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CHAIR-BOAT EQUILIBRIA IN BICYCLO[3.3.1]NONANE AND SOME 3- AND 3,7-SUBSTITUTED DERIVATIVES; THERMODYNAMIC PARAMETERS AND GEOMETRY OF THE CONFORMERS AS OBTAINED BY MOLECULAR MECHANICS

J. A. PETERS,* J. M. A. BAAS, B. VAN DE GRAAF, J. M. VAN DER TOORN
and H. VAN BEKKUM
Laboratory of Organic Chemistry, Delft University of Technology, Julianalaan 136, Delft, The Netherlands

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Abstract—ΔG-Values for conformational equilibria in 3,7-substituted bicyclo[3.3.1]nonanes have been obtained by means of epimerisation experiments (**cc** $\rightleftharpoons$ **bc**) and by variable temperature ^{13}C NMR (**bc** $\rightleftharpoons$ **bb**). The results of these experiments fit well with those of molecular mechanics using the Schleyer force field. In bicyclo[3.3.1]nonane and 3β-substituted derivatives the **cc** conformation predominates; however, the bulky 3β-substituent *t*-butyl, is found to have a destabilizing effect. A 3α-substituent forces the substituted wing into the boat conformation. For the 3α,7α-substituted derivatives the conformational preferences depend on the size of the substituents: for 3α-methyl-7α-*t*-butylbicyclo[3.3.1]nonane the **cb** and **t-bb** conformers are of approximately equal enthalpy. The geometries, obtained by the calculations, show that the conformers of bicyclo[3.3.1]nonane (**cc**, **bc** and **t-bb**) are all distinctly flattened. The boat wings of **bc** conformers are not twisted to any extent. The **t-bb** is the most stable **bb** conformation. The influence of substitution at positions 3 or 7 is discussed in detail; in general, a bulky substituent, such as *t*-butyl, affects the geometry of both wings of the ring system. The calculated geometries are in good agreement with the conclusions of previous ^{1}H NMR investigations.

INTRODUCTION

For the bicyclo[3.3.1]nonane system three groups of conformations should be envisaged: (i) the rigid double chair (**cc**), (ii) the rigid chair-boats (**bc** and **cb**) and (iii) the double boats (**bb**) ranging from the eclipsed double boat (**e-bb**) to the double twist-boats (**t-bb**).[1,2] Previously, with the aid of ^{1}H and ^{13}C NMR spectroscopy,[3,4] we have shown that substituents at the 3- and 7-positions govern the conformation of these compounds. In 3β- and/or 7β-substituted systems the **cc** conformation predominates, whereas a substituent at the 3α- or 7α-position forces the ring involved into the boat conformation. When both the 3α- and 7α-positions are substituted, the conformational preference (**bc** $\rightleftharpoons$ **bb** $\rightleftharpoons$ **cb**) strongly depends on the size of the substituents. From vicinal proton–proton coupling constants of 3,7-substituted bicyclo[3.3.1]nonanes it was concluded that in these compounds both the chair and the boat wings of the **cc**, **bc** and **cb** conformers are flattened.

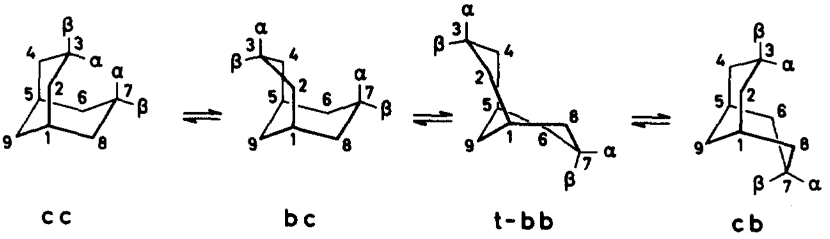
However, alternative explanations for the magnitudes of the coupling constants cannot be excluded completely. For example, instead of flattening of the boat part in **cb** and **bc** conformers, some twisting or contributions of other conformers could also explain the coupling constants observed. Moreover, the interpretation of coupling constants is based on the assumption that an ideal tetrahedral geometry exists around the carbon atoms.

The aim of the present investigation was to establish the conformation of 3,7-substituted bicyclo[3.3.1]nonanes with exclusion of the ambiguities cited above. Therefore, accurate geometries as well as thermodynamic parameters are required. In the present paper three approaches are used, namely epimerisation experiments, ^{13}C variable temperature experiments, and empirical force field calculations.

ΔG-values for **cc**/**bc** equilibria of 3(7)α-alkylbicyclo[3.3.1]nonanes have been obtained from epimerisation experiments with the corresponding 3-CO_2Me derivatives. A comparison is made with literature data.

So far no ΔG- or ΔH-values for **bc**/**bb** equilibria have been reported. Previously, it was shown that the chemical shifts in ^{13}C NMR spectra are rather sensitive to the conformation.[4,5] Therefore, ^{13}C NMR spectroscopy at variable temperature may be a useful technique for the determination of thermodynamic parameters of **bc**/**bb** equilibria. A prerequisite is that the absolute ΔG-values are not too large. For the study of the **cb**/**bb** equilibrium some 3α,7α-substituted bicyclo[3.3.1]nonanes, in which both the **cb** and the **bb** conformers are populated to a reasonable extent, were selected.

