A New Approach of Aromatic Solvent-induced Shifts (ASIS) in ^{13}C N.M.R. Spectroscopy for Solving Stereochemical Problems in Some Carbonyl Compounds

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A simple method for the estimation of aromatic solvent-induced shifts (ASIS) in ^{13}C n.m.r. spectroscopy is reported. The ^{13}C ASIS values produced by perdeuteriobenzene (C_6D_6) are obtained for a variety of structurally different compounds containing carbonyl groups. The ^{13}C ASIS values observed vary from compound to compound, depending upon conformational variations involving the carbonyl groups. A useful relationship between the magnitude of the ^{13}C ASIS values and the geometrical factors estimated on the basis of an assumed model for a 1 : 1 solute–C_6D_6 association is presented as a new approach for the prediction of preferential conformations of cyclohexanones in solution at room temperature.

Aromatic solvent-induced shifts (ASIS) in ^1H n.m.r. spectroscopy are well known to be a simple powerful tool in signal assignment and structural elucidation of organic compounds.[1] The ASIS method is also useful in view of the easy recovery of the samples. In particular, numerous applications of the ASIS in ^1H n.m.r. spectroscopy (hereafter abbreviated as ^1H ASIS) to carbonyl compounds have appeared, because their ^1H ASIS can easily be accounted for by an empirical rule, the so-called 'carbonyl reference-plane rule'.[2,†] In contrast with the large number of ^1H ASIS studies, definite information about the ASIS in ^{13}C n.m.r. spectroscopy is still lacking. This may be attributed to the difficulty in estimating ^{13}C ASIS ordinarily masked by other large solvent shifts such as the van der Waals contribution;[4] ^{13}C chemical shifts occur over a far greater range than do ^1H chemical shifts. For a specific solvent–solute association, however, effects of solvent anisotropies on ^{13}C chemical shifts cannot be neglected.[4] Since ^{13}C chemical shifts observed for a given compound provide direct information concerning its molecular backbone, the ^{13}C ASIS method is also expected to be a useful means of solving stereochemical problems.

Here, we wish to report a new approach of the ^{13}C ASIS for the assignment of stereochemistry to cyclohexanones in solution at room temperature.

Experimental

All ^{13}C n.m.r. spectra were measured with an ANELVA NV-21 spectrometer operating at 22.6 MHz at the normal probe temperature (*ca.* 30 °C), except for the case of (**15**) which was recorded on an XL-200 spectrometer operating at 50.3 MHz. The sample concentration was usually 15 mol% for all the carbonyl compounds. For non-deuteriated solvent, the deuteron signal of D_2O sealed in a capillary inserted into the tube, was employed as the internal reference signal. The digital resolution for both spectrometers was *ca.* 1.4 Hz. The details for the other conditions for the determination of the spectra were as previously described.[4a,b]

The ^{13}C signals were assigned using the known chemical-shift rule,[5] literature data (on analogous compounds), ^1H signal frequency off-resonance decoupling techniques, and selective decoupling techniques as described in the literature;[6] this method is particularly useful for spectral assignments of closely spaced ^{13}C signals.

Results and Discussion

In ^1H n.m.r. spectroscopy the ASIS values ($\Delta\delta$) can be defined by the solvent shifts produced by aromatic solvents such as C_6D_6 or hexafluorobenzene (C_6F_6) relative to $CDCl_3$ or CCl_4, as shown in equation (1). On the other hand, for the estimation

$$\Delta\delta/\text{p.p.m.} = \delta(\text{aromatic solvent}) - \delta(CDCl_3 \text{ or } CCl_4) \quad (1)$$

of the ^{13}C ASIS values induced by C_6D_6, we recommend equation (2) rather than equation (1) because of the ^{13}C

$$\Delta\delta/\text{p.p.m.} = \delta(C_6D_6) - \delta(ClCH_2CH_2Cl) \quad (2)$$

chemical shift comparison (CSC) plots;[4a,b] the method of the CSC plot produces reliable ^{13}C ASIS values for both C_6D_6 and C_6F_6, but the procedure seems to be rather laborious when widely applied to organic chemistry. In equation (2), 1,2-dichloroethane is used as the reference solvent, and also the C_6F_6-induced ^{13}C ASIS values cannot be estimated from equation (2).[4a] The validity of equation (2), however, is based on the assumption that the CSC plot holds in a range of solvents including $ClCH_2CH_2Cl$ and C_6D_6. Therefore, the scope of equation (2) was examined by the CSC method using the ^{13}C solvent shift data‡ on several carbonyl compounds [(**1**), (**8**), (**12**), (**13**), and (**14**)]; some of these results have been previously reported.[4b] Thus, we found a few cases (*i*)–(*iv*) in which the CSC

