Tetrahedron Vol. 38, No. 15, pp. 2327 to 2337, 1982
Printed in Great Britain.

0040-4020/82/152327-11$03.00/0
Pergamon Press Ltd.

FORCE FIELD AND ^{13}C-NMR INVESTIGATIONS OF SUBSTITUTED CYCLOPENTANES. A CONCEPT FOR THE ADAPTION OF ^{13}C NMR SHIFTS TO VARYING TORSIONAL ARRANGEMENTS IN FLEXIBLE CONFORMERS[1]

HANS-JÖRG SCHNEIDER,* NGE NGUYEN-BA and FRED THOMAS
Fachrichtung Organische Chemie der Universität des Saarlandes D 6600 Saarbrücken 11, West Germany

(*Received in Germany* 28 *October* 1981)

Abstract—MM2 Exploration of the conformational space for methylcyclopentane, in contrast to cyclopentanone yields more and flatter minima than known previously. Calculations of cyclopentanes with substituents X = F, Cl, $CHMe_2$, and CMe_3 with two stable conformations indicate $< 2°$ torsional angle changes with the different substituents. Cyclopentanes bearing not more than 2 substituents can accommodate all groups in pseudoequatorial positions without changing the basic envelope and twist chair geometries significantly. A model for ^{13}C-shift calculation is proposed in which shift increments for the different torsional arrangements are obtained by linear interpolation between corresponding cyclohexane values. After correction for the nonequivalent carbon shifts in the hydrocarbon itself, again using the linear interpolation, a significant improvement of the shift correlations is observed. For disubstituted cyclopentanes these predict the shifts within ± 1.7 ppm with Me, $CHMe_2$, CMe_3, Cl, Br and OH as substituents. Configurational assignments are difficult with 1,3-di-substituted cyclopentanes, but straightforward with 1,2-di- and trisubstituted compounds. Thus, due to the presence of smaller torsional angles between, e.g. diequatorial vicinal substituents in the 1,2- *cis* series as compared to the *trans* compounds, the latter show deshielding, particularly at C2, by 1–4 ppm. Several epimers are stereo-selectively prepared by suitable ketone reduction and displacement methods.

The manifold conformations of cyclopentanes have stimulated more investigations than any other ring and are of continuing interest, also in view of their significance in natural products (furanose, steroid or prostaglandin derivatives). All the earlier literature has been thoroughly reviewed recently by Fuchs[2] and indicates the envelope and twist chair forms (**1** and **2**) as the most stable conformations of similar energy for the parent hydrocarbon.

The high flexibility of the fivemembered ring makes energy minimum conformations, particularly of substituted cyclopentanes, difficult to assign. *Ab initio* MO calculations[3] on the methyl cyclopentane predict **1** with methyl in 1a and 1e orientations as conformers of similar energy. However a geometry optimization extending to the many other possible conformations using MO calculations with a sufficiently large basis set seems to be precluded by the high computation costs involved.

Force field calculations

Semiempirical force fields can provide an economical access to the multiple cyclopentane conformers and to a reliable basis for the interpretation of their spectroscopic properties. By energy minimizations using molecular mechanics Allinger *et al.* obtained for methylcyclopentane four conformations of comparable energy (**1**, 1e-Me: ≡0.0; **2**, 3e-Me 0.13; **2**, 2e-Me 0.47; **2**, 1i-Me 0.85 kcal/mol, respectively).[4] Lugar and Brutcher calculated **2**, 1i-Me as particularly stable and predicted substantial changes also of the geometries with increasing size of the substituent.[2,5] Since straightforward geometry optimizations can eventually miss the true energy minima, particularly in the case of flat profiles (such as in pseudorotating cyclopentanes), and in fact may fail to yield local minima[6] we have scanned the methyl cyclopentane energy surface by a MM2[7] calculation of the steric energy as function of a torsional angle (C2–C3–C4–C5; Fig. 1). The result is that (i) the strain energy differences ΔSI are smaller than calculated previously,[4] (ii) there are additional minima for **1**, 2e-Me ΔSI = 0.08 and **1**, 3e-Me 0.28 (again relative to **1**, 1e–Me ΔSI ≡ 0.0 kcal/mol); (iii) the ring geometry in the stable conformations is not altered by introduction of the methyl group as compared to cyclopentane itself (Tables 1 and 2).

For other substituents calculations were carried out only for some representative cases (Tables 1, and 2) which again indicate only minor changes of geometry and relative stability. Thus ΔSI between **1**, 1e-X and **2**, 3e-X increases only slightly from X = Me to CH_2Me, $CHMe_2$ and CMe_3 (if ΔSIMe ≡ 0.0 CH_2Me: 0.05, $CHMe_2$: 0.06, CMe_3: 0.16 kcal/mol, respectively). Also, contrary to earlier reports,[2,5] even bulky substituents lead to torsional angle changes of less than 2° (< 6%) (Tables 1 and 2); the stiffer bond angles and bond lengths are calculated to remain constant within 1% and 0.5%, respectively. Whereas even a t-butyl substituent obviously does not significantly shift the conformational equilibria, introduction of an oxo group seems to lead to a stronger preference of the twist form **2**, 1-oxo, which, e.g. is calculated to be 0.92 kcal/mol more stable than **1**, 3-oxo (see the corresponding MM2 calculation of the cyclopentanone pseudorotation circle, Fig. 2). In conclusion the force field calculations, which did not include possible differential entropy contributions, predict that substituents of all kinds can be accommodated at (pseudo)equatorial positions on the fivemembered ring with energy differences of less than 0.2 kcal/mol (Fig. 3). The relative stabilities for conformers of poly-substituted cyclopentanes may therefore be inferred from the methylcyclopentane ΔSI values (Fig. 3) as long as the substituents are in e- or i-positions, and do not interact with each other significantly, as in 1,3-disubstituted rings. Thus, 1,3-dimethyl cyclopentane could assume the forms