Empirical force field calculations may be an attractive approach to obtain thermodynamic parameters as well as geometries. Though calculations on bicyclo[3.3.1]nonane and some of its derivatives have been performed,[6–8] a



systematical study of 3,7-substituted systems is not available. In this paper the results of calculations on bicyclo[3.3.1]nonane and a number of its 3- and 7-alkyl substituted derivatives are presented and discussed. The calculated geometries are compared with experimental data.[1]

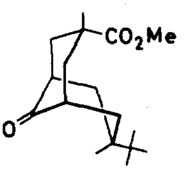
EPIMERISATION EXPERIMENTS

It has been suggested that the ΔG-value for the epimerisation equilibrium of methyl bicyclo[3.3.1]nonane-3-carboxylates reasonably represents the difference in free enthalpy between the **cc** and **bc** conformations of bicyclo[3.3.1]nonane.[9] Since the ΔG-value 3α/3β-hydroxybicyclo[3.3.1]nonane is about the same, it was assumed that the influence of substituents at the 3α-position on the energy of the **bc** conformation is close to that of 3β-substituents on the energy of the **cc** conformation.[10]

We have extended the above series of ΔG-values for epimerisation with data on the methyl 7β-*t*-butylbicyclo[3.3.1]nonane-3-carboxylates and the corresponding 9-oxo derivatives (see Table 1). By this choice of substituents the intercomparison of the results of the epimerisation experiments, the ^{13}C NMR measurements and the force field calculations is facilitated. The magnitudes of the ΔG-values for the 7β-*t*-butylderivatives (**2, 4**) are distinctly lower than those of the other compounds. Apparently the *t*-butyl group exerts a destabilizing effect on the **cc** conformation (exceeding any effect of this kind on the **bc** conformation).

In the oxo system the effect of a 7β-*t*-butyl group is less pronounced; we suggest that both the **cc** and the **bc** conformation are destabilized by the *t*-butyl group. In the **bc** conformation a decrease of flattening of the boat wing—bringing $H_{2\alpha}$ and $H_{4\alpha}$ closer together—is opposed by the tendency of the *t*-butyl group to bring about puckering at C_7 (see later).

^{13}C NMR MEASUREMENTS



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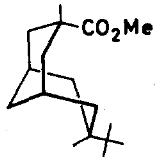

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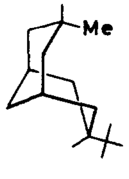

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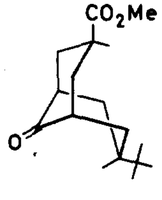

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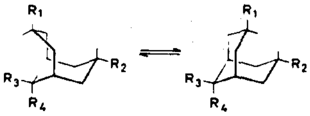
For the ^{13}C NMR spectroscopic studies at variable temperatures some 7α-*t*-butylbicyclo[3.3.1]nonanes (**5**–**7**) were selected. In these compounds the bulky 7α-*t*-butyl group fixes the ring involved in the boat conformation. The other ring may adopt the chair as well as the boat conformation. The population of the **cb** and **bb** conformers will depend on the temperature.

In order to correct the ^{13}C chemical shifts of compounds **5**–**7** for temperature influences, which are not caused by changes in conformational populations, spectra of compound **8** were measured at variable temperature. For this conformationally homogeneous compound the temperature dependencies of the chemical shifts were linear and small (0.004 ppm/°C).[11] These temperature influences were used to correct the chemical shifts of the corresponding carbon atoms in compounds **5**–**7**. Then, it appeared that, in particular, the ^{13}C chemical shifts of C_3, C_6 and C_9 of compounds **5** and **6** are strongly dependent on temperature (in a non-linear way), whereas the ^{13}C chemical shifts for compound **7** are rather independent on the temperature. We assume that the corrected temperature influences are due to shifts in the **cb**/**bb** equilibria of **5**–**7**. Then, these equilibria can be analyzed by relation (1), where δ_T is the corrected ^{13}C chemical shift measured at temperature T, δ_{cb} is the chemical shift of the carbon atom under consideration in

Table 1. ΔG-values for epimerisation of 3-substituted bicyclo[3.3.1]nonanes at 25° in CH_3OH solution



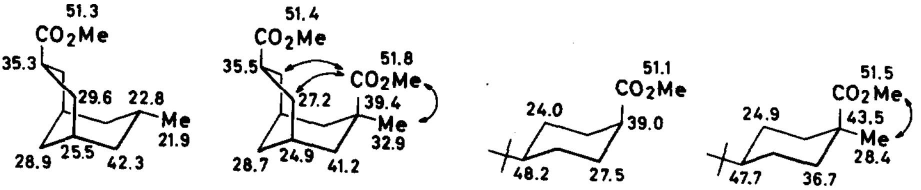
Nr	Substituents	ΔG kcal/mole[a]	ref.
1	$R_1=CO_2Me$; $R_2,R_3,R_4=H$	-2.7	9
2	$R_1=CO_2Me$; $R_2=t\text{-}Bu$; $R_3,R_4=H$	-1.3	b
3	$R_1=CO_2Me$; $R_2=H$; $R_3/R_4=O$	-1.6	b
4	$R_1=CO_2Me$; $R_2=t\text{-}Bu$; $R_3/R_4=O$	-1.1	b

[a] ± 0.2 kcal/mole; the equilibrium was approached from both sides; [b] this work

the **cb** conformation and δ_{bb} its chemical shift in the **bb** conformation.

$$-\ln\frac{\delta_T-\delta_{cb}}{\delta_{bb}-\delta_T}=\frac{\Delta H}{RT}-\frac{\Delta S}{R}. \qquad (1)$$

The value of δ_{bb} was estimated by adding substituent effects to the chemical shift of the carbon atom in the **bb** conformation of bicyclo[3.3.1]nonane.[4] An analogous procedure seems not to be allowed for δ_{cb}. A substituent at the 3α-position of the chair wing experiences strong non-bonding interactions from $H_{6\alpha}$ and $H_{8\alpha}$, which might be reflected in the chemical shifts, in particular of C_3 and $C_{6/8}$. Therefore increments, obtained from a study of the model compound **10** and some related compounds (**9**, **11**, **12**), were added to the initial approximations of δ_{cb} for C_3 and $C_{6/8}$.



9 **10** **11** **12**

Fig. 1. ^{13}C Chemical shifts of some model compounds[a] (in $CDCl_3$ solution).