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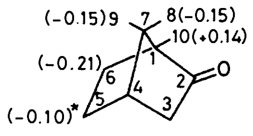
† The carbonyl reference plane (*P*) is drawn through the carbon of the carbonyl group at right angles to the carbon–oxygen bond. In C_6D_6, protons (carbons) in front of the plane (*P*) are deshielded, while protons (carbons) behind are shielded. A reverse shift is observed in C_6F_6.[3,8] Protons (carbons) on the plane (*P*) show insignificant shift.

‡ Detailed ^{13}C solvent-shift data for the CSC plots are available from the authors on request.



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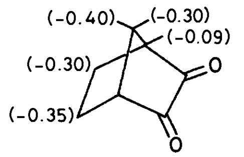

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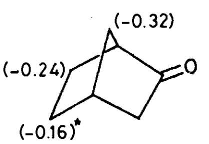

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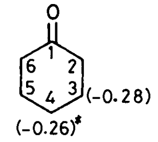

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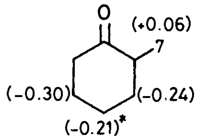

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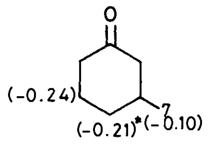

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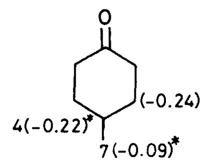

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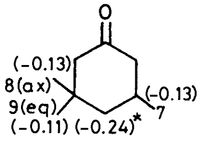

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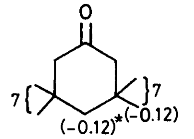

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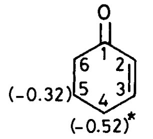

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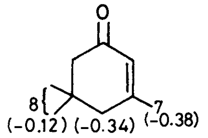

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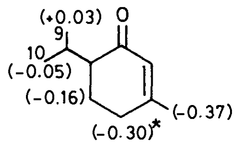

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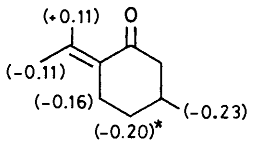

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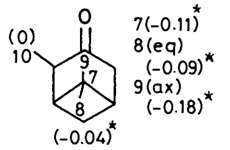

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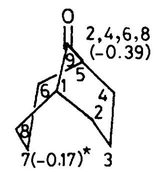
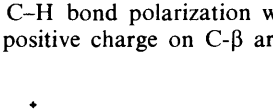


(15)

Figure 1. The ^{13}C ASIS values for compounds (1)–(15) estimated from equation (2). The values with an asterisk (carbon on the *DP*-plane) were used for the correlation shown in Figure 3.

plots do not hold:[4b] (*i*) the carbonyl carbon, (*ii*) C-α relative to the carbonyl group, (*iii*) C(α)=C(β), and (*iv*) tertiary and quaternary C-β. The deviation from the CSC plots in (*i*)–(*iv*) may be attributed to the transmission of the electronic effects arising from specific interactions such as weak hydrogen bonds and/or dipole association between the C=O group and a solvent molecule. Therefore, the specific solvent effects on carbon atoms further away than the β position are negligibly small;[4b] the distance from the C=O group renders the specific solvent effects small. In the case of (*iv*), the deviations from the CSC plots are very small; the primary and secondary β-carbons show much better CSC plots. A possible explanation for this observation is the effect of the $\overset{-}{C}$–$\overset{+}{H}$ bond polarization which will partially compensate the positive charge on C-β arising from specific solvent such as