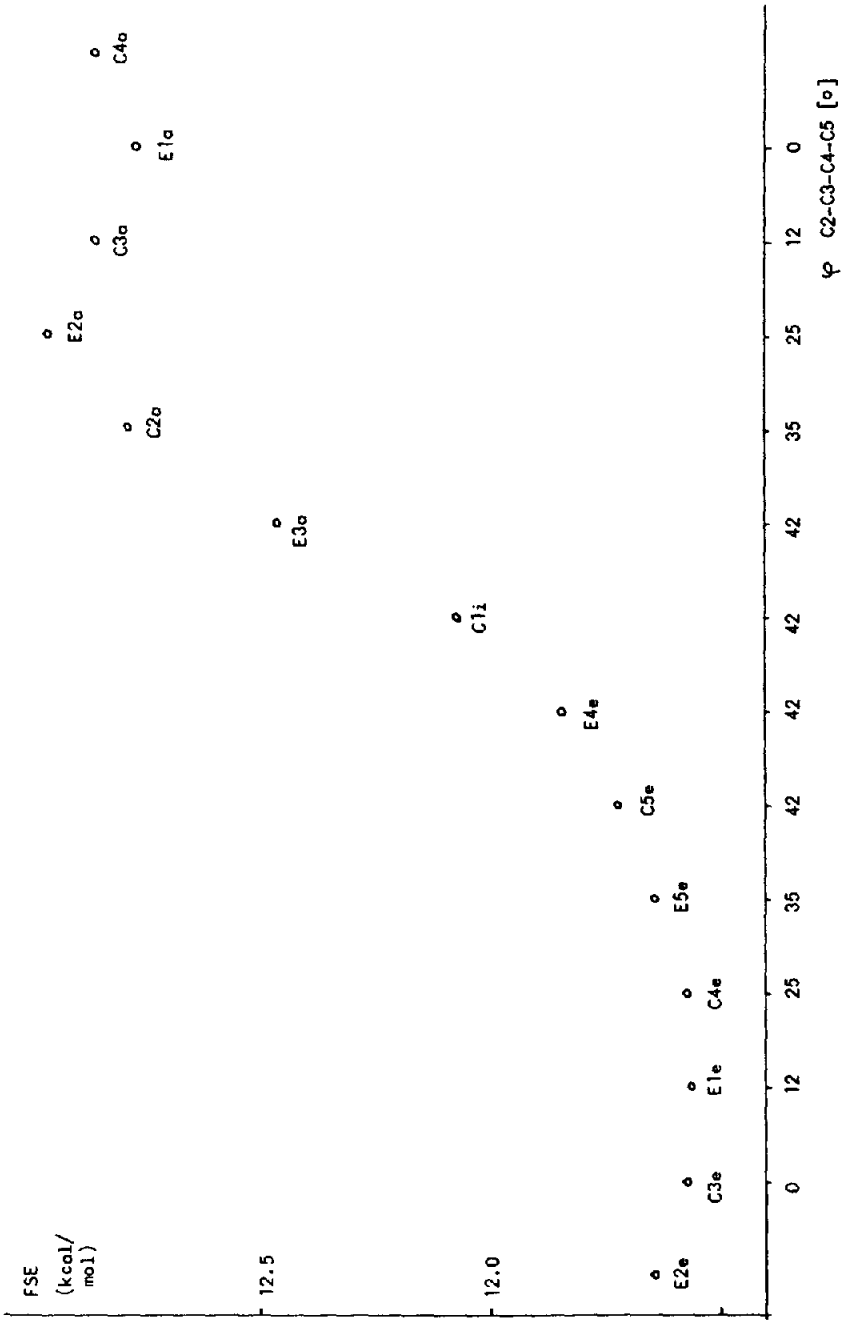


Fig. 1. Pseudorotational energy profile for methylcyclopentane; E envelope, C twist chair form, substituent position as in formulae 1 and 2.

Table 1. Torsional CCCC angles ϕ in envelope forms[a]

		1-2-3-4	1-5-4-3	2-1-5-4	2-1-5-X	2-3-4-5	3-2-1-5	3-4-5-X
H	MM2	3.3	39.4	41.4	163.0	22.3	27.7	161.0
X=Me	MM2	3.3	39.6	41.6	166.3	22.5	27.8	164.2
F	MM1	3.1	40.7	42.5	161.4	23.0	27.8	160.0
Cl	MM1	3.1	41.4	43.3	165.0	23.4	28.4	163.0
$CHMe_2$ [b]	MM1	3.3	40.0	42.0	171.0	22.7	28.1	169.5
CMe_3 [c]	MM1	1.0	39.8	40.5	171.7	24.3	25.9	171.0

a) Substituent X in position 5e; MM1 or MM2 energy minimizations as indicated, ϕ in (°); b) 1-5-6-Me: 73.8 and 52.7° ; c) 1-5-6-Me: 59.1, 61.7, 180.0° (X=C6).

Table 2. Torsional CCCC angles ϕ in twist chair forms[a]

X		1-2-3-4	1-2-3-X	1-5-4-3	2-1-5-4	2-3-4-5	3-2-1-5	5-4-3-6
H	MM1	35.7	158.8	34.2	12.1	43.2	14.6	166.6
H	MM2	35.2	155.7	33.8	12.1	42.6	14.3	164.5
Me	MM1	33.5	158.2	35.7	14.9	42.8	11.5	167.9
Me	MM2	32.6	155.8	36.5	16.4	42.6	10.1	166.0
$CHMe_2$ [b, c]	MM1	35.3	164.7	34.5	12.5 [b]	43.1	14.2	172.2
CMe_3 [d]	MM1	35.4[d]	166.0	35.0	12.7	43.4	14.2	174.4

a) Substituent X in position 3e; MM1 or MM2 calculations as indicated; ϕ in (°)
b) Fixed value ("Driver" Routine) for 2-1-5-4 12.5°.
c) 2-3-6-Me: 161.4, 72.3°; X-C5; d) Fixed value for 1-2-3-4 35.4°.

1, 1e, 3e; 1, 2e, 5e; 2, 3e, 5e; 2, 1i, 3e for the *cis* isomer with $\Delta SI < 0.18$ kcal/mol, and 1, 2e, 4e; 2, 2e, 5e, 2, 1i, 3e with $\Delta SI < 0.08$ kcal/mol for the *trans* epimer, showing an average difference SI (*trans*)-SI (*cis*) $\cong$ 0.1 kcal/mol. This is in agreement with some MM1 calculations, which for disubstituted rings were carried out only for 1-bromo, -3-methyl cyclopentane in the conformations 1, 1e, 3e $\Delta SI = 4.7$ kcal/mol), 2, 2e, 4e (4.55), *-cis-*, and 2, 1i, 3e (4.77), *-trans-*, yielding similar small differences in the bracketed strain energies. 1,2-Disubstituted cyclopentanes, which also can accommodate all substituents in e-positions for both epimers, again are expected to show small strain energy differences, particularly if there is little or no repulsion between the vicinal groups, as, e.g. in the case of vicinal bromine and methyl.[8] Similar small energy variations have been calculated earlier[4,9] and explain the small differences in stability[2a] and reactivity[2a,10] between configurational isomers of cyclopentanes as compared to cyclohexanes. Conformational differences due to alternative (pseudo) e-or a-substitution in cyclopentanes can therefore only be expected for tri- and higher substituted, or annelated rings where a group can be forced into a pseudoaxial position.

