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CONFORMATIONAL ANALYSIS BY NUCLEAR MAGNETIC RESONANCE—VI[1]

THE CONFORMATIONS OF SIXTEEN STEREOISOMERIC 2,5-DIALKYL CYCLOHEXANOLS OF THE MENTHOL TYPE

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Abstract—The conformations of sixteen 2,5-dialkyl cyclohexanols have been investigated by measuring the band width of the X proton in the NMR spectra. The results are mostly in good agreement with the equilibrium positions predicted from the known ΔG values of the substituents, when the assumption is made that the ΔG value of the molecule is the sum of the ΔG values of the involved substituents.

A t-butyl group attached to a cyclohexane ring in the *e* position seemed to cause no ring deformation; however all groups fixed in the *a* position did cause such a deformation. It has been shown that J_{ae} does not equal J_{ea} in similar molecules (probably due to this ring deformation), whilst it was observed in these compounds that J_{ee} was 2·0–2·2 c/s.

In a recent series of papers[2] the measurement of the band width of the X proton of substituted cyclohexanes has been used as a means of determining the conformational equilibrium of such molecules. This method of analysis has now been applied to the considerably more difficult 2,5-dialkyl cyclohexanols of the menthol type, and it was found that this method had far fewer drawbacks than other NMR methods previously reported.[3–6] The compounds investigated have the general structure shown in Fig. 1, and the four groups of compounds shown in Table 1 have been examined.

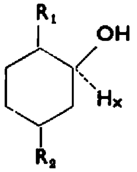

Fig. 1. General formula

Each of these four types of compounds exist in four stereoisomeric forms (configurations, Table 2), each of which can theoretically appear in the two different conformations with the hydroxyl group either axial (conformation *a*), or equatorial (conformation *e*). In order to have an easily identifiable way of referring to these

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[1] Part V: H. Feltkamp and N. C. Franklin, *J. Amer. Chem. Soc.* in press.

[2] [a] H. Feltkamp and N. C. Franklin, *Liebigs Ann.* **683**, 55 (1965).
[b] H. Feltkamp, N. C. Franklin, K. D. Thomas and W. Brügel, *Ibid.* **683**, 64 (1965).
[c] H. Feltkamp, N. C. Franklin, W. Kraus and W. Brügel, *Ibid.* **683**, 75 (1965).
[d] H. Feltkamp, N. C. Franklin, M. Hanack and K.-W. Heinz, *Tetrahedron Letters* 3535 (1964).

[3] E. L. Eliel, *Chem. & Ind.* 568 (1959).

[4] A. J. Berlin and F. R. Jensen, *Chem. & Ind.* 998 (1960).

[5] R. J. Ouellette, *J. Amer. Chem. Soc.* **86**, 3089 (1964).

[6] H. Booth, *Tetrahedron* **20**, 2211 (1964).

TABLE 1. SUMMARY OF THE INVESTIGATED COMPOUNDS

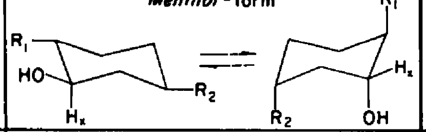
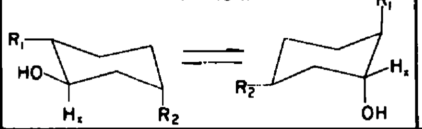
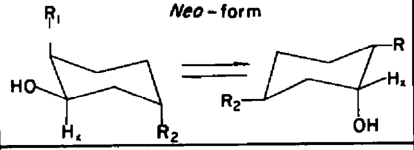
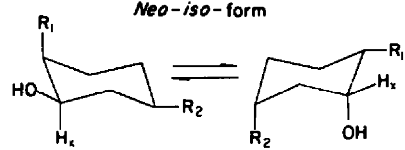
Type	R_1	R_2	Trivial name
I	CH_3	CH_3	Methyl menthols
II	$(CH_3)_2CH$	CH_3	Menthols
III	CH_3	$(CH_3)_2CH$	Carvomenthols
IV	$(CH_3)_3C$	CH_3	t-Butyl menthols

groups of compounds, and to show the relationship between them and the very thoroughly investigated menthols, these configurations (Table 2) have been referred to as the *menthol-*, *iso-*, *neo-* and *neo-iso-*form of compounds I–IV.