The ^{13}C chemical-shift data on compounds (1)–(15) in C_6D_6 and $ClCH_2CH_2Cl$ are given in the Table and Figure 1 summarize the ^{13}C ASIS values estimated by using equation (2), except for the cases of (*i*)–(*iv*). As a brief check on the reliability of the ^{13}C ASIS values obtained, they were compared with the corresponding ^{1}H ASIS values. Since both ^{13}C and ^{1}H nuclei of the alkyl group in question have almost the same spatial relationship with respect to the aromatic solvent molecules solvating the C=O group, they are expected to have ASIS values of similar magnitude.[7] In fact, for the methyl groups of (1), (7), and (12), the magnitude and the direction of the ^{13}C ASIS values correspond well to those of the ^{1}H ASIS values[8] [^{1}H ASIS/ppm: (**1**) 8-H = −0.23, 9-H = −0.30, and 10-H = +0.04; (**7**) 7-H = −0.28, 9-H = +0.13, and 10-H = −0.28; (**12**) 7-H = −0.48, 9-H = +0.03, and 10-H = −0.03]. Furthermore, an investigation of concentration effects on the ^{13}C chemical shifts of (**1**) shows insignificant variation of the ^{13}C ASIS values (C-5, -6, -8, -9, and -10) (Table).

An inspection of the ^{13}C ASIS values (Figure 1) indicates that the carbonyl reference-plane rule[2] (or dipole-plane rule[9]) holds good for all the compounds studied here. For example, in both (**12**) and (**13**), the ^{13}C ASIS values for the 9-Me carbons, which lie in front of the carbonyl reference plane, are positive, whereas those for the other carbons such as 10-Me or C-4, lying behind the carbonyl plane, are negative. This observation indicates that in addition to ASIS, the carbonyl reference-plane rule in ^{13}C ASIS can be adopted for solving problems such as ^{13}C signal assignments and structural elucidations. For (**13**), the earlier assignment of the 9- and 10-Me carbon resonances was made tentatively assuming an upfield shift arising from the steric interaction between the 9-Me and the C=O group.[10] On the other hand, the ^{13}C ASIS method allows straightforward differentiation between the 9- and 10-Me carbon signals. The high- and low-field resonances can be unequivocally assigned to 10-Me (negative ^{13}C ASIS) and 9-Me (positive ^{13}C ASIS), respectively, by application of the carbonyl reference-plane rule; this is the opposite of the assignment expected on the basis of the

Table. ^{13}C Chemical-shift data[a] for compounds (**1**)–(**15**) in C_6D_6 and 1,2-dichloroethane (DCE).

Carbon	(**1**)		(**2**)		(**3**)	
	C_6D_6	DCE	C_6D_6	DCE	C_6D_6	DCE
1	57.21 (57.23)	57.49 (57.54)	58.47	58.75	49.75	50.01
2	216.03 (215.85)	217.63 (217.93)	204.23	204.77	214.71	216.41
3	43.16 (43.22)	43.35 (43.43)	202.10	202.69	44.99	45.26
4	43.16 (43.32)	43.45 (43.43)	58.17	58.36	35.43	35.74
5	27.22 (27.29)	27.32 (27.37)	22.15	22.50	27.36	27.52
6	29.98 (30.04)	30.19 (30.23)	29.88	30.18	24.21	24.45
7	46.76 (46.82)	46.49 (46.50)	42.26	42.61	37.50	37.82
8	19.66 (19.69)	19.81 (19.84)	17.07	17.37		
9	19.05 (19.09)	19.20 (19.22)	20.57	20.97		
10	9.53 (9.55)	9.39 (9.43)	8.73	8.82		

Carbon	(**4**)		(**5**)		(**6**)		(**7**)	
	C_6D_6	DCE	C_6D_6	DCE	C_6D_6	DCE	C_6D_6	DCE
1	208.58	210.19	210.28	211.78	208.33	209.96	209.83	211.48
2	41.90	42.11	45.19	45.42	49.88	50.09	40.55	40.75
3	27.10	27.38	36.51	36.27	25.35	25.59	34.91	35.15
4	25.15	25.41	25.41	25.62	33.42	33.63	31.14	31.36
5	27.10	27.38	27.99	28.29	25.35	25.59	34.91	35.15
6	41.90	42.11	41.80	42.00	40.98	41.21	40.55	40.75
7			14.99	14.93	22.08	22.18	21.05	21.14

