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CONFORMATION OF NON-AROMATIC RING COMPOUNDS—XXXIII[1]

TRANS-1,2-DIHALOGENOCYCLOHEXANES, *TRANS*-1,2-DIHALOGENOCYCLOPENTANES AND α-HALOGENOCYCLOHEXANONES; CORRELATION BETWEEN DIPOLE MOMENTS AND VICINAL PROTON SPIN COUPLING CONSTANTS

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Abstract—For a series of conformation-inverting ring compounds having similar geometry and containing the same or similar vicinal polar substituents a linear relation exists between the squares of the electric dipole moments and the sum of the vicinal coupling constants $J_{AX} + J_{BX}$. An analysis of this relation in terms of the *Karplus* constants is developed. It is shown that the combination of dipole moment data with coupling constants yields valuable quantitative information on *Karplus* parameters, ring deformation and conformational equilibrium constants.

INTRODUCTION

One of the main difficulties[2] encountered in the study of mobile systems under conformational equilibrium by the measurement of electric dipole moments or NMR spectroscopy is that parameters of the individual conformers are a prerequisite and often they are not directly attainable by experiment. In favourable cases conformationally homogeneous systems furnish the necessary data. Use of such a technique requires the assumption that the geometry of the molecule does not suffer from deformation by the substituent used as a holding group (cf. p. 2277). In the absence of such substrates the parameters of the individual conformers under equilibrium must be estimated.

We introduce here a method that utilizes the correlation between two physical properties P and Q of an equilibrium mixture of two forms E and A as follows: The properties P and Q are equated to the properties P_A, P_E, etc. of the individual conformers by:

$$P = x_E P_E + (1 - x_E)P_A \qquad (1)$$

$$Q = x_E Q_E + (1 - x_E)Q_A \qquad (2)$$

where x_E is the molar fraction of component E ($x_E + x_A = 1$). From (1) and (2) it follows that:

$$dP/dQ = (P_E - P_A)/(Q_E - Q_A) = \Delta P/\Delta Q = \text{constant} \qquad (3)$$

Provided the properties P_A, P_E, Q_A, Q_E are independent of the external influences that are used to vary the equilibrium constant (e.g. change of solvent or temperature) a shift of the equilibrium yields a linear relation between P and Q with slope $\Delta P/\Delta Q$. In principle this relation can be extended to three or more dimensions. In particular,

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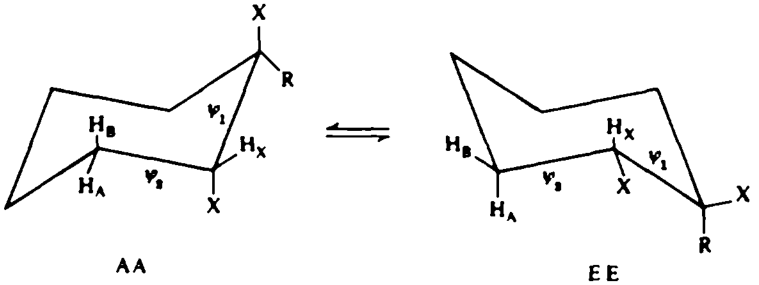
[1] Part XXXII: C. Altona, H. J. Geise and C. Romers, *Rec. Trav. Chim.* in press.

[2] E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis* Chap. 7, and Refs. cited therein. Wiley, New York (N.Y.) (1965).

the object of the present paper is to show that the *combination* of dipole moments and NMR coupling constants yields useful information on mobile as well as on fixed ring systems that contain two vicinal dipoles. The method is worked out in detail for *vic*-dihalogeno substituted 5- and 6-membered cycloalkanes and for α-halocyclohexanones. It can easily be adapted to other systems and/or other properties.

DISCUSSION

Consider the rapidly equilibrating two-conformer system:



The proton couplings of interest are those between H_X and H_A, H_B (ABX-type). Observed couplings are assumed to be time averages of the couplings of the two forms under equilibrium. For the compounds under consideration (X = halogen) the equilibrium constant is highly solvent dependent.

Writing $J_{AA} = (J_{AX} + J_{BX})_{AA}$ (H_X equatorial) and $J_{EE} = (J_{AX} + J_{BX})_{EE}$ gives the observed separation $J = J_{AX} + J_{BX}$ of the terminal lines of the H_X signal of the equilibrium mixture as a sum:

$$J = (1 - x_{EE})J_{AA} + x_{EE}J_{EE} \tag{1A}$$

Similarly, the squares of the electric moments are related by the expression:

$$\mu^2 = (1 - x_{EE})\mu_{AA}^2 + x_{EE}\mu_{EE}^2 \tag{2A}$$

Combining (1A) and (2A), it is seen that a linear relation between μ^2 and J should hold with a slope H equal to:

$$H = d\mu^2/dJ = (\mu_{EE}^2 - \mu_{AA}^2)/(J_{EE} - J_{AA}) \tag{3A}$$

Strictly speaking, Eq. (3A) is valid for a given compound measured in a series of solvents, under the assumption that the moments and coupling constants of each conformer are practically solvent-independent. However, expression (3A) can be applied in a more general way. The experimental results indicate that for a series of compounds in various solvents a single straight line is obtained, provided all the compounds have similar geometry (i.e. are isogeometric) and carry the same or similar polar substituents. It was considered worthwhile to investigate the physical significance of H in terms of molecular geometry with the aid of the *Karplus* equation[3] (keeping in mind its approximative nature) and the usual vector calculation of dipole moments. To this end equations are developed in which $\Delta\mu^2$ and ΔJ are written as functions of the appropriate dihedral angles (or projected valency angles) of the ring.

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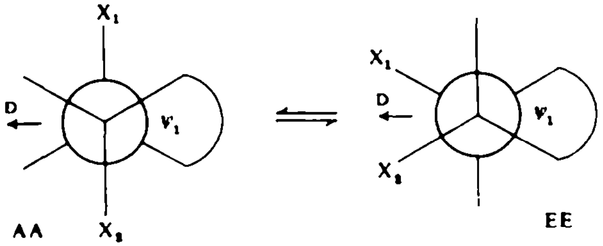
[3] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959); *J. Am. Chem. Soc.* **85**, 2870 (1963).