^{13}C-NMR shielding constants

^{13}C-NMR Shifts can be used successfully, and often straightforwardly, for conformational and configurational analyses of molecules which are geometrically well defined, and preferably contain largely undistorted "ideal" 60°/180° torsional arrangements, such as cyclohexane-like systems.[11] More flexible open chain alkanes are amenable to shielding analysis if the individual conformers are studied at sufficiently low temperature,[12] or if the time averaged conformer populations are weighted and represented by suitable increments,[13,14] assuming again ideal torsional angles. Cyclopentanes are typical for compounds in which individual conformers cannot be seen spectroscopically, and in which there are no ideal vicinal angles close to 60° or 180°, and which therefore need another approach.

The averaged chemical shift S_m of a particular carbon atom bearing a substituent X in a system occurring in rapidly equilibrating conformers A, B, C ... I is:

$$S_m = aS_A + bS_{B...} + iS_I$$

where a, b ... i are mole fractions and S_A, S_B ... S_i intrinsic shifts. We assume that the shift is the sum of (1) a geometry independent substituent effect S_X, which can be taken e.g. from cyclohexyl derivatives,[15] (2) a ring carbon shift S_{ni}, which is not equivalent for the different atoms in cyclopentane (see below), and (3) a substituent increment $S_{X\varphi i}$ which depends on the orientation of X, characterized by the XCCC torsional angle φ:

$$S_m = S_X + iS_{ni} + iS_{X\varphi i}.$$

This implies that the geometry in the individual conformers is independent of X, which is justified by our

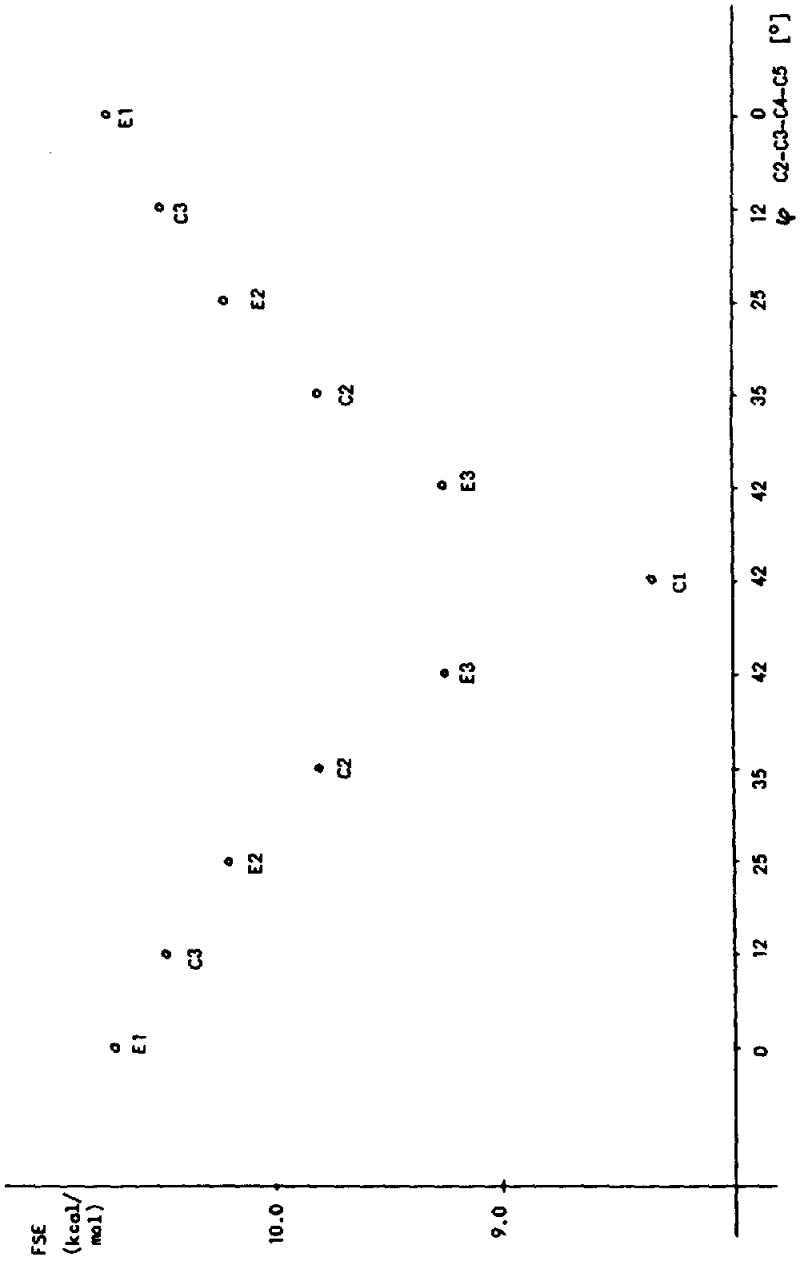


Fig. 2. Pseudorotational energy profile for cyclopentanone.

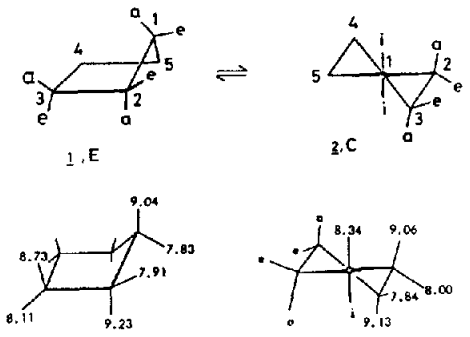


Fig. 3. Strain Energies SI (kcal/mol) for different methylcyclopentane conformations; the values refer to SI for the methyl group in the given position.

force field calculations for the predominant (pseudo)-equatorial forms. Although the sensitivity of α, β and particularly substituent effects on ^{13}C shielding against torsional angle changes is well known,[11] as illustrated in Fig. 4, it is not possible at the present time to deduce exact $S_{X\varphi}$ values for a given angle φ theoretically or empirically. The typical scatter observed in Fig. 4 only warrants as a most simple approximation a linear dependence of $S_{X\varphi}$ on the torsional angle change $\Delta\varphi$:

$$S_{X\varphi} = S \cdot \Delta\varphi i.$$

From the mole fraction a ... i and the angles $\varphi a \ldots \varphi i$ of the individual conformers, which are calculated by the force field, an average torsional angle φ_m is obtained.

$$\varphi_m = a\varphi_A + b\varphi_B \ldots + i\varphi_i + i\varphi_l.$$

One arrives at a value of $\varphi_m = 140°$ for X = Me, which can be used also for other substituents in view of the small differences found in the force field results for other cyclopentane derivatives (see above).

With respect to the shielding differences for the carbon atoms in the basic ring system itself, again the variation of the torsional angles is taken into account only, since there is no indication of bond angle or bond length differences found in the calculated structures.

Thus, e.g. C2 in 1 is part of fragment with $\varphi = 0°$ and $\varphi = 40°$, yielding $\varphi_m = 20°$ and, by linear interpolation from cyclohexane values (Fig. 4), $S_{C2,20°} = -8.6$ ppm.