Carbon	(**8**)		(**9**)		(**10**)		(**11**)	
	C_6D_6	DCE	C_6D_6	DCE	C_6D_6	DCE	C_6D_6	DCE
1	208.36	209.98	208.91	210.55	197.41	198.64	197.11	198.29
2	53.95	54.22	53.73	53.95	130.19	130.06	125.95	125.67
3	34.86	35.21	35.73	36.05	149.15	150.53	157.81	159.39
4	47.28	47.52	51.58	51.70	25.52	26.04	44.98	45.32
5	29.49	29.82	35.73	36.05	22.91	23.23	33.16	33.51
6	49.09	49.30	53.73	53.95	38.27	38.46	50.93	50.98
7	32.04	32.17	31.27	31.39			23.99	24.37
8	22.44	22.57					28.20	28.32
9	25.72	25.83						

Carbon	(**12**)		(**13**)		(**14**)		(**15**)	
	C_6D_6	DCE	C_6D_6	DCE	C_6D_6	DCE	C_6D_6	DCE
1	198.74	199.77	201.35	202.54	211.10	212.97	46.66	46.92
2	127.07	126.78	50.09	51.03	44.63	44.81	34.18	34.57
3	159.11	160.63	31.52	31.78	39.32	39.43	20.86	21.03
4	30.24	30.54	32.94	33.14	34.52	34.56	34.18	34.57
5	23.08	23.24	28.67	28.83	45.28	45.41	46.66	46.92
6	51.46	51.65	131.92	132.05	51.26	51.39	34.18	34.57
7	23.41	23.78	21.78	22.01	39.32	39.43	20.86	21.03
8	25.96	25.97	140.77	141.18	27.08	27.17	34.18	34.57
9	18.53	18.50	23.04	22.93	21.76	21.94	217.88	219.82
10	20.54	20.59	21.78	21.89	16.88	16.88		

[a] In ppm from internal $SiMe_4$. Numbering of the carbons is shown in the Scheme. Values in parentheses for (**1**) were measured at a lower concentration of the solute (7.5 mol%).

steric effects. Our assignment was also confirmed by reported selective decoupling techniques.[6]

From the comparison of the ^{13}C ASIS values for (**1**) with those for (**2**), it was noted that (**2**), containing two quasi-equivalent C=O groups at the 2 and 3 positions, displays much larger negative ^{13}C ASIS values than (**1**) containing the only one C=O group at the 2 position. This observation suggests additivity of the ^{13}C ASIS values; similar additivity was also found in the ^{1}H ASIS investigations.[11]

In the hope of finding a new empirical relationship between the magnitude of the ^{13}C ASIS values and conformational variations in the carbonyl compounds, the ^{13}C ASIS values were compared with each other. For example, for a group of cyclohexanones (**4**)–(**9**), the ^{13}C ASIS values for C-4 (-0.21 to -0.26), are very similar except for the case of (**9**) which shows a marked decrease (-0.12). Also, the C-4 ^{13}C ASIS values for the cyclohexenones (**10**) and (**11**) are 1.5–2.0 times the magnitude of those for C-4 in the corresponding cyclohexanones (**4**) and (**8**). A similar trend is also observed for the ^{13}C ASIS values of the 7-Me in (**8**) and (**11**). In the cyclohexenones series, the increased ^{13}C ASIS values of C-4 and Me, compared with those of cyclohexanones, can be adequately explained by taking into

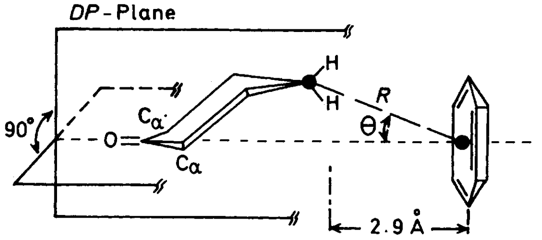


Figure 2. Schematic representation of the assumed model for a 1:1 solute (**5**)–C_6D_6 association.