A. *Dipole moments*

Consider the systems:



where the arrows represent dipole moment vectors. The squares of the electric moments follow from the equations (assuming trigonal symmetry about the projection axis):

$$\mu_{EE}^2 = 4M \cos^2 \tfrac{1}{2}(120 - \psi_1) + D \tag{4}$$

$$\mu_{AA}^2 = 4M \cos^2 \tfrac{1}{2}(120 + \psi_1) + D \tag{5}$$

$M = \mu_D^2 \sin^2 \alpha$, where μ_D is the partial moment along the C—X bond and α is the valency angle C—C—X. A correction term D has been introduced because, at least for (aa)-1,2-dihalogenocyclohexanes, μ_{AA}^2 found is larger than calculated owing to the induced moment in the ring.[4–7] The possibility that D is a function of ψ is ignored in the present approach; in practice $D \approx 0{\cdot}8$–$1{\cdot}2$. From (4) and (5):

$$\Delta\mu^2 = \mu_{EE}^2 - \mu_{AA}^2 = 2\sqrt{3}\, M \sin \psi_1 \tag{6A}$$

For $D \neq 0$, Eq. (6A) is valid for $0° < \psi_1 < 60°$, for $60° < \psi_1 < 90°$ we find:

$$\Delta\mu^2 = 4M(1 - \tfrac{1}{2} \cos \psi_1) \tag{6B}$$

B. *Coupling constants*

The *Karplus* equation is utilized in the following form:

$$J = A \cos^2 \psi_{HH} - B \cos \psi_{HH} + C \qquad (0° < \psi < 180°) \tag{7}$$

The theoretical *Karplus* constants,[3] adjusted to Eq. (7), are: $A = 9{\cdot}0$, $B = 0{\cdot}5$, $C = -0{\cdot}3$ c/s. Recent MO calculations[8] of vicinal couplings in ethane yielded coupling constants for various ψ values that can be approximated (error $< 0{\cdot}2$ c/s for $0° < \psi < 180°$) by Eq. (7) with: $A = 9{\cdot}4$–$9{\cdot}6$, $B = 1{\cdot}9$–$2{\cdot}0$, $C = 0{\cdot}2$ c/s. In the present state of our knowledge these "constants" seem best treated as empirically adjustable parameters with special emphasis on the greatest constant A. Introduction

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[4] E. C. Wessels, Thesis, Leiden, 1960.

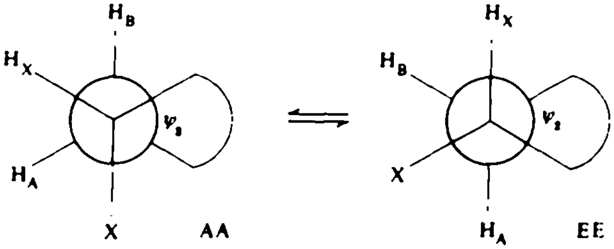
[5] H. J. Geise, Thesis, Leiden, 1964.

[6a] H. J. Hageman, Thesis, Leiden, 1965; [6b] H. J. Hageman and E. Havinga, *Tetrahedron* **22**, 2271 (1966).

[7] H. J. Geise, A. Tieleman and E. Havinga, *Tetrahedron* **22**, 183 (1966).

[8] R. C. Fahey, G. C. Graham and R. L. Piccioni, *J. Am. Chem. Soc.* **88**, 193 (1966).

of the ring dihedral angle ψ_2 ($0° < \psi_2 < 90°$)[9] gives:



$$\begin{aligned} J_{EE} &= J_{aa} + J_{ae} = J(120 + \psi_2) + J(\psi_2) \\ J_{AA} &= J_{ee} + J_{ea} = J(120 - \psi_2) + J(\psi_2) \end{aligned} \tag{8}$$

For the *trans*-1,2-dihalogenocyclohexanes $J_{ae} \cong J_{ea}$, the difference $J_{ea} - J_{ae}$ being of the order of magnitude of 0·1–0·2 c/s[10]; Eq. (9) can then be derived from (7) and (8):

$$\Delta J = J_{EE} - J_{AA} = \sqrt{3} \sin \psi_2 (A \cos \psi_2 + B) \tag{9}$$

Throughout this paper an arbitrary value of B = 0·5 c/s will be retained (it is known that $J(\psi = 0°) < J(\psi = 180°)$); A is the "constant" to be determined (the parameter C drops out in the difference ΔJ). It is easily verified that a different choice of B, adapting the value of A so that for a certain ψ range (e.g. ψ = 50–55°) the term $A \cos \psi_2 + B$ remains constant, has practically no influence on the numerical value of ΔJ (Eq. 9) in the range $0° < \psi_2 < 60°$. The same argument applies to the expressions (10), (11), (12) and (13) derived below. We will return to this point later.

The expression (9) has a maximum value near $\psi = 45°$ (Fig. 1). A few conclusions can be drawn from this graph: (i) The value of ΔJ is highly dependent on A in the most interesting region $35° < \psi_2 < 60°$ (i.e. the range expected for dihedral angles of 6-membered rings in chair or twisted boat forms, the puckered part of 5-membered rings, etc). (ii) In the same range ΔJ changes only by ~0·5 c/s for any given A. Consequently, the experimental determination of ΔJ may be expected to yield a reasonable value for A (valid for the system under investigation) *even when the geometry* (ψ_2) *about the given bond is not exactly known.*

Of interest are also the curves J_{AA} and J_{EE} *vs* ψ_2 (Fig. 2) obtained from (7) and (8):

$$J_{EE} = \tfrac{1}{2} \cos \psi_2 (A \cos \psi_2 - B) + \tfrac{1}{2}\sqrt{3} \sin \psi_2 (A \cos \psi_2 + B) + 2C + \tfrac{3}{2} \,.\, A \tag{10}$$

$$J_{AA} = \tfrac{1}{2} \cos \psi_2 (A \cos \psi_2 - B) - \tfrac{1}{2}\sqrt{3} \sin \psi_2 (A \cos \psi_2 + B) + 2C + \tfrac{3}{2} \,.\, A \tag{11}$$

Because the unknown C enters into the numerical values, one cannot hope to calculate ψ_2 with some confidence from (10) or (11). On the other hand, when A is known even approximately from ΔJ (Eq. 9) a graph such as Fig. 2 may serve to predict the effect of a given change in geometry (e.g. a flattening of the ring due to steric strain) on J_{AA} and J_{EE}. The slope of the curves and the positions of the maximum and minimum are quite insensitive to the exact value of A. It is seen that over the region of ψ_2 that

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[9] It is to be noted that a different ψ enters here because now one is viewing along the C_1—C_2 bond. Deviations from trigonal symmetry about the projection axis can be calculated for each case or, preferably, taken from X-ray or neutron diffraction or similar methods.

[10] R. U. Lemieux and J. W. Lown, *Canad. J. Chem.* **42**, 893 (1964).