Similarly, one obtains $S_{C1,25°} = -8.3$ and $S_{C3,33°} = -7.9$ ppm. These shifts reflect the variations due to the different geometric environment of the ring carbons, which have to be added to, or subtracted from the experimental averaged shielding of cyclopentane. Figure 5 illustrates, that the shifts for the carbon atoms in both envelope and twist chair forms are expected to vary by less than 0.4 ppm from the average cyclopentane value. A comparison between experimental (Table 4) and geometry-corrected shifts from cyclohexanes indeed shows an improved correlation with respect to uncorrected cyclohexane values (Table 5), which is particularly noteworthy for the most geometry-sensitive γ-carbon shielding.

Configurational isomers

^{13}C-NMR spectra of several cyclopentanes bearing one or more substituents have been discussed already many years ago qualitatively on the basis of selected conformations.[16,17] The weaker substituent effects of a supposedly pseudoaxial methyl group in suitable dimethylcyclopentanes as compared to cyclohexanes with

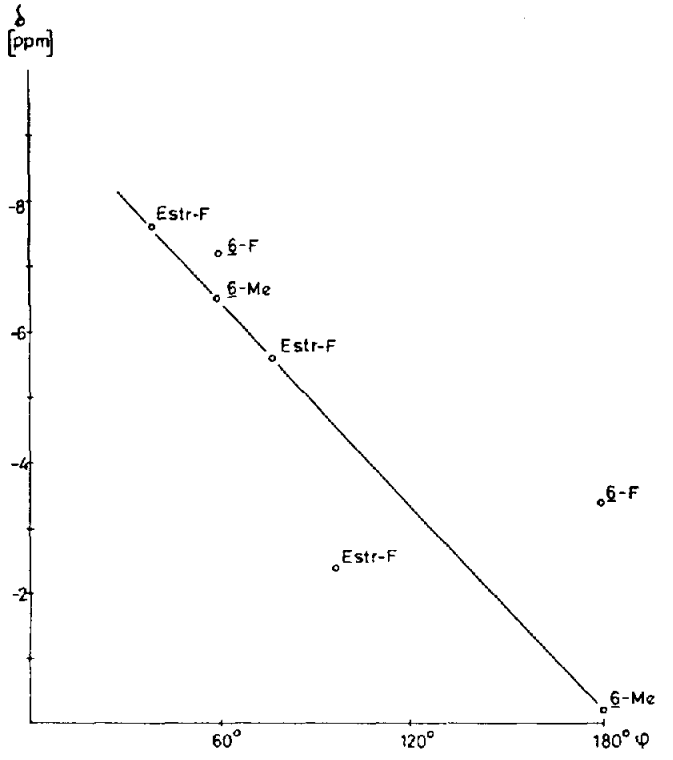


Fig. 4. Substituent induced ^{13}C-shielding effect on γ-carbon atoms as a function of the X-Cα-Cβ-Cγ^* torsional angle. 6-X: cyclohexanes, Estr-X: 17-X-estrenes {H.-J. Schneider, W. Gschwendtner and U. Buchheit, *J. Magn. Res.* **26**, 175 (1977)}.

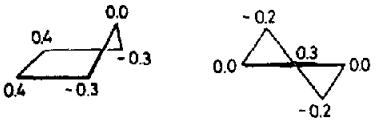
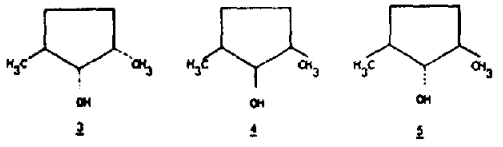


Fig. 5. ^{13}C-NMR shielding differences in cyclopentane as calculated by linear interpolation (see text).



2 4 5

1,3-disubstituted methylcyclopentanes (Tables 6, 7 and Ref. 16).

Almost all observed signal pairs of diastereotopic carbon atoms (82 out of 84, Tables 6 and 7) show significant shielding differences. This makes ^{13}C-NMR spectroscopy to an ideal method for the differentiation of stereoisomers which by other spectroscopic techniques may exhibit very little useful distinctions.[18] Moreover, the isomers can be measured in mixtures, as was usually done in the present work, where due to economical considerations the compounds where usually prepared from epimeric mixtures.

Configurational assignment for the stereo isomers will be possible, if regular shift differences Δ over a wide

Table 3. Torsional angles ϕ(°) in twist chair form of 2- and 3-Bromo-methyl-cyclopentanes (MM1 calculations)

Me	Br		1-2-3-4	1-5-4-3	2-1-5-4	2-3-4-5	3-2-1-5	2-3-4-Br	1-5-4-Br	1-2-3-Me	5-4-3-Me
4a	3e	cis-1.2-	33.5	33.1	12.5	41.3	13.0	76.8	86.3	163.7	170.0
4e	3e	trans-1.2-	35.5	35.1	12.5	43.7	14.5	166.1	157.7	160.4	167.4
										4-3-2-Me	5-1-2-Me
4e	2e	cis-1.3	36.3	35.3	12.5	44.5	14.9	166.8	157.3	162.4	140.4
3e	1i	trans-1.3	38.6	34.5	10.5	44.9	17.2	167.3	156.5	161.7	114.0

Table 4. ^{13}C-NMR shifts in monosubstituted cyclopentanes[a]

R	α	β	γ	C_R
F [b]	70.02	7.33	-3.00	
Cl [c]	36.3	12.0	-2.2	
Br [c]	27.6	12.9	-1.8	
I [c]	3.2	15.2	-0.6	
OH [d]	46.98	8.98	-2.80	
NH_2	26.99	9.96	-2.45	
Me [d]	9.3	9.3	-0.1	21.4
$CHMe_2$	21.92	4.55	-0.82	33.9 (CH), 21.7(CH_3)
CMe_3	24.78	0.99	-0.44	32.5 (qC), 27.6(CH_3)
CH_2OH	15.68	2.81	-0.96	67.01
CH_2OTs [e]	12.24	2.55	-1.22	74.29
COOH	17.50	3.66	-0.44	183.81
CN	1.51	4.96	-1.35	123.43
=O [f]	188.3	11.4	-3.3	
OCH_3	56.69	5.94	-2.42	56.03

a) α,β,γ: Substituent effects in (ppm) relative to R=H (25.50 ppm); C_R relative to TMS; 25-35% in $CDCl_3$ with 10% TMS, ambient temperature; b) $J_{^{19}F^{13}C}$: ^1J = 173.5 Hz, ^2J = 22.1 Hz, ^3J <1.5 Hz; Cf. K. Kanohta, Eisei Shikenjo Hokoku 90, 11 (1972); d) Cf. Ref. 16; e) CH_3: 21.58; arom. C: 144.75, 133.50, 129.93, 127.91; f) Cf. F.J. Weigert and J.D. Roberts, J.Am.Chem.Soc. 92, 1347 (1970).