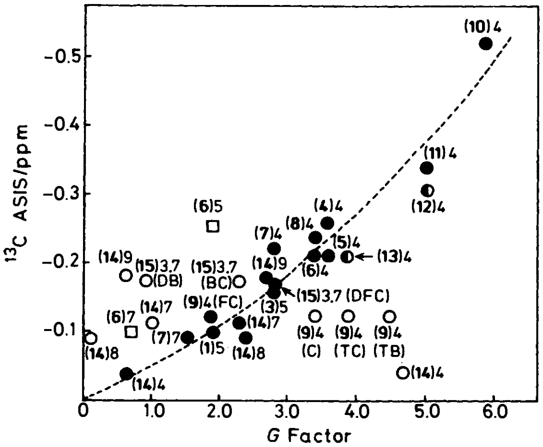
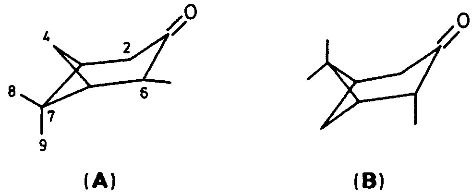


Figure 3. Correlation between the ^{13}C ASIS values and the geometrical factors (G). The bold numbers represent the carbon of the carbonyl compounds (Figure 1): ●, the most stable conformation; ○, less stable conformation; ◐, less reliable G factor (see the text); □, the carbons remote from the DP-plane. C = Chair; B = boat; F = flattened; T = twist; D = double.

account a (further) flattening of cyclohexanones arising from the additional trigonal carbons, and because C-4 and Me in the flattened structures are well within the shielding region of the C_6D_6 molecule as shown in the model in Figure 2 (see below). Thus, the ^{13}C ASIS values are found to vary from compound to compound, even in the same carbon site relative to the C=O group, depending upon their conformational variations. In order to account for these important variations in the ^{13}C ASIS values, we assumed a 1:1 solute–C_6D_6 association model in which the C=O dipole is collinear with the sixfold axis of the C_6D_6 ring (Figure 2). In the 1:1 simplified model, the distance between the C_6D_6 molecule and the solute molecule is considered to be the distance of closest approach, *i.e.* the sum of the van der Waals radii for the interacting groups [H atom (1.0 Å) and the half-thickness of the π-electron cloud of the C_6D_6 molecule (1.85 Å)]. Using this model, the R and θ values (Figure 2) were measured on a Dreiding model, from which can be estimated the geometrical factor (G) of McConnell equation:[12]

$$G = [1 - 3\cos^2(90° - \theta)] \times 10^3/3R^3$$

which is anticipated to affect directly the ^{13}C ASIS character. From a comparison of the geometrical factor (G) with the ^{13}C ASIS values for the carbons [such as C-4, -7, -8, and -9 of (**14**)] lying on the DP-plane (the plane containing the C=O dipole: Figure 2), a good correlation is found to exist between compounds (**1**) and (**3**)–(**15**), as can be seen in Figure 3. In the estimation of the G factors, the cyclohexanones (**4**)–(**7**) and (**13**) and the cyclohexenones (**10**)–(**12**) were assumed to exist preferentially in the chair and half-chair conformations, respectively. In the cyclohexenones (**10**)–(**12**), and (**13**), however, the direction and strength of the solute dipole appear to differ slightly from those of the cyclohexanones, owing to the presence of conjugation in the system. In spite of this, (**10**) and (**11**) experience the same correlation (Figure 3) as the cyclohexanones, while (**12**) and (**13**) in which there is a large substituent at the 6 position, produce some deviations. In the case of (**12**) and (**13**), the geometrical factors estimated from Dreiding models do not seem to reflect their true structures. This is because serious repulsion between isopropyl or isopropylidene group, respectively, and the carbonyl group results in larger torsional angles, thus resulting in larger values of θ in the G factors. In both (**1**) and (**3**) the structures are rigid and the ^{13}C ASIS values for C-5 satisfactorily fit the correlation line, although C-5 is slightly away from the DP-plane. Furthermore, for (**8**), (**9**), (**14**), and (**15**), their conformations are discussed below on the basis of the proposed correlation.