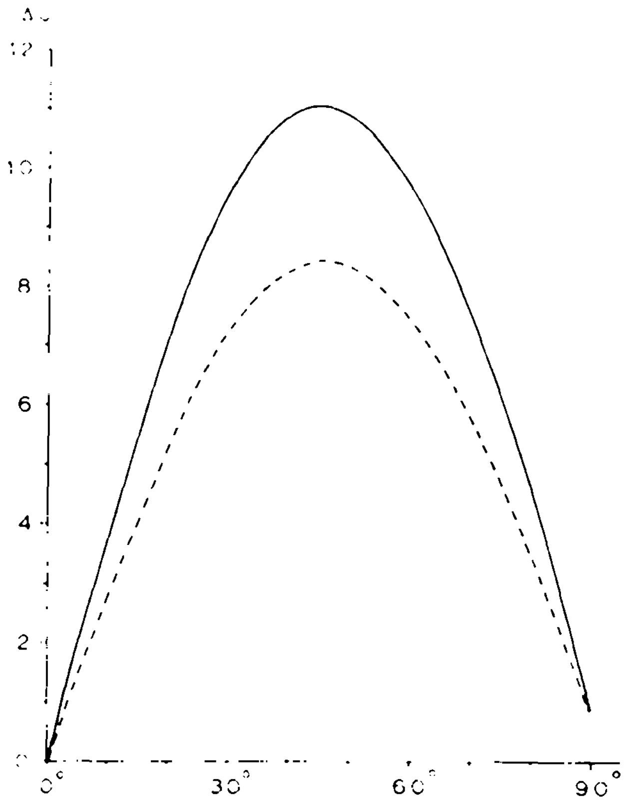

FIG. 1. $\Delta J = J_{BB} - J_{AA}$ as function of the ring dihedral angle of the CH_2—CHX fragment. Full line: A = 12, B = 0·5 c/s; dotted line: A = 9, B = 0·5 c/s, see text.

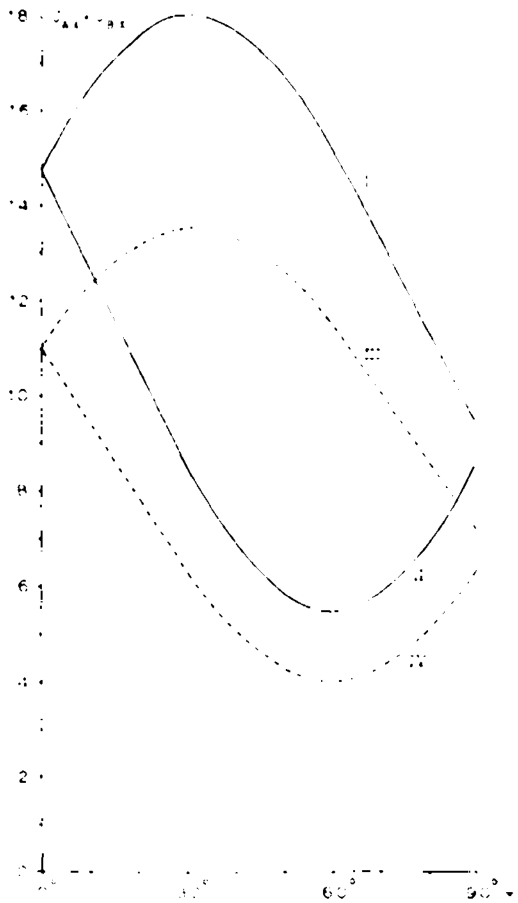

FIG. 2. J_{BB} (curves I and III) and J_{AA} (curves II and IV) plotted against ring dihedral angle. Full lines: A = 12, B = 0·5, C = 0 c/s; dotted lines: A = 9, B = 0·5, C = 0 c/s. See text.

is most important for cyclohexane stereochemistry J_{AA} (X-proton equatorial) varies much less with ψ than J_{EE}. Therefore, assuming that rotation-dependent electronegativity effects do not interfere, measurements of J_{EE} seem to provide a sensitive method for studying the effect of steric strain on ring geometry.

C. *Relation between μ^2 and J*

Combining the expressions (3A), (6A) and (9) we have:

$$H = d\mu^2/dJ = \frac{2M \sin \psi_1}{(A \cos \psi_2 + B) \sin \psi_2} \tag{12}$$

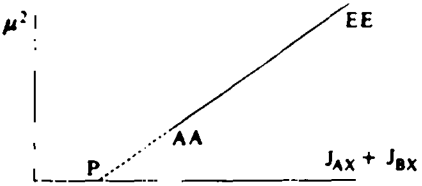

FIG. 3. Theoretical relation between μ^2 and $J_{AX} + J_{BX}$.

with the condition $0° < \psi < 60°$. For the 6-membered ring ($\psi_1 \simeq \psi_2$) this equation simplifies to:

$$H = \frac{2M}{A \cos \psi + B} \tag{13}$$

The relation between H and ψ is depicted in Fig. 4 (full line) using the following parameters valid for the *trans*-1,2-dihalogenocyclohexanes: $\mu_p = 2{\cdot}0D$, $\alpha = 110{\cdot}5°$, $A = 12{\cdot}0$ c/s, $B = 0{\cdot}5$ c/s. The A value (12·0) was so chosen as to yield the experimental slope ($H = 0{\cdot}91$) for an assumed value of $\psi = 53°$.[11] The curve for $A = 9$, $B = 0{\cdot}5$ is also shown (dotted line). As remarked above, any combination of A and B can be chosen on condition that $A \cos \psi + B$ is constant for the given ψ, i.e. A and B cannot be determined independently by the present method. For example, taking $B = 0$ yields $A = 12{\cdot}8$ c/s; for $B = 1{\cdot}5$ c/s, $A = 10{\cdot}3$ c/s. The interesting point is that the resulting curves ($B = 0 \rightarrow B = 1{\cdot}5$) of H *vs* ψ differ maximally 4% in H near $\psi = 0$ from the one shown in Fig. 4 (full line), and much less near the chosen ψ value where the curves cross. Therefore, when ψ and the partial electric moments are known,[15] the experimental determination of H for a series of iso-geometric molecules also yields A and thus the angular dependence of H on ψ. Because the location of the curve H *vs* ψ is a sensitive function of the parameter A (see Fig. 4), this procedure seems to be potentially valid for determining this parameter. Experimental data on equilibrium mixtures suffice, whereas application of equations (9), (10) and (11) is only feasible when A is known.

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[11] This value is chosen in accordance with electron diffraction data for cyclohexane[12]: $\psi = 54{\cdot}5°$, and allowing for a slight extra flattening due to the substituents.[13,14]

[12] M. Davis and O. Hassel, *Acta Chem. Scand.* 17, 1181 (1963).

[13] C. Altona, Thesis, Leiden, 1964.

[14] H. J. Geise, C. Altona and C. Romers, *Tetrahedron* 23, 439 (1967).

[15] ψ is often accessible from physical studies on the parent rings; the electric moments can usually be taken safely from model compounds.