The approximations of δ_{cb} and δ_{bb} were used as starting parameters in a non-linear regression procedure, by which the experimental ^{13}C chemical shift data of C_3 and C_6 were fitted to relation (1). The ΔH- and ΔS-values obtained are given in Table 2. The limiting δ_{cb} and δ_{bb} values obtained for C_3 and C_6 of compounds **5** and **6** (see Table 3) were close to the original estimates (within 0.5 ppm).

The ΔH-value of the **cb**/**bb** equilibrium in compound **5** matches the conclusions reached from previous ^{1}H NMR and IR studies and from the pK_a^* of the corresponding carboxylic acid.[3] The same ΔH-value was estimated on the basis of an enthalpy difference between the **bb** and the **cb** conformation of bicyclo[3.3.1]nonane of 5.7 kcal/mole.[3] The difference in ΔH-values between compounds **5** and **6** may be due to a difference in 7,9-interaction in these compounds. The relatively low ΔH-value of the **cb**/**bb** equilibrium in compound **7** may be explained by the somewhat higher steric requirements of a Me group compared with a CO_2Me group. This will have a relative destabilizing effect on the **cb** conformation of compound **7**.

CALCULATED THERMODYNAMIC PARAMETERS

Empirical force field calculations on bicyclo[3.3.1]nonane (**13**), on its 3α- and 3β-methyl and *t*-butyl derivatives (**14**–**17**), and on the four 3-methyl-7-*t*-

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[a] The assignment of some signals of the carboxylic acids corresponding to compounds **10** and **12** in Ref. 1 (numbered as **4c** and **2b** respectively) should be revised.

Table 2. ΔH- and ΔS-values for **cb** ⇄ **bb** equilibria in some bicyclo[3.3.1]nonane derivatives obtained from variable temperature ^{13}C NMR

Compound	ΔH kcal/mole	ΔS cal. K^{-1} mole^{-1}
5	1.0 ± 0.1	2.4 ± 0.2
6	1.8 ± 0.2	3.9 ± 1
7	0.0 ± 0.5	1 ± 2

Table 3. ^{13}C chemical shifts (δ_{cb} and δ_{bb}) in ppm in CD_2Cl_2 solution at 34°, obtained from variable temperature measurements

	Compound 5		Compound 6		Compound 7[a]	
	C_3	C_6	C_3	C_6	C_3	C_6
δ_{cb}	32.1	29.2	32.8	26.0	21.7	39.1
δ_{bb}	38.3	35.2	37.4	33.1	26.3	40.6

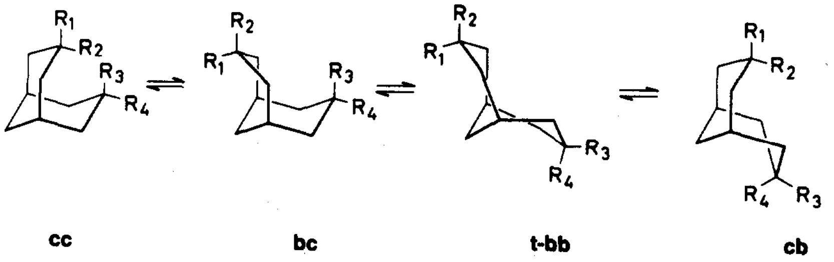
[a] Original estimates. Since ΔH and ΔS are about zero, the calculations were rather insensitive to variations of chemical shifts.

butyl-bicyclo[3.3.1]nonane isomers (**18–21**) were performed using the "Schleyer 1973" force field.[6][b] The strain energies obtained are given in Table 4. The results for the unsubstituted system (**13**) are identical with those reported by Schleyer *et al.*[6]

The calculations confirm the conclusions obtained from earlier experimental data.[1] Bicyclo[3.3.1]nonane (**13**) as well as its 3β- (and 3β,7β-) derivatives (**14**, **15**, **18**) occur predominantly in the **cc** conformation. A 3β-*t*-butyl group has a small destabilizing effect on this conformation. In the 3α- (and 3α,7β- or 3β,7α-) substituted derivatives (**16**, **17**, **19**, **21**) the **bc** conformation predominates; the contribution of the **bb** conformation can be ignored. The situation in 3α,7α-substituted compounds will be somewhat more complex. From Table 4 it can be deduced that the conformational enthalpy for the **cb**/**bb** equilibrium in the 3α-Me,7α-*t*-Bu derivative (**20**) is only 0.72 kcal/mole: the **cb** and the **bb** conformer contribute to a reasonable extent to the equilibrium. We anticipate that with bulky substituents at both the 3α- and 7α-positions the **t-bb** conformation will predominate, whereas with a small substituent at one of the positions mentioned and a bulky one at the other the **cb** (**bc**) conformation will predominate. The large contribution of the identical **cb** and **bc** conformers to the conformational equilibrium of the 3α,7α-di-CO_2Me substituted derivative, which was previously demonstrated,[1] can be rationalized with these data too.

NMR data[1] were not conclusive with respect to the question whether the **bb** conformation in bicyclo[3.3.1]nonanes is twisted or not. The calculations showed that for compounds **13**, **14**, **17** and **20** the double-twist boat (**t-bb**) is the most stable **bb** conformation. The strain energy of this conformation was 3–5 kcal/mole lower than that of the **e-bb** conformation.[c]

Since the steric requirements of a methyl and a carboxymethyl group are roughly of the same order of magnitude, it may be assumed that the influence of these groups on the strain energy is about the same. Therefore a comparison between the ΔG- and ΔH-values, obtained



13: R_1, R_2, R_3, R_4 = H
14: R_1 = Me; R_2, R_3, R_4 = H
15: R_1 = t-Bu; R_2, R_3, R_4 = H
16: R_2 = Me; R_1, R_3, R_4 = H
17: R_2 = t-Bu; R_1, R_3, R_4 = H