Table 2 also indicates the involved coupling constants, (neglecting long range couplings), which are expected for the two conformations, *e* and *a*, of each form; the band widths are seen to be the sum of the involved coupling constants.

TABLE 2. CONFORMATIONS AND COUPLING CONSTANTS OF THE INVESTIGATED COMPOUNDS

Table 2

Theoretical band width w_e	Conformation *e* Conformation *a*	Theoretical band width w_c
$2J_{aa} + J_{ea}$	*Menthol*-form 	$2J_{ee} + J_{ae}$
$2J_{aa} + J_{ec}$	*Iso*-form 	$2J_{ee} + J_{ae}$
$J_{ca} + 2J_{ea}$	*Neo*-form 	$J_{ee} + 2J_{ae}$
$J_{aa} + 2J_{ea}$	*Neo-iso*-form 	$J_{ee} + 2J_{ae}$

The conformational properties of the substituents attached to the cyclohexane ring are now well known, whilst the energy required to move a group from the equatorial to the axial position (ΔG value), has been investigated by many authors. It is now accepted that these values are for the hydroxyl group 0·8–1·0 Kcal/mole,[7] for the methyl group 1·7–1·9 Kcal/mole[7] and for the isopropyl group 2·0–2·2 Kcal/mole,[7] whilst a t-butyl group when attached to a mobile cyclohexane system, cannot be moved

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[7] See recent survey: M. Hanack, *Conformation Theory*. Academic Press, N.Y. (1965).

into the axial position.[8] The measurements obtained from the NMR spectra of these sixteen compounds are set out in Table 3.

TABLE 3. SUMMARY OF NMR DATA

			X proton		Coupling constant in c/s				Equilibrium, % of e conformer	
			τ	W in cps	J_{aa}	J_{ea}	J_{ae}	J_{ee}	calc.[a]	expected[a]
Menthol-form	I	Methyl menthol	6·92	23·0					100	100
	II	Menthol	6·62	23·0	9·4	4·2			100	100
	III	Carvomenthol	7·02	23·5					100	100
	IV	t-Butyl menthol	6·50	23·0	9·4	4·2			100	100
Iso-form	I	Iso-methyl menthol	6·27	17·0					74	79
	II	Iso-menthol	6·25	18·5	6·7[b]	5·1[b]			85	88
	III	Iso-carvomenthol	6·50	16·5					70	70
	IV	Iso-t-butyl menthol	6·20	20·5	7·6	5·2			100	100
Neo-form	I	Neo-methyl menthol	6·53	7·5	not split				0	0
	II	Neo-menthol	5·95	8·5	not split				0	0
	III	Neo-carvomenthol	6·17	8·0			3·0[c]	2·0	0	0
	IV	Neo-t-butyl menthol	5·85	8·5	not split				0	0
Neo-iso-form	I	Neo-iso-methyl menthol	6·30	19·5	10·5	4·5			100	?
	II	Neo-iso menthol	6·05	13·0	split, but possibly second order				29	70
	III	Neo-iso carvomenthol	6·35	19·2	10·0	4·6			100	100
	IV	Neo-iso-t-butyl menthol	5·77	9·5			3·6	2·2	0	0

[a] In order to calculate the equilibrium position, expressed as the mole fraction of conformer e, we have used the equations (1), (2) and (3).

$$K = \frac{W_a - W}{W - W_e} \tag{1}$$

$$\Delta G = -RT \cdot \ln K \tag{2}$$

$$m = \frac{K}{K + 1} \tag{3}$$

[b] Time averaged coupling constants.

[c] Calculated value from incompletely resolved spectrum.

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[8] [a] R. D. Stolow and M. M. Bonaventura, *J. Amer. Chem. Soc.* **85**, 3636 (1963);
[b] S. Winstein and N. J. Holness, *Ibid.* **77**, 5562 (1955).