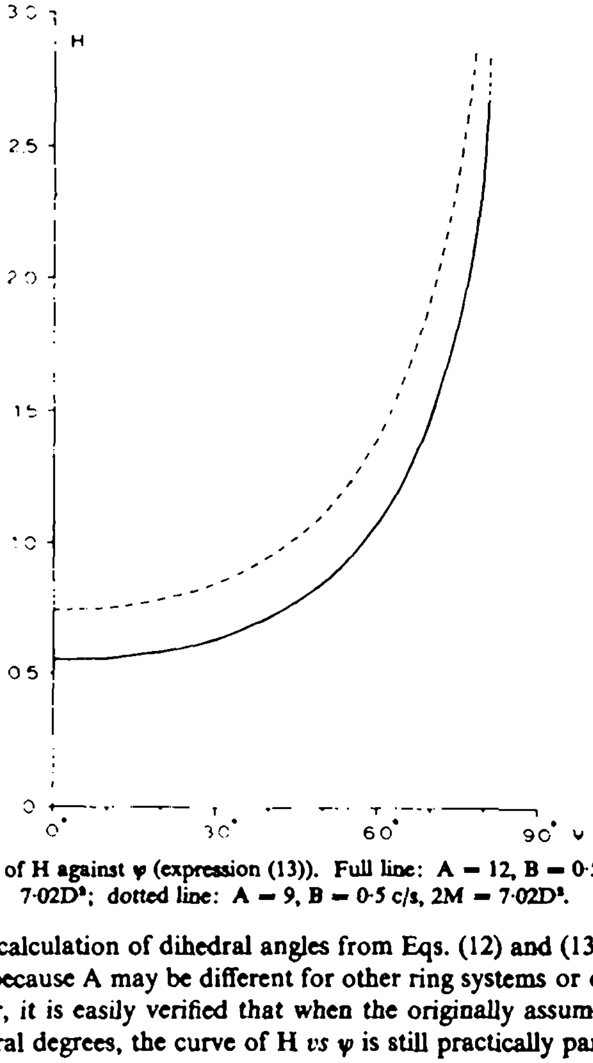

FIG. 4. Plot of H against ψ (expression (13)). Full line: A = 12, B = 0·5 c/s, 2M = 7·02D²; dotted line: A = 9, B = 0·5 c/s, 2M = 7·02D².

The *a priori* calculation of dihedral angles from Eqs. (12) and (13) seems to be of doubtful value because A may be different for other ring systems or different substituents. However, it is easily verified that when the originally assumed value of ψ is in error by several degrees, the curve of H *vs* ψ is still practically parallel to the true one, hence a *change* in H can be correlated, at least semiquantitatively, to a *change* in ψ. In this connection it is also interesting to look at the point of intersection (P) of the straight line μ^2 *vs* J with the J-axis (Fig. 3). Formally, we may write:

$$J_P = J_{AA} - \mu_{AA}^2/H \tag{14}$$

Substitution of (5), (11) and (13) in expression (14) yields a rather unwieldy relation between J_P and ψ, which is graphically presented in Fig. 5, using the same parameters as before. Combination of Figs. 4 and 5 allows a full exploitation of the available information. For example, the increase in ring strain on introducing bulky axial substituents in *vic*-1,2-dihalogenocyclohexanes will be relieved by a certain amount of flattening of the ring (cf. the results of the X-ray analyses of diaxial and diequatorial 2,3-dihalogenocholestanes[5,14]) which in turn should lead to a shift of the line μ^2 *vs* J to the right and a decrease in H. Both predictions are in agreement with the experimental results.

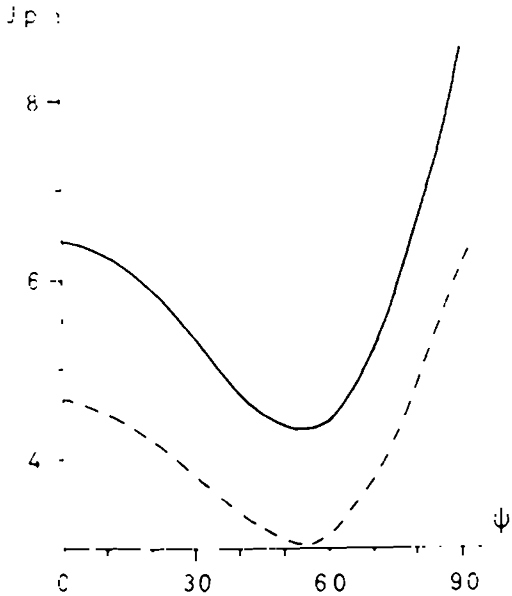

Fig. 5. J_P as function of ring dihedral angle ψ. Full line: A = 12, B = 0·5, C = 0 c/s, dotted line: A = 9, B = 0·5, C = 0 c/s.

More complex cases will be dealt with here only briefly. In molecules where each AA and EE conformer consists of two conformations of equal energy, interconverting via the pseudorotation pathway (as might be the case with certain derivatives of cyclopentane[16] and cycloheptane), there are in general two values of ψ_2 (e.g. 46·1° and 28·6° for the envelope form of cyclopentane[17]) and the expression in the denominator of Eq. (12) becomes more complicated.[18] In the case of a three-conformer system the relation between μ^2 and J is no longer unambiguous. It can be shown[18] that a straight line is obtained only when special conditions are fulfilled, e.g. where the molar fraction of one of the conformers is solvent independent.

RESULTS

A. trans-1,2-*Dihalogenocyclohexanes and related compounds*

The experimental results are shown in Table 1. The coupling constants for *trans*-1,2-dichloro- (**1**) and *trans*-1,2-dibromocyclohexane (**2**) in benzene and carbon tetrachloride based on spin decoupling experiments on the compounds deuterated at C(1) and C(4)[10] were used. In our experience deuteration is not prerequisite to obtain the correct value of $J_{AX} + J_{BX}$ in the cases where the H_X protons are equivalent by symmetry (AA′BB′XX′ system). For low concentrations (< 10 mole %) the outer peaks in the H_X-patterns of **1** and **2** are clearly visible and their distance corresponds closely (within 0·2 c/s) to the values quoted.[10] This fact has been used in the analysis of the NMR spectrum of compound **5** and of the *trans*-1,2-dihalogenocyclopentanes (cf. the discussion in Ref. 16*b*). The H_X-pattern of compound **10** is

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[16a] C. Altona, H. R. Buys and E. Havinga, *Rec. Trav. Chim.* **85**, 973 (1966); [b] *Ibid.* **85**, 983 (1966).

[17] K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.* **81**, 3213 (1959).

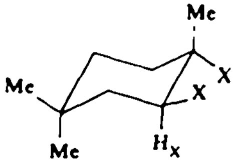
[18] H. R. Buys, forthcoming thesis, Leiden.