18: R_1 = Me; R_4 = t-Bu; R_2, R_3 = H
19: R_2 = Me; R_4 = t-Bu; R_1, R_3 = H
20: R_2 = Me; R_3 = t-Bu; R_1, R_4 = H
21: R_1 = Me; R_3 = t-Bu; R_2, R_4 = H

Table 4. Strain energies of some bicyclo[3.3.1]nonane derivatives (kcal/mole)

Nr	Substituents				Strain energies (kcal/mole)				
	3α	3β	7α	7β	cc	bc	t-bb	cb	e-bb[a]
13	H	H	H	H	9.59	12.08	17.82	12.08	20.27
14	H	Me	H	H	9.13	16.56	19.76	11.45	25.00
15	H	t-Bu	H	H	13.54			15.75	
16	Me	H	H	H		11.42	17.15	16.23	
17	t-Bu	H	H	H		15.71	21.07		24.22
18	H	Me	H	t-Bu	13.11				
19	Me	H	H	t-Bu		15.03			
20	Me	H	t-Bu	H			20.35	19.63	23.61
21	H	Me	t-Bu	H				14.99	

[a] This is a saddle-point, as follows from the calculation of the eigenvalues of the final force constant matrix

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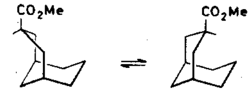
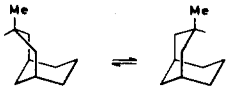
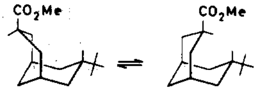
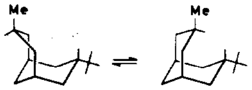
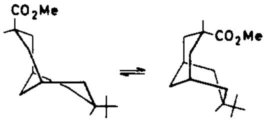
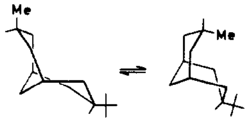
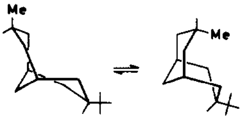
[b] All calculations were also performed with the "Allinger 1971" force field.[7] The trends in the results of these calculations are in agreement with those obtained with the "Schleyer 1973" force field. In general the agreement between experimental data and calculations is better with the latter force field.

[c] The **e-bb** conformation is not an energy minimum, but a saddle-point, as follows from the calculation of the eigenvalues of the final force constant matrix. This conformation is the transition-state between the two **t-bb** conformers.[17]

from the epimerisation and the ^{13}C NMR experiments, with conformational energies of related compounds as calculated from Table 4, seems of interest. Table 5 shows that a good agreement exists between these data.

From Table 4 strain energy increments for a methyl and a *t*-butyl group at position 3 or 7 for different conformations can be derived (see Table 6). The increments for the cc and t-bb conformations parallel those for the corresponding conformations in cyclohexane,[12] indicating that here analogous interactions are responsible for these increments. Remarkably, the magnitudes of the increments for the 3α- (boat wing) and 7β-substituents (chair wing) for the bc conformation are about the same. As will be shown later on, the effects of introduction of a 3α-substituent resemble those of introduction of a 7β-substituent.

Table 5. ΔG, ΔH, and ΔS values for chair-boat equilibria in some bicyclo[3.3.1]nonanes at 25°; a comparison between experimental and calculated values

Experimental values	ΔG^b	ΔH^b	ΔS^c	Calculated values^a	ΔG^b	ΔH^b	ΔS^c
	-2.7^d				-2.4	-2.3	$+0.5$
	-1.3^d				-2.3	-1.9	$+1.3$
	-0.6^e	-1.8	-3.9				
	$+0.3^e$	0.0	-1.0		-0.1	-0.7	-1.8

[a] from force field calculations; [b] kcal/mole; [c] cal. k^{-1} mole^{-1}; [d] from epimerisation experiments; [e] from ^{13}C NMR at variable temperature

Table 6. Mean strain energy differences due to alkyl substitution (kcal/mole)[a]

Bicyclo[3.3.1]nonanes

substitutent	cc	bc	t-bb	cb
3β-Me	-0.45	4.48	1.94	-0.68
3α-Me		-0.46	-0.70	4.08
3β-t-Bu	3.97			3.64
3α-t-Bu		3.52	3.23	

Cyclohexanes[b]

substituent	chair	twist-boat
equatorial Me	-0.56	
"equatorial" t-Bu	3.99	3.26

[a] Cf. Ref 12; [b] ref 14

CALCULATED GEOMETRIES

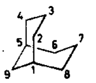
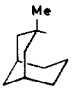
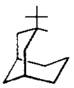
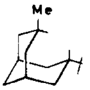
Systems with a double-chair conformation

The results of the force field calculations on the cc conformation of bicyclo[3.3.1]nonane (**22**) (see Table 7) show that the molecule has C_{2v}-symmetry. The distance between $H_{3\alpha}$ and $H_{7\alpha}$ is calculated to be 2.12 Å, whereas in a perfect cc conformation the separation is only 0.76 Å. As is shown by the internal ring torsion angles (see Fig. 2), the severe interaction between these atoms gives rise to a distinct flattening of the wings of the ring system. Moreover, a larger separation between the wings is achieved by increased $C_2C_1C_8$ and $C_4C_5C_6$ valency angles. The results of the calculations are in agreement with those of previous molecular mechanical studies[6,7] and with the results of recent electron diffraction studies.[13]