axial substituents were attributed to the flattened five-membered ring leading to less strong nonbonded interactions. The force field calculations, however, clearly demonstrate, that all disubstituted epimers predominate in pseudo-equatorial forms, which is entirely in accordance with the negligible shift differences for the methyl carbon between all configurational isomers of range of compounds are visible, and if these variations are predictable within the framework of cyclopentane conformations and known structure shielding relations. These prerequisites are met in the 1,2-disubstituted cyclopentanes, which on the basis of the strain energies for the different methyl positions as given in Fig. 3 will predominate for the *cis*-epimer in the forms 1, 3e, 4e and

Table 5. Correlation of substituent effects on ^{13}C shifts of Cα, Cβ and Cγ[a] between cyclopentanes[b] and cyclohexanes[c]

		m		b		r	Ψ (%)
Cα	e	1.07 ±	0.02	0.56 ±	0.59	0.9988	5.6
	a	1.12 ±	0.08	1.13 ±	2.58	0.9765	24.1
	corr.	1.08 ±	0.03	1.19 ±	0.91	0.9970	8.6
Cβ	e	0.88 ±	0.06	1.54 ±	0.79	0.9788	22.9
	a	1.15 ±	0.12	2.55 ±	0.71	0.9525	34.1
	corr.	1.09 ±	0.08	1.37 ±	0.62	0.9757	24.5
Cγ	e	0.42 ±	0.16	1.28 ±	0.30	0.66	84
	a	0.36 ±	0.14	−0.36 ±	0.72	0.71	79
	corr.	0.56 ±	0.14	0.27 ±	0.40	0.81	66

a) Slope m, abscissa b, correlation coefficient r, probability index $\Psi = n(1-r^2)/(n-2)$; maximum $\Psi = 0\%$; $r = 1.00$; n number of value pairs; b) From table 4 c) Alternatively with equatorial or axial substituents, data from ref. 15.

2, 1i, 2e and therefore contain X-Ca-Cβ-Y arrangements with smaller torsional angles than the *trans*-epimer, which is largely populated in the forms 1, 1e, 2e or 2e, 3e and 2, 2e, 3e or 3e, 4e. Consequently, shielding of *cis* relative to *trans* is expected for the terminal atoms (e.g. for $X = CH_3$) and, to a lesser degree, for the central atoms Cα and Cβ, as usual in *gauche* as compared to *trans* butane-like fragments.[11] Indeed, we observe for all *cis*-1,2-compounds higher shifts at C2 (by 1 to 5 ppm), and, with the exception of 2-iodomethylcyclopentane, also at the terminal methyl carbon. A comparable attenuation of shielding effects in the sequence OH, CH_3, Cl, Br, J has been observed in cyclohexanes.[15] For the functional Cα there is even a change of sign for the *gauche-trans* difference in the sequence from F to J,[15] which again is in accord with the measurements in cyclopentanes (Table 7).

Whereas configurational assignments in the 1,2-series are straightforward, particularly with the aid of C2 signals, the differences between the 1,3 epimers are as expected much smaller and need quantitative consideration of all possible conformers and their geometries if safe predictions are to be made. As pointed out already, alkyl substituents are equatorial in all the epimers and therefore show almost no shift differences (Tables 6 and 7). There is a constantly higher shielding for the *trans* compound at C3, again indicative of stronger gauche interactions, but perusual of the values given in Figs. 3 and 5 does not as convincingly predict these differences as in the case of the 1,2-epimers.

Calculations of the shifts using the linear interpolation model described above were performed for disubstituted cyclopentanes on the basis of conformation 2, 3e, 5e (*cis*), and 2, 1i, 3e (*trans*), and reproduced most of the experimental shielding differences correctly. A full analysis would require extensive force field calculations and also should await the advent of more detailed structure-shielding relations. It is, however, noteworthy that even the shifts calculated on the restricted conformational basis using linear interpolation agree closely with the experimental values, not only for the *trans* 1,2/*cis* 1,3 series, but also the *cis* 1,2/*trans* 1,3 series (Figs. 6 and 7).

The configuration of the three trisubstituted cyclopentanes 3, 4 and 5 can be unambiguously deduced from their ^{13}C-NMR spectra. 4 and 5 have a plane of symmetry[19] and therefore show only four carbon signals, whereas 3 with C_2-symmetry exhibits six signals of the seven possible (Table 8).

For 4 and 5 the predominant conformation, again as deduced from the methyl SI values in Fig. 3, are 1, 1e, 2a, 3e or 2a, 3e, 4e and 2, 1i, 2e, 5a or 1i, 2e, 3a (epimer 4), and 1, 1e, 2e, 5e (epimer 5). Thus, 4 contains one (pseudo)axial substituent, which gives rise to upfield shifts as compared to 5 by up to 4 ppm (Table 7). This analysis proves the configurations of 3–5, which had been assumed previously[20] on the basis of selective reactions.

Synthetic routes and stereoselective reactions

Whereas all the monosubstituted compounds can be prepared by standard methods, it is often difficult to obtain stereoisomeric cyclopentanes in high purity.[2a] Since one can, however, take advantage of the possibility of estimating mixtures by ^{13}C-NMR (see above), it is sufficient to prepare either isomers differing in their ratio by at least ~60 : 40, or to measure two mixtures differing in their composition by ~10–20%, depending on the attainable signal to noise ratio.

As evident from the early work by Hückel *et al.*[21] 2-alkyl-cyclopentanols of either preferably *cis* or *trans* configuration are easily accessible by varying the method of ketone reduction. Nucleophilic attack with bulkier hydride transfer reagents as lithium aluminium hydride (LAH) and particularly trialkylborohydrides[22] ($Li(CH_3CH_2CHCH_3)_3$ BH, LSE) leads to early transition

Table 6. ^{13}C-NMR shifts of alkylcyclopentanols[a]

Cyclopentan-1-ol,-	C_1	C_2	C_3	C_4	C_5	C_R
1-Me	79.88	41.53	24.24	24.24	41.53	28.34
1-$CHMe_2$	85.21	38.21	24.18	24.18	38.21	CH:37.31, $(CH_3)_2$:17.94
1-CMe_3	87.14	35.22	26.63	26.63	35.22	-C-:36.72, $(CH_3)_2$:25.87
cis-2-$CHMe_2$	73.83	54.46	27.55	22.03	35.16	CH:28.21, $(CH_3)_2$:22.29
trans-2-$CHMe_2$	76.96	55.50	28.21	22.94	36.07	CH:30.81, $(CH_3)_2$:21.64
cis-3-$CHMe_2$	73.38	40.56	46.28	28.34	35.36	CH:33.99, $(CH_3)_2$:21.38
trans-2-$CHMe_2$	73.51	40.62	45.11	28.79	35.36	CH:33.67, $(CH_3)_3$:21.38
cis-2-CMe_3	74.81	56.28	23.33	21.54	35.74	-C-:33.65, $(CH_3)_3$:29.44
trans-2-CMe_3	74.81	59.40	27.55	23.91	37.17	-C-:31.91, $(CH_3)_3$:27.88

a) See footnote [a)] to Tabel 4, for methylcyclopentanoles see Table 7

Table 7. ^{13}C-NMR shifts of substituted methylcyclopentanes[a]