TABLE 1. DIPOLE MOMENTS (D) AND $J_{AX} + J_{BX}$ (c/s) OF *trans*-VICINAL DIHALIDES OF SATURATED SIX-MEMBERED RING SYSTEMS

Compound	Solvent[a]	μ	$J_{AX} + J_{BX}$	mole % EE	$\Delta G°$ kcal/mole
1 *trans*-1,2-Dichlorocyclohexane	ct	2·30[b]	10·4[c]	43	0·17
	bz	2·63[d]	11·9[c]	59	−0·22
2 *trans*-1,2-Dibromocyclohexane	ct	1·78[b]	7·9[c]	21	0·78
	bz	2·15[b]	9·3[c]	35	0·37
3 *trans*-1,2-Dichloro-1-methylcyclohexane	ct	1·66[b]	7·6	18	0·90
	bz	1·99[b]	8·6	28	0·56
4 *trans*-1,2-Dibromo-1-methylcyclohexane	ct	1·36[b]	6·6	8	1·45
	bz	1·65[b]	7·2	15	1·03
5 2a,3a-Dibromo-*trans*-decalin	ct	1·15[e]	5·9	0	—
6 1a,9a-Dibromo-*trans*-decalin	ct	0·86[e]	5·0	0	—
7 2β,3α-Dibromo-3β-methylcholestane	bz	1·39	6·6	0	—
8 5α,6β-Dichlorocholestane	ct	1·11[f]	5·4	0	—
9 *trans*-1,2-Dichloro-1,4,4-trimethylcyclohexane	ct	2·96[b]	15·8	86	−1·07
	bz	3·12[b]	16·7	96	−1·88
10 2e,3e-Dibromo-*trans*-decalin	ct	3·28[g]	15·6	100	—

[a] ct = CCl_4, bz = benzene; [b] Ref. 6; [c] Ref. 10; [d] W. Kwestroo, F. A. Meijer and E. Havinga, *Rec. Trav. Chim.* 73, 717 (1954); [e] A. Adriaanse, private communication; [f] Ref. 7; [g] Assumed to be equal to the dipole moment of 1a,2a-dibromo-4-t-butylcyclohexane.[4]

more complicated. The peaks (separated 15·6 c/s) that we used to determine $J_{AX} + J_{BX}$ are accompanied by other absorptions (separations 22·4 and 30·8 c/s). The latter separations would lead to an abnormally high dipole moment and were neglected. Compounds **5**–**8** are conformationally homogeneous (diaxial), as is compound **10** (diequatorial). The remaining compounds are equilibrium mixtures aa ⇌ ee. Figure 6 indicates that the linear relation (3) is obeyed within the error of measurement,[19] with the exception of compound **9**. The slope H is equal to 0·91 while compound **9** which



mainly consists of the ee-conformer displays a significantly smaller slope (H = 0·79). The point at the hypothetical J_P of the latter line was calculated using an iterative procedure based on Fig. 5. The experimental results (compounds **1**–**4**) are adequately

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[19] It may be seem curious at first sight that the points for the diaxial substrates **5**–**8** are scattered along the line, i.e. there are no definitive values for μ_{AA} and J_{AA} that represent *the* diaxial conformation. This effect is ascribed to different degrees of substitution (secondary and tertiary axial halogens have slightly different electric moments[6]) and differences in geometry. Calculation shows that the relation between μ_{AA}^2 and J_{AA} for *diaxial* forms with different ψ values is not strictly linear, but still follows the general trend of Fig. 6.

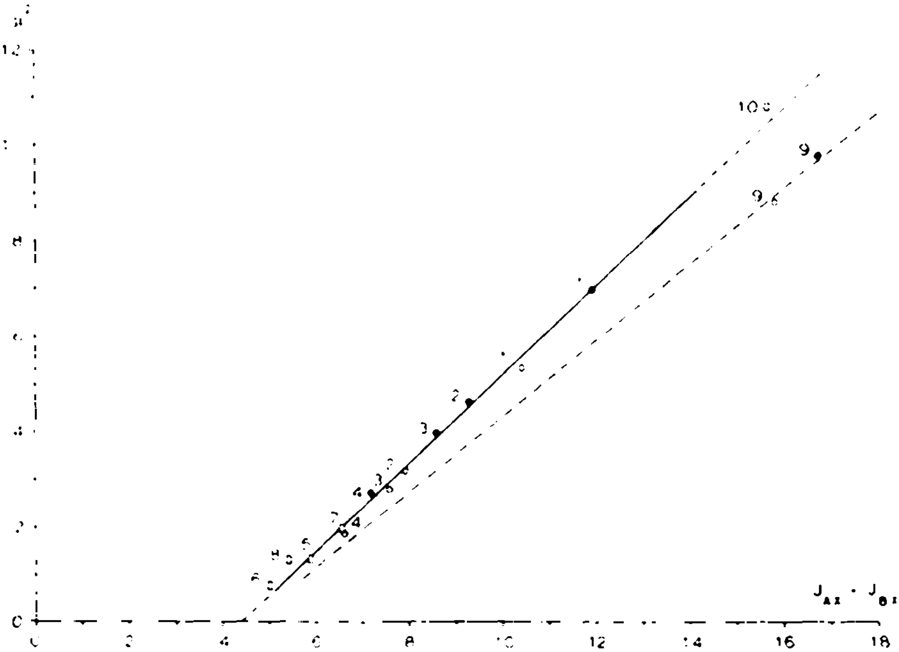

Fig. 6. Values of μ^2 plotted against $J_{AX} + J_{BX}$ of *trans*-1,2-dihalogenocyclohexanes and related compounds. The numerals refer to the compounds listed in Table 1. □ Conformationally homogeneous molecules, ○ Solutions in carbon tetrachloride, ● Solutions in benzene.

described by the following set of parameters, using equations (7), (10), (11), (13) and $H_{exp} = 0{\cdot}91$: $A = 12{\cdot}0$, $B = 0{\cdot}5$, $C = 0$ c/s, $2M = 7{\cdot}02D^2$, $\psi_1 = \psi_2 = 53°$.

For conformationally homogeneous AA and EE dihalogenides having the same geometry the above parameters yield: $J_{AA} = J_{ee} + J_{ea} = 5{\cdot}6$ c/s, $J_{EE} = J_{aa} + J_{ae} = 16{\cdot}3$ c/s, $\mu_{AA} = 1{\cdot}07D$, $\mu_{EE} = 3{\cdot}32D$, all in good agreement with current figures, obtained from similar systems[6,20,21] ($J_{aa} = 10{\cdot}2$–$12{\cdot}4$ c/s, $J_{ae} \cong J_{ea} = 3{\cdot}5$–$4{\cdot}2$ c/s, $J_{ee} = 2$–3 c/s, $\mu_{AA} = 1{\cdot}1 \pm 0{\cdot}2D$, $\mu_{EE} = 3{\cdot}4 \pm 0{\cdot}2D$). Our value for J_{EE} is larger than that derived in Ref. 10 (13·94 c/s); however, the latter was based on molar fractions x_{AA} and x_{EE} calculated with the assumption that $\mu_{AA} = 0$.