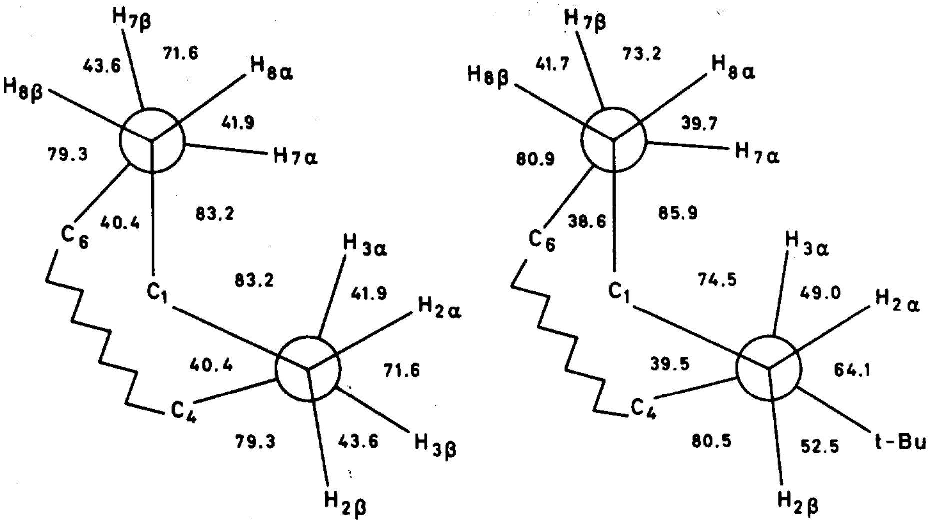
Introduction of a *t*-butyl group on the 3β-position will cause several gauche butane interactions in the six-membered ring involved (*cf.* Table 6). As may be expected from previous calculations on alkylcyclohexanes,[12] this results in bending of $H_{3\alpha}$ into the direction of the center of the ring (see Fig. 2), an increase of the $C_1C_2C_3$ and $C_3C_4C_5$ valency angles (see Table 7) and an increase of the C_2C_3 and C_3C_4 bond lengths. As a consequence of the displacement of $H_{3\alpha}$, its interaction with $H_{7\alpha}$ becomes slightly more severe, which results in analogous phenomena in the other wing. As should be expected the effects there are more pronounced than in the substituted ring. It should be noted that in the 3β-methyl compound still a plane of symmetry through C_3, C_7 and C_9 is present, whereas in the *t*-butyl derivatives (**24**, **25**) the symmetry is no longer preserved: the *t*-butyl group has no perfectly staggered position with respect to C_3. A similar situation was calculated for *t*-butylcyclohexane.[12]

Since the steric demands of a methyl group are roughly of the same order of magnitude as those of a methoxycarbonyl group, a comparison of the calculated geometries of **23** and **25** with the results of previous ^{1}H NMR studies on methyl bicyclo[3.3.1]nonane-3β-carboxylate (**26**), its 7β-*t*-butyl derivative (**27**) and the related 9-oxo compounds (**28** and **29**) seems of interest.[1,3] As Table 8 shows, the magnitudes of the vicinal proton-proton coupling constants $J_{12\beta}$, $J_{2\alpha3\alpha}$ and $J_{2\beta3\alpha}$ are in accordance with the calculated dihedral angles in compounds **26**–**29**.[15]

Table 7. Selected ring torsion angles, valency angles and bond lengths of the cc conformations of bicyclo[3.3.1]nonane derivatives[a]

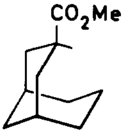
	 22	 23	 24[b]	 25[b]
ring torsion angles				
$C_1C_2C_3C_4$	40.4	40.6	39.5	38.7
$C_3C_4C_5C_9$	52.3	52.6	52.7	52.2
$C_1C_8C_7C_6$	40.4	39.3	38.6	38.1
valency angles				
$C_8C_1C_2$	115.1	115.2	115.3	115.5
$C_1C_2C_3$	115.0	115.3	116.3	115.7
$C_2C_3C_4$	113.4	112.6	111.3	112.6
$C_1C_8C_7$	115.0	115.2	115.3	116.5
$C_6C_7C_8$	113.4	113.6	113.5	111.5
$R_1C_3H_{3\alpha}$	103.8	105.5	103.3	105.0
bond lengths				
C_2C_3	1.537	1.539	1.545	1.539
C_7C_8	1.537	1.538	1.537	1.546

[a] Complete Tables of geometric parameters are available from the authors on request; [b] in compounds **24** and **25** the symmetry of the molecule is somewhat distorted. The figures given are averages of corresponding values. The maximum deviations from the values given are: 0.3° (torsion angles) and 0.1° (valency angles).



22 24

Fig. 2. cc Conformations; torsion angles around C_2C_3 (C_3C_4) and C_6C_7 (C_7C_8).



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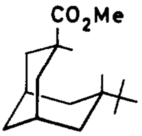

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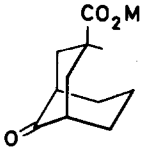

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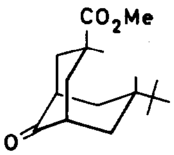

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Systems with a boat-chair conformation

The calculations show that in the bc conformation of unsubstituted bicyclo[3.3.1]nonane a mirror plane through C_3, C_7 and C_9 is present: the boat wing is not twisted. As can be seen from the internal ring torsion angles and the valency angles (see Table 9), again both wings of the system are distinctly flattened, although less than in the cc conformation. This flattening may be attributed to the interaction between $H_{3\beta}$ and H_9 and between $H_{7\alpha}$ and $H_{2\alpha}$ and $H_{4\alpha}$. Flattening of the chair moves $H_{7\alpha}$ away from $H_{2\alpha}$ and $H_{4\alpha}$, whereas flattening of the boat part results in a larger separation of $H_{2\alpha}$ and $H_{4\alpha}$ and therefore an increase of the distances between these atoms and $H_{7\alpha}$ is achieved. This hypothesis is supported by the influences of substitution of the 3- and/or 7-positions on the geometry of the bc conformation. The impact of a 7β-alkyl substituent again is analogous to that of such a group on the geometry of cyclohexane (see Table 10). In these compounds the displacement of $H_{7\alpha}$ towards the center of the system may be responsible for the increased flattening of the boat wing.