(A) **(B)**

Figure 4. Two possible conformations of isopinocamphone.

The success of the correlation indicates that the ^{13}C ASIS values for the carbons on the DP-plane are mainly governed by anisotropy of the closest C_6D_6 molecule, which is attracted by an intermolecular C=O···π association. The empirical correlation line obtained, however, is slightly curved. Also, the ^{13}C ASIS values for the carbons [such as 7-Me and C-5 of (**6**)] remote from the DP-plane do not fall on the same correlation line, showing a rather scattered diagram (Figure 3). These two observations can probably be ascribed to the simplified model (Figure 2) in which only one C_6D_6 molecule associating with the solute molecule participates in the determination of the ASIS values; a 1:n solute–C_6D_6 model[9] would seem to be better than the 1:1 model, but for this case it is extremely difficult to formulate an empirical rule governing the ^{13}C ASIS values. During the actual solvation, a second and/or a third C_6D_6 molecule(s) solvating the solute dipole brings about additional anisotropy effects on the ^{13}C ASIS values.

It is particularly noteworthy that our correlation can be adopted for solving stereochemical problems. For compound (**8**), a plot of the ^{13}C ASIS value for C-4 against the G factor (3.4) estimated for a chair form, is found to fall on the correlation line, as do the other cyclohexanones (**4**)–(**7**). In contrast, a marked decrease of the ^{13}C ASIS value for C-4 is observed for (**9**), compared with that for (**8**), thus suggesting a strong deformation from the chair form. Indeed, the G factor (3.4) for the chair form does not fit the correlation line. The unusually small ^{13}C ASIS value may be explained in terms of a flattened chair form with G = 1.8 in which the distance of the diaxial Me–Me groups is taken to be 3.4 Å [sum of the van der Waals radius of the Me group (1.7 Å)] (Figure 3). Other possible conformations such as the twist–chair (G = 3.9) and a twist-boat (G = 4.5) also show large deviations from the correlation. The previous ^{1}H ASIS study[13] also suggested its deformation, a flattened chair or a twist–chair conformation, based on the ^{1}H ASIS value of 7-Me signal for (**9**), but a clear assignment of its stereochemistry could not be made from the ^{1}H ASIS value. Isopinocamphone (**14**) can adopt two possible conformations (**A**) and (**B**) (Figure 4). A choice between (**A**) and (**B**) can be made on the basis of our correlation-fit method. All of the ^{13}C ASIS values of C-4, -7, -8, and -9 on the DP-plane correlate nicely with the G factors for conformation (**A**) in which C-1, -2,

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* A mean value for the G factors for the boat and chair forms was used.

-3, -7, -5, and -6 assume a chair conformation (G = 0.6, C-4; 2.3, C-7; 2.4, C-8; 2.7, C-9). Furthermore, 10-Me (^{13}C ASIS = 0) can be assigned as equatorial, since its protons are expected to be located near the carbonyl reference plane in the bicyclic skeleton; an axial 10-Me would produce a large negative ^{13}C ASIS value. In conformation (**B**), however, the G factors (4.7, C-4; 1.0, C-7; 0.1, C-8; 0.6, C-9) display serious deviations from the correlation; in this conformation, the steric repulsion between 9-Me and the C=O group appears to become significant.

For (**15**), there are three possible conformations, a double flattened chair (DFC) (G = 2.8 for C-3 and -7), a boat–chair (BC) (G = 2.3),* and a double boat (DB) (G = 1.0); serious repulsion between C-3 and C-7 makes the existence of a true double chair (DC) form very improbable. The G factor for the DCF form was obtained on the basis of recent theoretical data [14] on the geometry of bicyclo[3.3.1]nonane; the distance of the C-3 ••• C-7 interaction being 3.2 Å. Thus, the DFC form is found to provide the best fit to the correlation, which is consistent with recent ^{1}H n.m.r. spectroscopic results.[15]

In conclusion, our method can be used for the assignation of stereochemistry in closely related compounds such as cyclohexanones, although the general applicability of this model seems to be rather limited.

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