Using the above values of J_{AA}, J_{EE}, $\mu_{AA}{}^2$ and $\mu_{EE}{}^2$ the molar fraction x_{AA} and the conformational preference $\Delta G°$ was calculated for compounds 1–4 at infinite dilution in benzene and in carbon tetrachloride (Table 1). These results are probably more accurate than data from either the NMR method or the dipole moment method. The smaller slope for compound 9 is consistent with $\psi_1 = \psi_2 = 46°$ (retaining the remaining parameters), i.e. the ring is flattened by about 7°. Evidently, this flattening partly relieves the steric crowding in the molecule, which contains two axial methyl groups.[22] The following values are calculated for 9: $J_{AA} = 6{\cdot}2$ c/s, $J_{EE} = 17{\cdot}2$ c/s; $\mu_{AA} = 1{\cdot}14D$, $\mu_{EE} = 3{\cdot}17D$.

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[20] A. C. Huitrick, J. B. Carr, W. F. Trager and B. J. Nist, *Tetrahedron* **19**, 2145 (1963).

[21] H. J. Hageman and E. Havinga, to be published.

[22] It is estimated that a decrease of all dihedral angles by 7° with a concomitant increase of the C-C-C valency angles from 112·0 to 114·2° increases the enthalpy of the molecule by about 2–2·5 kcal/mole, a reasonable value in view of the known $\Delta H°$ of a single methyl group[6] (ca. 1·6 kcal/mole).

B trans-1,2-*Dihalogenocyclopentanes*

In the conformational analysis of the *trans*-1,2-dihalogenocyclopentanes the flexibility of the saturated 5-membered ring must be taken into account, i.e. the possible existence of a continuous range of conformations of practically equal energy (pseudolibration[16]): In a series of previous papers[16] it was shown that the physical data can be interpreted as follows. Mainly two conformers, differing in polarity ("diaxial" and "diequatorial") are in dynamic equilibrium. The halogen atoms occupy the most puckered part of the ring and the conformers partaking in the equilibrium seem well represented as in Fig. 7. The H_X-patterns were analysed in the same way as those of the cyclohexane compounds[23] (see Fig. 3 in Ref. 16*b* for a description of the spectrum). The results are presented in Table 2. Figure 8 shows that the expected linear relation (3) is obeyed within the limits of error. Introducing the following set of parameters into expressions (12) and (9): $H_{exp} = 1{\cdot}05$, $\varphi_1 = 48{\cdot}1°$, $\varphi_2 = 39{\cdot}5°$,[17]

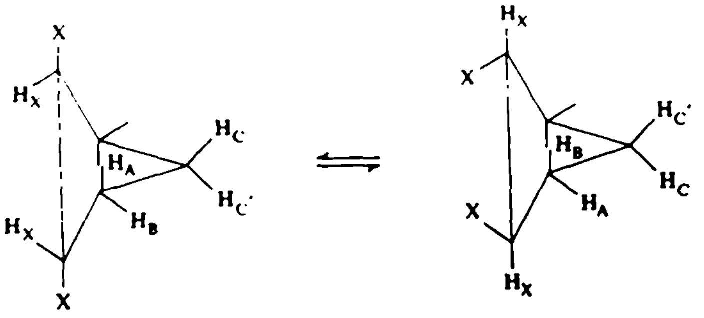

FIG. 7

TABLE 2. DIPOLE MOMENTS (D) AND $J_{AX} + J_{BX}$ (c/s) OF *trans*-1,2-DIHALOGENOCYCLOPENTANES[16]

Compound	solvent*	μ	$J_{AX} + J_{BX}$	mole % EE	ΔG° (kcal/mole)
11 *trans*-1,2-Dichlorocyclo-pentane	ct	1·48	7·6	16	1·00
	bz	1·64	8·1	21	0·77
12 *trans*-1,2-Dibromocyclo-pentane	ct	1·40	7·4	13	1·21
	bz	1·56	7·8	18	0·90
13 *trans*-1,2-Dibromo-1-methyl-cyclopentane	ct	1·19	6·8	7	1·58
	bz	1·34	7·2	11	1·23

* ct = CCl_4, bz = benzene.

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[23] An alternative interpretation of the measured H_X spectrum would yield slightly different constants, as follows: If the separation between the outer peaks of each triplet (1–1·3 c/s) is due to a real long-range coupling between H_X and one of the protons H_A', H_B', H_C or H_C', the graph of μ^2 *vs* J (Fig. 8) should be shifted to lower J-values. Because of the probable stereospecificity of this long-range coupling, the measured slope may be in error by an unknown amount, not exceeding 10%. In order to test this possibility spin–spin decoupling experiments were carried out at 100 Mc. Besides confirming the original assignment[16] of the multiplets at $\delta = 2{\cdot}58$, $\delta = 1{\cdot}79$ and $\delta = 1{\cdot}56$ ppm (benzene) as being due to the A, B and C protons, respectively, it appeared that $^4J_{XC} = {}^4J_{XC'} = 0$. Decoupling H_B yielded an X-doublet: $J_{AX} = J_{ae} = 5{\cdot}0$ c/s, from which we calculate: A = 9·0, B = 0·5, C = 0 c/s. Decoupling H_A gave a nonresolvable multiplet that could not be interpreted unambiguously (X part of BB'XX' spectrum).

the same partial electric moment as was used for the 6-membered analogues ($2M = 7{\cdot}02D^2$) and an estimated increment $D = 0{\cdot}8D^2$ to account for the moment induced in the ring (expressions (4) and (5)) we find: $A = 9{\cdot}5$, $B = 0{\cdot}5$, $C = 0{\cdot}4$ c/s; $J_{AA} = 6{\cdot}2$, $J_{EE} = 14{\cdot}9$ c/s; $\mu_{AA} = 0{\cdot}9$, $\mu_{EE} = 3{\cdot}16D$.[24] Molar fractions and $\Delta G°$ values were calculated as before (Table 2). It is interesting to note that for the cyclopentane derivatives the "constant" A is rather smaller than for the 6-membered compounds (12·0 c/s). Of course, the true values of ψ_1 and ψ_2 that go into the equations are not accurately known for lack of X-ray or electron-diffraction data. However, the cyclopentane ring would have to be severely puckered in order to bring its A-value near to that required by the cyclohexane rings. Even the so-called maximally puckered model[25] ($\psi_1 = 60°$, $\psi_2 = 50°$) yields an A value of only 11·0 c/s. On the other hand, it is now known[26] that the actual torsional angles in *trans*-fused D-rings in steroids are adequately represented (within 1–3°) by the Pitzer and Donath model,[17] which was also used in the present work. Therefore, the change of Karplus constant of the CHX—CH$_2$ fragment (X = Cl or Br) with ring size has to be accepted as essential. Whether in the description given this difference somehow presents a reflection of the difference in flexibility of the 5- and 6-membered ring systems (pseudolibration of the 5-ring conformers versus "rigidity" of the 6-ring chair form) has not yet been analysed.

