20 °C for 5 days. The usual work-up procedure gave the desired compound in 70% yield, m.p. 69 -72 °C (n-heptane/ethyl acetate); IR (CCl_4, cm^{-1}), 3010, 2910, 2835, 1595, 1490, 1445, 1355, 1365, 1185, 1170, 1090; ^1H NMR ($CDCl_3$, ppm) 7.25 - 7.75 (m, 8H, H-arcm.), 4.77 (m, 1H, CH-O), 4.26 (s, 3H, CH_2O), 2.43 (s, 3H, CH_3), 1.10 - 2.20 (m, 9H).

trans-2-Mercaptomethylcyclohexanethiol 7

In following the literature procedure[20] the ditosylate was transferred into compound 7 in 60% yield; b.p. 114 - 116 °C/10 mm Hg.

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