	C_1	C_2	C_3	C_4	C_5	CH_3	
cis-1-$CHMe_2$,2-Me	54.27	37.31	35.68	24.50	29.05	19.98	CH:30.87,$(CH_3)_2$:22.10
cis-1-$CHMe_2$,3-Me	46.40	38.67	35.36	33.67	29.90	20.70	CH:33.92,$(CH_3)_2$:21.58
tr.-1-$CHMe_2$,3-Me	48.49	40.82	34.77	34.12	29.90	20.7	CH:33.92,$(CH_3)_2$:21.58
cis-1-OH, 2-Me	75.91	39.78	30.81	22.10	34.51	13.71	
trans-1-OH, 2-Me	80.27	42.51	31.78	21.58	34.04	18.26	
cis-1-OH, 3-Me	73.70	44.32	33.08	32.36	35.55	21.18	
trans-1-OH,3-Me	73.70	44.46	31.97	32.69	35.42	20.79	
1-F, 1-Me	94.76	30.22	24.60	24.60	30.22	24.80	
1-Br, 1-Me	74.29	45.50	23.65	23.65	45.50	32.43	
cis-1-Cl,2-Me	68.89	40.68	30.09	21.70	36.59	15.79	
trans-1-Cl, 2-Me	66.88	45.22	31.71	21.83	35.94	18.13	
cis-1-Br, 2-Me	63.82	41.07	30.28	21.90	37.37	17.93	
trans-1-Br,2-Me	57.84	45.04	31.78	22.48	36.85	18.26	
cis-1-J, 2-Me	38.80	45.40	30.60	22.16	41.10	21.60	
trans-1-J, 2-Me	34.18	46.53	31.45	23.79	39.19	18.39	
cis-1-Cl, 3-Me	61.94	45.82	33.34	31.78	37.04	20.47	
trans-1-Cl, 3-Me	60.18	45.69	32.48	32.30	37.30	20.47	
cis-1-Br, 3-Me	50.30	46.60	33.73	32.80	38.02	21.18	
trans-1-Br,3-Me	52.97	46.60	32.56	32.04	37.82	20.47	
cis-1-J, 3-Me	23.65	48.48	34.31	33.40	39.64	20.79	
trans-1-J, 3-Me	27.68	48.22	33.49	33.14	39.90	20.40	

a) See footnote to table 4; shifts of the methylcyclopentanols agree with ref. [6] within ± 0.1 ppm (for functional C ± 0.3 ppm) if δ_{TMS} = 193.7 ppm; b) ^{13}C-^{19}F coupling constants (Hz); ^1J 170.6, ^2J 23.5 (27.9 to CH_3), ^3J < 3.0.

states, or to steric approach control in the terminology of Dauben,[23] and thus to 2-alkylcyclopentanoles containing up to > 99% of the *cis* epimer (see Experimental, reduction of 2-tert-butycyclopentanone etc.). Brown *et al.* report up to 94% *cis* alcohol from the reduction of 2-methylcyclopentanone.[24]

Reductions of 3-alkylcyclopentanones proceed with less stereoselectivity,[25] as to be expected in the absence of a alkyl group vicinal to carbonyl, which provides for the differential steric hindrance. The force field calculations yielded 2, 1-oxo as the most stable conformation (see Fig. 2), in which the accessibility from both sides of the oxo-group is exactly the same if no other substituent in the neighbourhood makes the two sides non-equivalent. Thus, even reduction of 3-methyl cyclopentanone with the usually very selective LSE-borohydride leads to a mixture containing 60 : 40 *cis* : *trans* alcohols.

Isomeric halides of well defined configuration could be prepared by the reaction of tosylates with magnesium iodide,[26] bromide[26] and chloride, which proceeds with 3-alkylcyclopentylsulfonates under clean inversion, as it was observed already by the earlier workers[26] with cyclohexane derivatives. The 2-alkyl cyclopentyltosylates by 1,2-hydride shift yielded substantial amounts of the tertiary halides, which, however, could be identified by comparison with authentic material.

EXPERIMENTAL SECTION AND COMPUTATIONAL DETAILS

^{13}C-NMR Spectra were recorded at 22.63 MHz in PFT mode with 0.68 sec aquisition time, no pulse delay, internal ^{2}H lock ($CDCl_3$) and ^{1}H noise decoupling under conditions given in Table 4. ^{13}C-NMR signal assignments were based on symmetry considerations, off-resonance decoupling experiments and shift correlations to substituted cyclohexanes.

Force field calculations were carried out using Allinger's MM1[5] program on the Telefunken computer TR 440 and MM2[7] on the Siemens 7760 of the Rechenzentrum der Universität des Saarlandes. The structures were usually energy minimized until the strain changed by < 1.5 cal/mol. The methyl- and oxo-cyclopentane conformations were obtained by minimization with structures having fixed C2-C3-C4-C5 torsional angles given in Figs. 1 and 2.

Alkylcyclopentanols were obtained as described in the literature[21,25] using standard reduction procedures of the ketones with lithium-aluminium hydride (LAH) and lithium tri-sec-butyl borohydride[22] (LSE). Application of lower temperatures was often sufficient to make the reduction enough stereoselective, as with 3-methylcyclopentanone and LAH, yielding at −70° 70% *cis*-product, instead of 60% *cis* alcohol at room temperature. LSE reaction on (a) 3-methyl, (b) 2-t-butyl, (c) *cis*-2,5-dimethyl

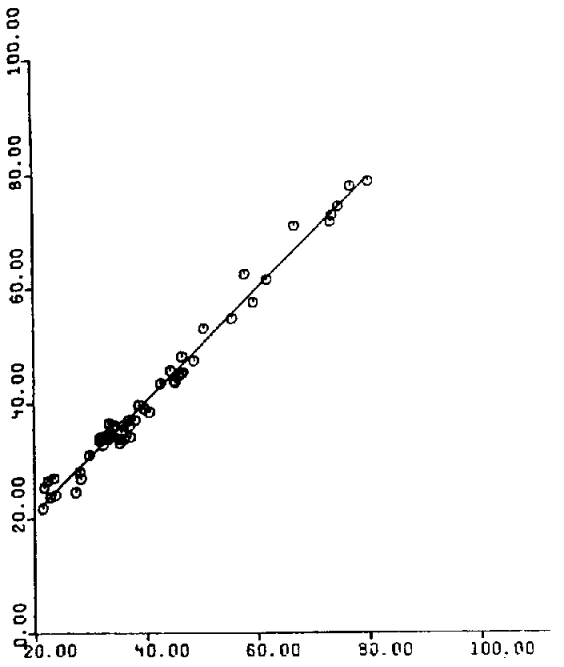


Fig. 6. Observed ^{13}C-NMR shifts in disubstituted cyclopentanes (without iodo derivatives, Tables 6 and 7) compared with shifts as calculated by the linear interpolation method (see text); *trans*-1,2- and *cis* 1,3-compounds: m = 0.979 ± 0.017, b = 1.08 ± 0.73, r = 0.992, Ψ = 12.7% (m, b, r, Ψ: see footnote to Table 5); standard deviation s = ± 1.84 ppm.