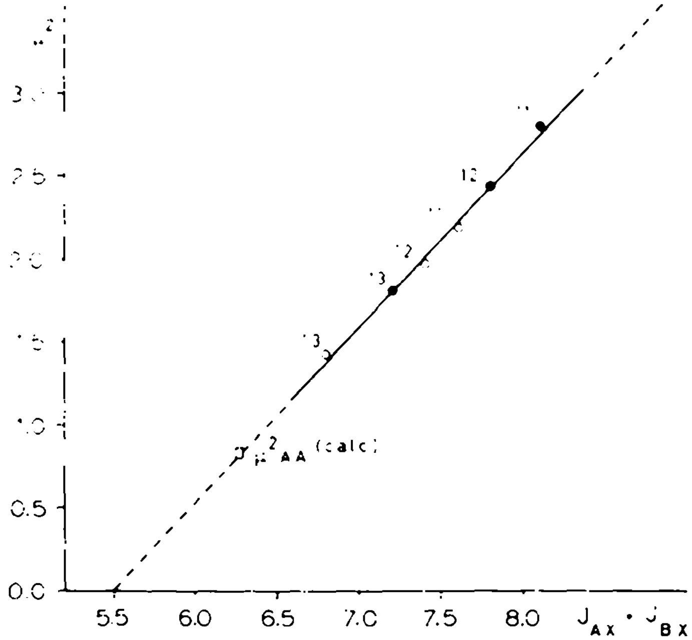

FIG. 8. Values of μ^2 against $J_{AX} + J_{BX}$ of *trans*-1,2-dihalogenocyclopentanes. The numerals refer to the compounds listed in Table 2. ○ Solutions in carbon tetrachloride ● Solutions in benzene.

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[24] These values differ slightly from those derived in Ref. 16*b* mainly because previously the theoretical parameter A = 9·0 c/s was retained.

[25] F. V. Brutcher and W. Bauer, *J. Am. Chem. Soc.* **84**, 2233 (1962).

[26] C. Altona, H. J. Geise and C. Romers, to be published.

C. α-*Halogenocyclohexanones*

A review of recent work on the axial-equatorial ratio of α-halogenocyclohexanones has appeared.[3] Excellent NMR and dipole moment data are available for the conformationally homogeneous axial and equatorial forms, so that the end points of the μ^2 *vs* J relation are well fixed. Table 3 lists the data for 4-*t*-butyl-2-halogenocyclohexanones as well as some intermediate values obtained from equilibrium mixtures a ⇌ e of 2-bromo- and 2-chlorocyclohexanone.

TABLE 3. DIPOLE MOMENTS (D) AND $J_{AX} + J_{BX}$ (c/s) OF α-HALOGENOCYCLOHEXANONES IN VARIOUS SOLVENTS[a]

Compound	μ	$J_{AX} + J_{BX}$	mole % E	ΔG°(kcal/mole)
14 *trans*-2-Bromo-4-*t*-butyl-cyclohexanone	3·20[b] (bz)	5·6[c] (ct)	0	—
15 2-Bromocyclohexanone	3·33[d] (ct)	6·8[c] (ct)	10	$1{\cdot}6_9$
16 *cis*-2-Bromo-4-*t*-butyl-cyclohexanone	4·27[b] (bz)	17·9[c]	100	—
17 *trans*-2-Chloro-4-*t*-butyl-cyclohexanone	3·17[e] (bz)	5·5[f] (ct)	0	—
18 2-Chlorocyclohexanone	3·58[f] (ct)	$9{\cdot}5_6$ (ct)	32	$0{\cdot}4_4$
	3·68[g]	$10{\cdot}7_6$[g]	42	$0{\cdot}2_9$
	3·72[h]	$11{\cdot}2_6$[h]	45	$0{\cdot}1_8$
	3·78[f] (bz)	$11{\cdot}8_0$ (bz)	50	0
19 *cis*-2-Chloro-4-*t*-butyl-cyclohexanone	4·29[e] (bz)	18·0[f]	100	—

[a] ct = CCl_4, bz. = benzene; [b] N. L. Allinger, J. Allinger and N. A. LeBel, *J. Am. Chem. Soc.* **82**, 2926 (1960); [c] Ref. 27; [d] T. N. Pliev, *Russ. J. Phys. Chem.* **35**, 1054 (1961); [e] Ref. 32; [f] Ref. 30; [g] Mixture of CCl_4 and benzene with molar ratio 50/50; [h] *idem*, Molar ratio 27/73.

Garbisch[27] and others[28] report that the signal due to the H_2 proton in several 2-bromocyclohexanones of fixed conformation is further split by about 1·5 c/s. This splitting is ascribed to a stereospecific long-range coupling to a H_6 proton (either ee[27] or aa[28]). Interestingly, we observe a similar effect ($^4J = 1{\cdot}3$ c/s) in the case of 2-chlorocyclohexanone (**18**, Fig. 9), although the H_2 proton here flips rapidly from a to e and *vice versa*. This is an example of long-range coupling in mobile systems.

It was found that $J_{AX} + J_{BX}$ of 2-chlorocyclohexanone is highly dependent upon the concentration in the two solvents investigated.[29] In order to make a reliable comparison with the dipole moment data the J-values were determined by measuring at least four solutions in each solvent (concentration range 2–6 mole percent) and extrapolating to infinite dilution. A plot of μ^2 against $J_{AX} + J_{BX}$ is shown in Fig. 10.

Within the experimental error the points from the a ⇌ e equilibrium and those from *cis* and *trans*-4-*t*-butyl compounds lie on a single straight line. This fact seems to establish the validity, at least for the α-halocyclohexanones, of the assumption made when working with model compounds,[3] *viz.* that as a first approximation the geometry of the molecule remains unchanged by the insertion of a *t*-butyl group. Calculation

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[27] E. W. Garbisch, *J. Am. Chem. Soc.* **86**, 1780 (1964); *Chem & Ind.* (1964), 1715.

[28] P. Laszlo and J. I. Musher, *Bull. Soc. Chim. Fr.* 2558 (1964).

[29] This finding harmonizes with the observations reported in Ref. 26 for 2-bromocyclohexanone in CCl_4 but not with other work.[30]

[30] C.-Y. Chen and R. J. W. LeFèvre, *J. Chem. Soc.* 3700 (1965).

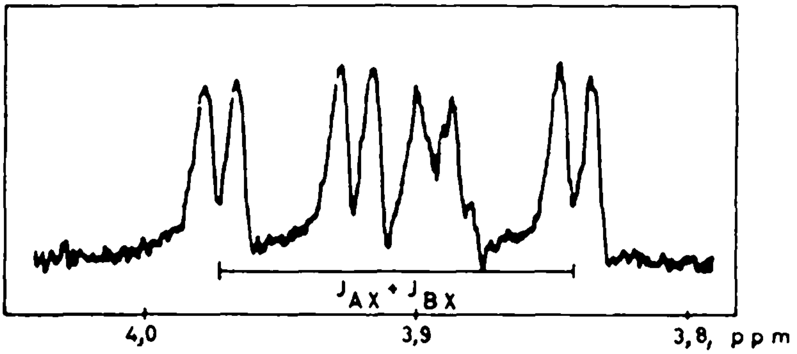

Fig. 9. H_2 proton signal of 2-chlorocyclohexanone in benzene (wt. fraction 0·18).