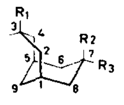
A bulky substituent at the 3α-position (pseudo-equatorial in the boat part) induces, in addition to analogous phenomena, an increased flattening of the boat part. The increased flattening of the boat-wing might be due to the increase of the 3,9-interaction upon bending of $H_{3\beta}$ into the direction of C_9. The distance between $H_{2\alpha}$ and $H_{4\alpha}$ is somewhat larger than in the unsubstituted system, due to the increased flattening. This is reflected in a decreased flattening in the chair wing (see, e.g. compound **34**).

Table 8. Comparison of calculated dihedral angles and vicinal proton–proton coupling constants

Fragment	calculated dihedral angles (degrees)		coupling constants observed[a] (Hz)			
	23	25	26	27	28	29
12β/4β5	49.9	49.3	4.0	4.5	4.3	4.2
2α3α/3α4α	45.6	43.6	5.3-6.0	5.7	5.2	5.5
2β3α/3α4β	160.8	158.5	12.6	12.4	12;7	12.0

[a] ± 0.2 Hz

Table 9. Selected ring torsion angles, valency angles and bond lengths of **bc** conformations of some bicyclo[3.3.1]nonanes



Nr	30	31	32	33	34[a]	35[a]	36[a]	37	38
R_1	H	H	H	Me	t-Bu	Me	t-Bu	H	t-Bu
R_2	H	H	H	H	H	H	H	Me	Me
R_3	H	Me	t-Bu	H	H	t-Bu	Me	H	H
internal ring torsion angles									
1234	44.3	43.8	43.2	43.9	39.9	42.6	38.9	39.6	39.1
3219	7.6	8.0	8.6	7.5	9.5	8.7	10.2	10.7	10.3
1876	48.4	48.4	48.0	48.4	49.2	48.2	49.5	38.1	37.1
7819	56.2	56.5	57.0	56.3	56.8	57.2	57.1	51.8	51.8
valency angles									
123	113.9	113.9	113.9	114.4	115.8	114.4	115.9	114.3	115.7
234	113.2	113.3	113.4	112.6	112.0	112.8	112.3	114.7	112.4
187	113.1	113.5	114.4	113.0	112.9	114.3	113.2	116.3	116.3
678	112.1	111.3	109.7	112.0	111.6	109.6	110.8	112.4	112.5
bond lengths									
23	1.537	1.537	1.537	1.538	1.546	1.538	1.547	1.538	1.547
67	1.536	1.538	1.545	1.536	1.535	1.545	1.537	1.543	1.542

[a] In these compounds the symmetry of the molecule is slightly distorted.

Averages of two corresponding values are given. The maximum deviation from the value given is 0.4° (torsion angles) and 0.1° (valency angles).

As should be expected, the calculations show that introduction of a 7α-methyl group (axial in the chair part) has rather dramatic consequences for the geometry of the **bc** conformation. The 1,3-diaxial interactions between the 7α-substituent and the other ring are decreased by a very strong flattening of the chair, accompanied by an increase of the valency angles $C_5C_6C_7$ and $C_7C_8C_1$ and a stretching of the C_6C_7 and C_7C_8 bonds. Moreover, the other ring is flattened too which results in a larger separation between $H_{2\alpha}$ and $H_{4\alpha}$.

From Table 11 it can be seen that the dihedral angles calculated for the **bc** conformations are in agreement with the magnitudes of vicinal proton–proton coupling constants observed in the related methoxycarbonyl derivatives **39–43**.[1,3]

Systems with a double twist-boat conformation

The double twist-boat conformation—the most stable **bb** conformation—of bicyclo[3.3.1]nonane (**44**) has a twofold axis of symmetry through C_9 and the mid-point of the line C_1C_5 (see Table 12). An inspection of a Dreiding model shows that two "ideal" double twist-boat conformations are possible in the bicyclo[3.3.1]nonane system. In these conformations strong non-bonding interactions occur between $H_{2\alpha}$ and $H_{6\alpha}$ and $H_{4\alpha}$ and $H_{8\alpha}$, respectively, and between $H_{3\beta}$ and $H_{7\beta}$ and the H_9 atoms. The low values for the calculated internal torsion angles $C_1C_2C_3C_4$ and $C_5C_6C_7C_8$ with respect to the corresponding torsion angles in the twist-boat conformation of cyclohexane,[12] reveal that the interactions are diminished by a distinct flattening of both wings. The dihedral angles show that the "twisting" is analogous to that in the twist-boat of cyclohexane.

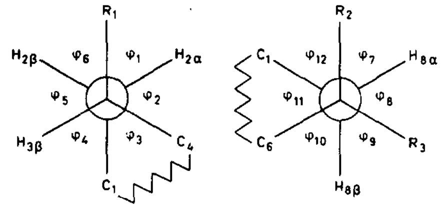
The most characteristic effect of the introduction of a *t*-butyl substituent at the 3α-position is a rotation of the *t*-butyl group and $H_{3\beta}$ away from the $H_{2\alpha}$ and $H_{4\alpha}$ atoms (see Fig. 3). This phenomenon is accompanied by some flattening (probably due to the flagpole interaction), stretching of the C_2C_3 and C_3C_4 bonds and a decrease of the valency angle $C_2C_3C_4$. The influences of the substitution on the geometry of the unsubstituted ring are of minor importance.