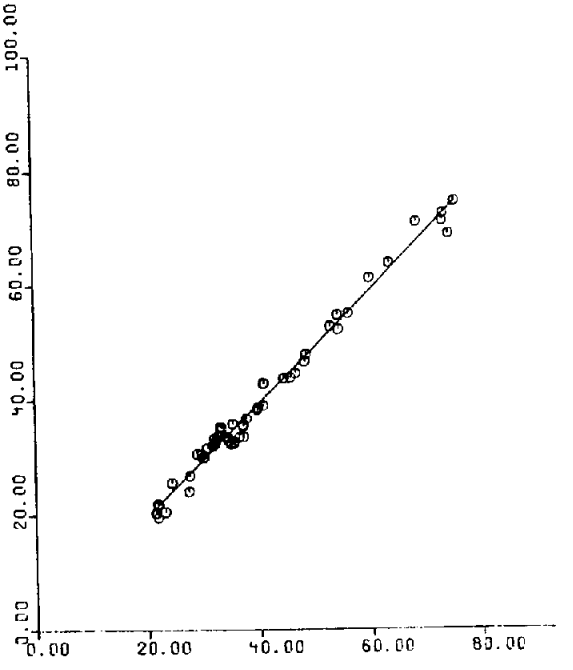


Fig. 7. Observed vs calculated shifts for *cis*-1,2- and *trans*-1,3 disubstituted cyclopentanes; m = 0.985 ± 0.016, b = 0.26 ± 0.68, r = 0.993, Ψ = 12.0%, s = 1.60 ppm (for explanations see Fig. 6).

cyclopentanone led to (a) 60 (b) > 99, (c) 95% *cis* hydroxy compound, respectively, as compared to (a) 60, (b) 58, (c) 24% *cis* with LAH at ambient temperature (^{13}C-NMR analysis, ± 2%).

2,5-Dimethylcyclopentanones were prepared from cyclopentanone dimethyl-hydrazone with methyliodide using the method described by Corey and Enders[27] for the preparation of *trans*-2,6-dimethylcyclohexanone. The first methylation product ($b.p._{17}$ 62–3°) was obtained in 75% yield, the second ($b.p._{15}$ 65–6°) in 70% yield. The 2,5-dimethyl cyclopentanone dimethylhydrazone (*cis* : *trans* = 50 : 50, by ^{13}C-NMR) was not formed stereoselectively as in the case of cyclohexanone.[27] Hydrolysis with 10% aqueous HCl yielded the epimeric ketone mixture (50 : 50), $b.p._{60}$ 95°, 55%.

2-t-Butylcyclopentanone was prepared from trimethyl silyloxy cyclopentene ($b.p._{20}$ 60°, 61%) with t-butyl chloride as an oil ($b.p._{22}$ 80–1°, 50%) using the procedure as given by Reetz and Maier.[28]

General procedure for the preparation of epimeric alkylcyclopentylhalides[26]

1,2-Dibromoethane (0.04 mol) in 10 ml ether was added with cooling to 2 g magnesium in 70 ml ether. The mixture was refluxed for 5 h, removed from excess magnesium, and added to 0.02 mol of the cyclopentyl tosylate (epimeric mixtures) in 40 ml ether, refluxed for 1 h, hydrolyzed with 100 ml water, and extracted with 3 × 50 ml ether. After neutralization and drying the ether was removed *in vacuo* and the residue subjected to NMR analysis without further purification. The ratio of isomers (by ^{13}C-NMR) always indicated complete inversion.

Table 8. ^{13}C-NMR shifts of 2,5-dimethylcyclopentanoles[a]

		C1	C2	C3	C4	C5	CH_3
3	1-r,2-trans, 5-cis exp.	86.90	41.86	29.51	29.51	41.80	18.39
	calc.[b]	84.16	41.90	32.02	32.02	41.90	
4	1-r,2-cis, 5-cis exp.	78.90	40.17	30.55	30.55	40.17	14.56
	calc.[b]	79.62	39.54	29.13	29.13	39.54	
5	1-r,2-trans,5-trans exp.	82.15	41.27	30.94	30.94	37.37	19.50,14.17
	calc.[b]	81.07	39.78	29.93	29.93	39.78	

a) See footnote to table 4; b) Shifts calculated as described in the text on the basis of conformation 2 (C), 1i-OH, 2e-Me, 5e-Me for 3; 1 (E) 1a-OH, 2e-Me, 5e-Me for 4; and 1 (E), 1e-OH, 2e-Me, 5e-Me for 5.

Table 9. ^{13}C-NMR shielding constants for various cyclopentane derivatives[a]

		C1	C2	C3	C4	C5	other
2-Methyl,1-tosyloxy[b]	cis	88.13	39.32	30.87*	21.89	32.56*	13.91 (CH_3)
2-Methyl,1-tosyloxy[b]	trans	90.34	40.36	31.20*	21.97	31.65*	17.68 (CH_3)
3-Methyl,1-tosyloxy[b]	cis	84.82	41.27	78.64	32.11*	33.21*	21.58 (CH_3)
3-Methyl,1-tosyloxy[b]	trans	85.60	41.92	x	32.76*	32.95*	20.60 (CH_3)
3-Isopropyl, 1-oxo		218.97	44.85	47.74	27.95	39.13	33.80 (CH), 21.38 (CH_3) 20.47 (CH_3)
2-t-Butyl, 1-oxo		219.70	58.04	26.45	20.27	40.23	32.50 (qC), 27.75 (CH_3)
Cyclopentene, 1-$OSiMe_3$		155.14	102.04	28.86*	21.45	33.60*	0.0 (CH_3)

a) See footnote to table 4; signals marked * etc. are interchangeable. x: signal not detected;

b) OTs-signals: C1' 144.45, Co 129.80, Cm 127.75, Cp 134.70, CH_3 21.52, within ± 0.2 ppm identical for all tosylates).