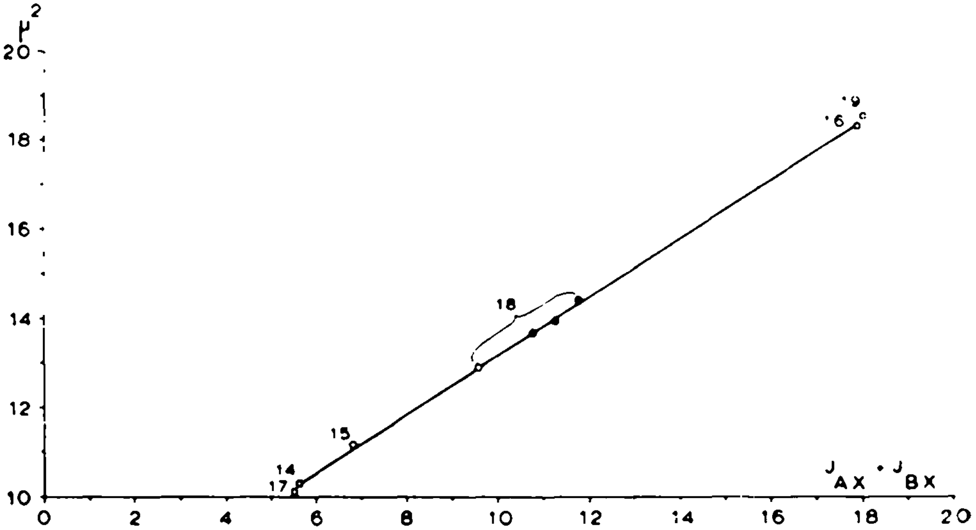

Fig. 10. Values of μ^2 plotted against $J_{AX} + J_{BX}$ of 2-halocyclohexanones. The numbers refer to the compounds listed in Table 3. □ Conformationally homogeneous molecules, ○ solutions in carbon tetrachloride, ● solutions in benzene.

shows that a change of 3° or even less in φ on substitution is likely detectable by the present method. Therefore, the *Karplus* parameters are best determined by using $\Delta J = J_A - J_E$ from the fixed compounds **14** and **16** (Table 3) in expression (9).[31] With $J = 12{\cdot}3$ c/s and $\varphi_2 = 52°$,[33] we obtain: $A = 13{\cdot}8$, $B = 0{\cdot}5$, $C = -0{\cdot}5$ c/s and therefore: $J_{aa} = 13{\cdot}5$, $J_{ee} = 1{\cdot}2$, $J_{ea} \cong J_{ae} = 4{\cdot}5$ c/s.

The above A, B and C values agree surprisingly well with those derived[34] from measurements on 2-bromo-3-oxosteroids by an entirely different method (solution of

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[31] Expression (12) cannot be applied here without corrections because the partial electric moments are known[32] to be dependent upon the position (a or e) of the halogen on C_2. We wish to point out again that all expressions involving J are developed on the basis of the supposition that $J_{ea} \cong J_{ae}$. The validity of this assumption has not yet been tested for the α-halocyclohexanones.

[32] N. L. Allinger, J. Allinger, L. A. Freiberg, R. F. Czaja and N. A. LeBel, *J. Am. Chem. Soc.* **82** 5876 (1960).

[33] φ_2 was calculated from the atomic coordinates of cyclohexanone given in Ref. 2, p. 454.

[34] R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.* 806 (1963).

a set of simultaneous equations on the assumption that the *Karplus* parameters are independent of the conformation of ring A). In the present notation their values are: $A = 13{\cdot}4 \pm 0{\cdot}5$, $B = 1{\cdot}0 \pm 0{\cdot}5$, $C = 0$ c/s. Recalculation of the dihedral angle in the CHBr—CH_2 fragment of equatorial 2α-bromocholestan-3-one with the new values yields $\psi_2 = 45°$ in good agreement with the former result:[24] $\psi_2 = 46°$.

Summarizing, the linear correlation of μ^2 and J for compounds having an equilibrium-dependent dipole moment and at least one equilibrium-dependent coupling constant may serve several useful purposes:

(i) it provides a ready check upon the reliability of the observed data. For example, apparent discrepancies between the mole fractions x_E of α-halocyclohexanones calculated from dipole moments and by the NMR method have been discussed[30] both in terms of abnormally high moments of the 4-*t*-butyl compounds as well as by taking association phenomena into account. It is easily seen that either explanation would require significant deviations from the linearity, whereas such deviations are in fact not observed (provided the measurements are carried out effectively at infinite dilution).

(ii) The method seems to be a sensitive test of isogeometry of a series of compounds.

(iii) Reasonable *Karplus* parameters and equilibrium constants can be obtained from conformationally inhomogeneous systems when the partial electric moments and the geometry of the molecule are roughly known.

It is observed that the points measured in benzene are often slightly above the μ^2/J line, those measured in carbon tetrachloride often slightly below (cf. Fig. 6). This effect is ascribed to the fact that halogenated compounds with non-rotating dipoles often display slightly larger electric moments in benzene than in other solvents. This solvent effect, albeit small (about 0·02–0·03D), makes it dangerous to determine the slope $d\mu^2/dJ$ from measurements on a single compound in benzene and in carbon tetrachloride. Several solvents and/or analogous compounds should be used whenever possible.

EXPERIMENTAL

The compounds used in the present study were prepared and purified by known methods (cf. compounds **1–4**, **7** and **9**:[4] **5** and **6**:[24] **8**:[7] **10**:[36] **11–13**:[16]). The purity was checked by means of IR spectra, NMR spectra and physical constants. Compound **10** was isolated[35b] in milligram amounts only and determination of its dipole moment was not feasible. However, the NMR spectrum is compatible with the structure presently assigned to this compound (2e,3e-dibromo-*trans*-decalin) and rules out the possibility[36] that it could be an 2e,3a-dibromide.

The NMR spectra were recorded on a Varian A-60 spectrometer (Tables 1 and 2) and on a Varian HA-100 spectrometer (**10**, **12** and **18**). The samples of the fixed compounds were 10–20% (wt. vol.); the spectra of the equilibrium mixtures were recorded for several concentrations in order to eliminate the possibility of equilibrium shifts. The values of $J_{AX} + J_{BX}$ are probably accurate to ±0·1–0·2 c/s. The dipole moments were determined at 25° as described.[10,11]

We are indebted to Mrs. P. Kranenburg and R. J. de Knegt for running the NMR spectra.

[35a] J. A. van der Linden, Thesis, Leiden, 1958; [b] A. Adriaanse, forthcoming thesis, Leiden.

[36] W. Hückel and H. Waiblinger, *Liebigs Ann.* **666**, 17 (1963).