CONCLUSIONS

A good agreement exists between the results of the force field calculations and those of the experimental

Table 10. **bc** Conformations; torsion angles around C_2C_3 and C_7C_8

	Nr	30	32[a]	34[a]	37
	R_1	H	H	t-Bu	H
	R_2	H	H	H	Me
	R_3	H	t-Bu	H	H
boat wing	ϕ_1	45.2	43.8	49.8	40.3
	ϕ_2	78.8	80.4	83.9	84.9
	ϕ_3	44.3	43.2	39.9	39.6
	ϕ_4	76.7	77.6	72.5	80.7
	ϕ_5	46.2	45.1	48.7	41.6
	ϕ_6	68.9	70.0	65.2	72.9
chair wing	ϕ_7	50.7	56.7	51.8	34.5
	ϕ_7	65.0	58.3	64.3	78.3
	ϕ_9	50.6	58.8	51.3	35.7
	ϕ_{10}	71.9	72.6	71.0	80.8
	ϕ_{11}	48.4	48.0	49.2	38.1
	ϕ_{12}	73.5	65.7	72.4	92.6



[a] See Table 9, note a

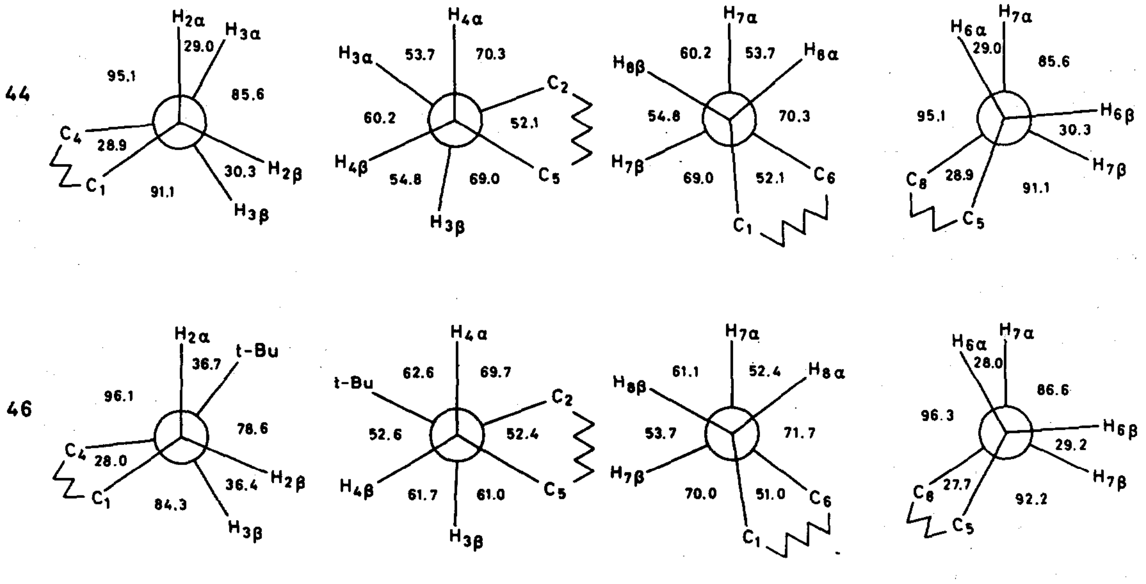
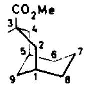


Fig. 3. Torsion angles around C_2C_3, C_3C_4, C_7C_8 and C_6C_7 of the **t-bb** conformations of bicyclo[3.3.1]nonane (**44**) and 3α-*t*-butyl-bicyclo[3.3.1]nonane (**46**).

Table 11. Comparison of calculated dihedral angles and observed proton–proton coupling constants for bc conformations of some bicyclo[3.3.1]nonane derivatives



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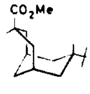

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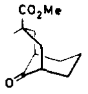

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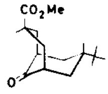

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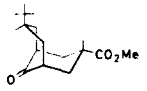

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	calculated dihedral angles[a] (degrees)			experimental coupling constants (Hz)				
	33	35	36	39	41	40	42	43[b]
12α/4α5	110.4	109.1	106.1	1-2	<3	<6	<3	--
12β/4β5	4.6	5.6	7.4	10.2	9	11.0	10	--
2α3β/3β4α	162.4	160.7	162.5	12.5	12.5	12.0	12.5	12.7
2β3β/3β4β	48.4	47.0	47.7	6.0	5.5	6.3	5.5	4.2
6α7α/7α8α	50.7	56.8	54.6	--	3.9	3.7	3.2	3.7
6β7α/7α8β	166.3	173.9	170.3	--	14	12.3	13.2	12.7

[a] See Table 9, note a; [b] in order to make comparison simple, an unusual numbering is used

Table 12. Selected ring torsion angles, valency angles and bond lengths of t-bb conformations of some bicyclo[3.3.1]nonane derivatives

44

45

46

47

	44	45	46	47
ring torsion angles				
1234	28.9	28.6	28.0	27.5
2345	52.1	52.1	52.4	52.0
3459	11.2	11.6	13.2	12.9
4591	49.8	49.5	48.6	48.8
5912	73.0	72.8	72.7	72.9
9123	31.3	31.3	31.9	32.3
valency angles				
123	113.1	113.6	114.6	114.6
345	113.6	114.0	114.6	114.6
234	112.9	112.2	110.5	110.6
$R_1 3 R_2$	105.7	107.0	104.7	104.7
bond lengths				
23	1.542	1.543	1.551	1.551
34	1.536	1.537	1.543	1.543

procedures. In bicyclo[3.3.1]nonane and its 3β-substituted derivatives the **cc** conformation predominates. 3α-Substituents force the substituted ring into the boat conformation. In these compounds the **bb** conformation can be ignored. For $3\alpha,7\alpha$-substituted derivatives the conformational preferences depend on the size of the substituents. With a 3α-methyl and a 7α-*t*-butyl substituent both the **cb** and the **bb** conformers contribute to the conformational equilibrium. The double-twist **bb** conformation is more stable than the eclipsed **bb** conformation.