The standard values W_e and W_a are, respectively, the band widths of the X proton when fixed axial in the *e* conformer, and when fixed equatorial in the *a* conformer. These values of W_e and W_a, to be used for each configuration of the compounds I–IV were not the same, and were chosen with extreme care from fixed compounds which approximated as near as possible to the investigated compound, with respect to the substitution pattern, orientation of the substituents, non-bonded interactions, and ring deformation. In some cases W_e and W_a could be taken from the measured values of similar fixed molecules, but occasionally they were calculated from the measured coupling constants in similar molecules. Thus for the *iso*-forms the value of W_e from iso-t-butyl-menthol was used whilst for the *menthol*-forms the different value of W_e from t-butyl-menthol was taken. Table 4 lists the values of W_e and W_a which were taken in each of the four forms, and the compounds from which they were taken.

TABLE 4. STANDARD VALUES OF THE BAND WIDTHS

Form	W_e c/s	Ref. compound used	W_a c/s	Ref. compound used
Menthol-form	23·0	t-butyl menthol	—	not required
Iso-form	20·5	iso-t-butyl menthol	7·0	calculated
Neo-form	—	not required	8·0	neo-carvomenthol
Neo-iso-form	19·5	neo-iso-methyl menthol	9·5	neo-iso-t-butyl menthol

Using these values, the equilibrium position in terms of the *e* conformer was calculated and compared with the expected result calculated from the known ΔG values of the substituents. These results are set out in Table 3.

Several points arose from the measurements listed in Table 2 and are worth discussing. Firstly it seems apparent that a t-butyl group itself caused negligible ring strain, for in the *menthol*-forms, the band width of the four types of compounds were the same, and where the coupling constants could be measured, these were also equivalent. However if a molecule was fixed using a t-butyl group, and a second substituent was introduced axially, as in iso-t-butyl-menthol the ring was then deformed. This was apparent from considering t-butyl-menthol and iso-t-butyl-menthol. It was expected that both these compounds would have the same band width for the X proton, as the environment is the same. This was not however so, a difference of 2·5 c/s being observed. Not only was the band width changed, but as expected, the coupling constants were also different. It seemed likely that the axial methyl group deformed the ring in such a way that the axial/axial coupling constant was decreased, whilst the equatorial/axial coupling constant was increased. It was highly unlikely that these measured coupling constants were the time averaged coupling constants as observed in a flexible molecule, and as calculated by Booth,[6] as this would infer that the t-butyl group moved into an axial position, or the molecule was in a twist form. The first inference is now known not to be possible,[8] whilst the second is extremely unlikely as the energy barrier is too great. It is possible that if a large group is fixed in the axial position, the coupling constants could be changed to such an extent, that both are then almost equal. This may in fact be an alternative explanation of the quintet observed in *cis*-4-t-butyl-1-phthalimidocyclohexane[9] and the molecule may not be in a boat form, but exist in a highly strained chair form with the phthalimido group still *axial*; an alternative explanation could be that this quintet is a further example of a "deceptively simple spectrum" as described by Abraham and Bernstein.[10] Iso-menthol itself, however, is a flexible interchanging molecule, thus a time averaged axial/axial coupling constant of 6·7 c/s and a time averaged equatorial/axial coupling constant of 5·1 c/s, were measured.

In both neo-methyl-menthol and neo-menthol, the bands due to the X proton were not split completely, however from the ΔG values of the substituents, it was expected that both would exist solely in the *a* conformation, as was observed. The difference in band widths observed in these compounds could be due to either the difficulty of measuring these accurately, or to the change in the involved coupling constants when the methyl group in the 2 position was replaced by an isopropyl group. Fortunately the X-part of the spectrum of neo-carvomenthol was slightly resolved which enabled J_{ee} to be measured (=2·0 c/s) and hence it was calculated that J_{ae} was only about 3·0 c/s This is a further example of a phenomenon which has recently been reported[11] that the coupling between an axial and an equatorial proton is not the same as that between an equatorial and an axial proton. The *e/a* coupling (equatorial hydroxyl, Fig. 2A) is about 50% larger than the corresponding *a/e* coupling (axial hydroxyl, Fig. 2B). The fact that neo-t-butyl-menthol itself had the same X-band width as the other three neo-forms is further proof that the t-butyl group did not cause any ring deformation.