Table A. ^{13}C-NMR shift differences Δ between epimeric cyclopentanes[a]

	C1	C2	C3	C4	C5	Me,other
1-Me, 2-Me[b]	5.1	(5.1)	2.2	0.1	(2.2)	3.6
1-OH, 2-Me	2.7	4.3	1.0	-0.5	-0.5	4.6
1-Cl, 2-Me	-2.0	4.3	1.6	0.1	-0.7	2.3
1-Br, 2-Me	-6.0	4.0	1.5	0.6	-0.6	0.4
1-J , 2-Me	-4.6	1.1	0.9	1.6	-1.9	-3.2
1-OH, 2-$CHMe_2$	3.1	1.1	0.7	0.9	0.9	CH 2.6, Me-0.7
1-OH, 2-CMe_3	0.0	3.1	4.2	2.4	1.4	Cq -1.7, Me-1.5
1-Me, 3-Me[b]	1.9	1.9	(1.9)	-0.9	(-0.9)	-0.3
1-$CHMe_2$, 3-Me	-2.1	-2.1	0.6	-0.4	0.0	CH,Me: 0.0
1-OH, 3-Me	0.0	-0.14	1.1	-0.3	0.1	0.5
1-Cl, 3-Me	1.7	0.1	0.8	-0.5	-0.3	0.0
1-Br, 3-Me	-2.7	0.0	1.1	0.8	0.2	0.7
1-J , 3-Me	-4.0	0.3	0.8	0.3	-0.3	-0.3
1-OH, 3-$CHMe_2$	-0.1	-0.1	1.2	-0.4	0.0	CH:0.3, Me:0.0

a) For 1,2-substituted compounds Δ=δ (trans) - δ (cis), for 1,3-substituted compounds Δ= δ (cis) - δ (trans).

b) Shifts from ref. 16.

REFERENCES AND NOTES

[1]Part 30. Stereochemical and ^{13}C-NMR Investigations. For Part 29 see H.-J. Schneider and Nghe Nguyen-Ba, *Org. Magn. Res.* **18**, 38 (1982).

[2a]B. Fuchs, in *Top. Stereochem.* (Edited by E. L. Eliel and N. L. Allinger) **10**, 1 (1978); see also [b]A. C. Legon, *Chem. Rev.* **80**, 231 (1980).

[3a]D. Cremer and J. A. Pople, *J. Am. Chem. Soc.* **97**, 1358 (1975); [b]D. Cremer, J. S. Binkley and J. A. Pople, *Ibid.* **98**, 6836 (1976).

[4]N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski and F. A. Van-Catledge, *Ibid.* **90**, 1199 (1968).

[5]R. C. Lugar, Ph.D. Thesis, University of Pennsylvania 1970; F. V. Brutcher, Jr., and R. C. Lugar, Abstracts of the 160th ACS Meeting 153, September 1970, as cited in Ref. 2a.

[6]See e.g. U. Burkert and N. L. Allinger, *J. Comput. Chem.* in press; H.-J. Schneider, W. Gschwendtner and E. F. Weigand, *J. Am. Chem. Soc.* **101**, 7195 (1979).

[7]N. L. Allinger, *Ibid.* **99**, 8127 (1977). We obtain SI = 8.11 kcal/mol for both **1** and **2**.

[8]See e.g. H.-J. Schneider, *Liebigs Ann. Chem.* **761**, 150 (1972).

[9]The strain energy differences obtained in some earlier force field calculations are likely to be exaggerated since no full relaxation of all internal coordinates as bond lengths or HCH bond angles was allowed for; see e.g. J. B. Hendrickson, *J. Am. Chem. Soc.* **83**, 4537 (1961); C. Ouannes and J. Jacques, *Bull. Soc. Chim. France* 3601 (1965).

[10a]See e.g. W. Hückel and M. Hanack, *Liebigs Ann. Chem.* **616**, 18 (1958); [b]W. Hückel and R. Bross, *Ibid.* **685**, 118 (1965), and Refs. cited therein.

[11]N. K. Wilson and J. B. Stothers, *Top. Stereochem.* (Edited by E. L. Eliel and N. L. Allinger) **8**, 1 (1974).

[12]See H.-J. Schneider and W. Freitag, *Isr. J. Chem.* **20**, 153 (1980), and Refs. cited therein.

[13]See H. Beierbeck and J. K. Saunders, *Can. J. Chem.* **58**, 1258 (1979); H. Beierbeck, J. K. Saunders and J. W. Apsimon, *Ibid.* **55**, 2813 (1977); and Refs. cited therein.

[14]K. D. Dalling and D. M. Grant, *J. Am. Chem. Soc.* **96**, 1827 (1974).

[15]See H.-J. Schneider and V. Hoppen, *J. Org. Chem.* **43**, 3866 (1978).

[16]M. Christl, H. J. Reich and J. D. Roberts, *J. Am. Chem. Soc.* **93**, 3463 (1971).

[17]J. B. Stothers and C. T. Tan, *Can J. Chem.* **52**, 308 (1974). See also: R. G. S. Ritchie, N. Cyr, B. Korsch, H. J. Koch and A. S. Perlin, *Can. J. Chem.* **53**, 1424 (1975).

[18]See e.g. H.-J. Schneider and D. Heiske, *J. Am. Chem. Soc.* **103**, 3501 (1981).

[19]See H.-J. Schneider and M. Lonsdorfer, *Org. Magn. Res.* **16**, 133 (1981) for a similar assignment of acyclic diastereomers.

[20]Min-Hon-Rei, *J. Org. Chem.* **43**, 2173 (1978).

[21]W. Hückel and G. Näher, *Chem. Ber.* **91**, 792 (1958).

[22]H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.* **94**, 7159 (1972).

[23]For reviews see H. O. House, *Modern Synthetic Reactions*, p.

54. Benjamin, Menlo Park, California (1972); For recent references see: E. C. Ashby and J. R. Boone, *J. Org. Chem.* **41**, 2890 (1976); E. C. Ashby and J. T. Laemmle, *Chem. Rev.* **75**, 521 (1975); D. C. Wigfield, *Tetrahedron* **35**, 449 (1979).
[24]H. C. Brown and V. Varma, *J. Org. Chem.* **39**, 1631 (1974).
[25a]W. Hückel and R. Bross, *Liebigs Ann. Chem.* **664**, 1 (1963); [b]R. G. Haber and B. Fuchs, *Tetrahedron Letters* 1447 (1966).
[26]P. Place, M.-L. Roumestant and J. Gore, *Bull. Soc. Chim. France* 169 (1976).
[27]E. J. Corey and D. Enders, *Chem. Ber.* **111**, 1337 (1978).
[28]M. T. Reetz and W. F. Maier, *Angew. Chem.* **90**, 50 (1978).