All conformations (**cc**, **cb**, **t-bb**) are distinctly flattened. Substitution of the 3 (and/or 7-) position affects both wings, in particular in the **cc** and **cb** conformations. The most characteristic effect of *t*-butyl substitution is a rotation of the substituted carbon atom away from the nearest H-atoms, accompanied by some flattening of the corresponding ring. Dramatic changes in calculated geometry occur when the 7α-position of the chair part in a **bc** conformation is substituted.

EXPERIMENTAL

NMR spectroscopy. ^{13}C NMR spectra (20 MHz) were recorded on a Varian CFT-20 apparatus at 35°. The variable temperature ^{13}C NMR spectra (25.2 MHz) were obtained with a Varian XL-100-15 NMR spectrometer system, equipped with a V-4412 universal probe, in the PFT-mode. The probe temperature was measured with a thermometer, which has the same shape as the sample tube, fixed in the spinner. The temperature measurements can be regarded as $\pm 0.5°$. The chemical shifts are given in ppm relative to TMS (δ). The variable temperature measurements were performed with CD_2Cl_2 solns. The concentrations were about 0.2 mole/l. For each compound the ^{13}C chemical shifts were measured at 8 temperatures between $-103°$ and $+34°$. For compound **5** also measurements in the temperature range 34–180° were performed (in DMSO-d_6 solution). The analysis of the resulting ^{13}C chemical shift data gave the same ΔH and ΔS-value as those obtained from the low-temperature measurements.

Calculations. The valence force field calculations were carried out using a fully analytical version of the Boyd 1968 minimization procedure[16] and an IBM 370/158 computer. The complete force-constant matrix was calculated at all extrema of all molecules studied. ΔS-values were calculated assuming harmonic normal modes and applying the formulae of statistical mechanics.[20] It should be noted, however, that the Schleyer 1973 force field is not designed to reproduce vibrational frequences on thermodynamic parameters. Complete Tables of thermodynamic and geometric parameters are available from the authors on request.

Epimerisations. The epimerisations were performed as described by Appleton *et al.*[8] The analyses of the resulting mixtures were carried out by means of GC with a 3m silar-5-CP column or by integration of the CO_2Me signals in the ^1H NMR spectrum after addition of a small amount of $Eu(fod)_3$.

Syntheses. The syntheses of all compounds, with the exception of compound **7**, have been described previously.[1,3] For compound **2** the procedure described by Schneider and Ansorge[5] was followed. Reduction of the Me ester of compound **2** with LAH, followed by conversion of the hydroxymethyl compound into the tosylate and subsequently another LAH reduction gave compound **7**.

7α-t-Butylbicyclo[3.3.1]*nonane-3α-carboxylic acid* (**2**). HCl-Gas was bubbled through a refluxing mixture of 3.05 g 7α-*t*-butyl-9-oxobicyclo[3.3.1]nonane-3α-carboxylic acid (12.8 mmole),[3] 80 g freshly prepared Zn–amalgame and 100 ml 37% HCl. After 3 h the conversion was complete. The mixture was diluted with 600 ml H_2O. The aqueous layer was extracted with ether (5×100 ml). The combined organic layers were washed with sat NaCl aq (100 ml) and then extracted with 2N KOH (4×60 ml). The KOH soln was washed with ether (2×70 ml) and then acidified with 37% HCl. The dispersion obtained was extracted with ether (4×50 ml). The ether soln was washed with H_2O (2×50 ml) and dried over $MgSO_4$. After evaporation of the solvents 2.68 g almost pure carboxylic acid (11.9 mmole, 93%) was obtained. Further purification was achieved by sublimation at 100°/10 mm and recrystallisation from light petroleum/EtOAc; m.p. 132–132.5°.[1]

7α-t-Butyl-3α-hydroxymethylbicyclo[3.3.1]*nonane.* The compound obtained in the preceding reaction step was esterified with CH_2N_2 in ether. A soln of 1.10 g of the Me ester thus obtained (4.8 mmole) in 10 ml ether was added dropwise to a suspension of 0.50 g LAH (13.2 mmole) in 15 ml ether. Then the reaction mixture was boiled for 3 h. After cooling 10 ml H_2O and subsequently 20 ml 4 N H_2SO_4 were added dropwise. The aqueous layer was extracted with ether (4×20 ml). The combined ether solns were washed with H_2O (2×20 ml) and dried over $MgSO_4$. After evaporation of the solvents 1.00 g of the hydroxymethyl compound (4.8 mmole, 100%) was obtained. This product was identical with an authentic sample.[1]

Tosylate of 7α-t-butyl-3α-hydroxymethylbicyclo[3.3.1]*nonane.* Tosylchloride (1.00 g, 4.4 mmole) was added to a soln of the product of the preceding step in 20 ml pyridine. The soln obtained was stored at 0° during 48 h. Then the reaction mixture was poured onto 200 ml 2 N HCl (0°). The precipitate was filtered, washed with ice water and dried over P_2O_5. Almost pure tosylate (1.569 g, 4.2 mmole, 87%) was obtained, which was used in the following step without further purification.

7α-t-Butyl-3α-methylbicyclo[3.3.1]*nonane* (**7**). A soln of 1.560 g of the product of the preceding step (4.1 mmole) in 30 ml ether was added dropwise to a suspension of 1.19 g LAH (31.3 mmole) in 30 ml ether. Then the mixture was stirred for 2 h at room temp. and 2 h at the boiling point. After cooling 10 ml H_2O and then 40 ml 4 N H_2SO_4 were added dropwise. The aqueous layer was extracted with ether (3×20 ml). The combined ethereal solns were washed with H_2O (3×20 ml) and dried over $MgSO_4$. The solvents were distilled off and the residue was purified by chromatography over alumina (elution with light petroleum). From the eluate the solvents were distilled off and the residue was distilled under reduced pressure to yield 0.536 g pure **7** (2.8 mmole, 67%); b.p. 130°/70 mm; mass spectrum important peaks at *m/e* 81, 95, 121, 123, 136 and 137.

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