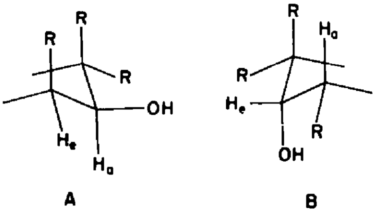

FIG. 2

The most interesting of the four forms was the neo-iso-form, and the results here illustrated how difficult it was to allow for all the variable factors. Neo-iso-methyl-menthol, in the ΔG difference, was almost equivalent to cyclohexanol, except that it had a strong 1:3 interaction between the axial methyl and the axial hydroxyl group in the *a* conformer. This interaction was so strong that it was sufficient to cause the molecule to exist at least 95% in the *e* conformer (possibly more than 95%). In order for this to occur the ΔG difference must be greater than 1·8 Kcal/mole, which suggested that the energy of this interaction was at least 1·0 Kcal/mole greater than a 1·3 hydroxyl-hydrogen interaction and probably much higher.[12] Bearing this fact in mind, it was difficult to explain why, using the information from the Tables, and the neccessary equations, it was found that neo-iso-menthol appeared to be fixed

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[9] H. Booth and G. C. Gidley, *Tetrahedron Letters* 1449 (1964).

[10] R. J. Abraham and H. J. Bernstein, *Canad. J. Chem.* **39**, 216 (1961).

[11] D. H. Williams and N. S. Bhacca, *J. Amer. Chem Soc.* **86**, 2742 (1964).

[12] E. L. Eliel and H. Haubenstock, *J. Org. Chem.* **26**, 3504 (1961).

71% in the *a* conformation, whilst it should be fixed 70% in the *e* conformation, purely on the ΔG differences.

It was however possible that the standard value W_a used to calculate K was not the band width of the X proton in the *a* conformer. However it was more likely that the band width W_e in the alternative conformation was influenced by the axial isopropyl group. As we have, as yet, no compound with a fixed axial isopropyl group, it is at present not possible to observe how the coupling constants, and hence the band widths, are altered by fixing such a large group in the axial position. No account has been taken of the possible entropy effect in the *e* conformer either, and there must surely be considerable hindrance to the free rotation of the isopropyl group when fixed in the axial position. This example illustrates how much the factors mentioned earlier can effect the results.[13]

Neo-iso-carvomenthol was probably fixed entirely in the *e* conformations as not only was there a ΔG difference of 1·2 Kcal/mole, but also in the alternative conformation there was the 1:3 axial isopropyl-axial hydroxyl interaction.[14] This was supported by the fact that neo-iso-methyl-menthol showed the same band width, although the calculated ΔG difference was even smaller than 1·2 Kcal/mole. But the additional steric repulsion between the axial methyl and hydroxyl groups was large enough to fix the molecule in the *e* conformation. In neo-iso-t-butyl-menthol, it was predicted by the simple treatment, that the band width would be the same as in neo-t-butyl-menthol as the environment was the same. However this was not so, and further consideration showed that not only the ring was strained by the fixed axial methyl group, but also by the 1:3 axial methyl–axial hydroxyl interaction. If in fact this methyl–hydroxyl interaction was only about 1·0 Kcal/mole, then the molecule would exist only in a strained chair form. However if the strain was much larger it would be possible that a percentage of this molecule would exist in a twist conformation. Without knowing the exact magnitude of this 1:3 interaction, it was impossible to predict which explanation was nearer the truth.

An assessment of the accuracy of this method has been attempted and it is believed that in the range 20% to 80% of conformer *e* the results are more accurate that ±5%.

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[13] For a further discussion of the relative "size" of the isopropyl group, see R. D. Stolow, *J. Amer. Chem. Soc.* **86**, 2170 (1964).

[14] [a] S. Schroeter and E. L. Eliel, *J. Amer. Chem. Soc.* **86**, 2066 (1964);
[b] Y. R. Naves, *Helv. Chim. Acta* **47**, 1617 (1964).