

## THREE-CHROMOPHORE COMPOUNDS—III<sup>1</sup> STEREOCHEMICAL STUDIES OF 3,5-DISUBSTITUTED CYCLOHEXANONES

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**Abstract**—The stereochemistry of three 3,5-diarylcyclohexanones, prepared by catalytic reduction of the corresponding 3,5-diaryl-2-cyclohexenones, has been derived from dipole moment measurements, as well as from NMR spectra and quantum-chemical relationships. The two phenyl groups in the 3,5-diphenylcyclohexanone so prepared are *cis*, occupying equatorial positions on a somewhat distorted chair-form ring. The 3-*p*-chlorophenyl-5-phenylcyclohexanone obtained is *trans*, with equatorial chlorophenyl and axial phenyl. 3,5-Di(*p*-chlorophenyl)cyclohexanone is also *trans*; it adopts a flexible structure, with an angle of +35° between the planes C<sub>6</sub>C<sub>1</sub>C<sub>2</sub> and C<sub>1</sub>C<sub>2</sub>C<sub>3</sub>. Meerwein-Ponndorf-Verley reduction converts the latter compound to a chair-form alcohol with an equatorial OH group.

IN PART I of this series<sup>2</sup> we reported the preparation of three 3,5-diarylcyclohexanones (Ia–c) by catalytic reduction of the corresponding parent olefins (IIa–c). Compound Ia was obtained<sup>3</sup> by Pd/C-catalyzed hydrogenation of Ha, whereas the chlorine-containing molecules, Iib and Iic, were reduced with rhodiumchlorotris(triphenylphosphine) to Ib and Ic; with this catalyst, Iia produced the same saturated ketone as with Pd/C.

The olefinic compounds II are known<sup>4</sup> to carry the 5-aryl group in a quasiequatorial position. A way to elucidate the configuration, *cis* or *trans*, of the saturated products I is the reduction of the carbonyl to an OH group (II–III): a *cis*-structure (IV) of II may lead to two epimeric alcohols (Va, b), whereas a *trans*-form (VI) of II can yield only one (VIIa ≡ VIIb). Balasubramanian and D'Souza have shown<sup>3</sup> by this method that the two phenyl groups in Ia are *cis* to each other. Among the reducing agents examined by these authors, aluminium isopropoxide in 2-propanol—which provides a 1:1 mixture of the two alcohols—seems to be the least stereospecific, and therefore the most useful.

We report some experimental data concerning the stereochemistry of the three saturated ketones Ia–c, and also extend the theoretical analysis of the flexible cyclohexanone\* to cover those of its derivatives that carry electron-attracting substituents at positions 3 and 5. Structural assignments are based mainly on the comparison of experimental dipole moments with the appropriate vectorial sums of group moments.<sup>5,6</sup> Geometrical constructions follow either Corey and Sneen<sup>7</sup> (rigid ring)

\* In six-membered rings,<sup>8</sup> we distinguish the rigid ("chair", D<sub>3d</sub> symmetry) from the flexible forms, the latter being sub-divided further into distorted boats and distorted twist forms, depending on whether they are closer to the regular boat (C<sub>2v</sub>) or to the twist form (D<sub>2</sub>). The flexible forms of cyclohexanone are characterized either by the pseudorotational phase<sup>9</sup> or by the dihedral angle<sup>1</sup> C<sub>6</sub>C<sub>1</sub>C<sub>2</sub>/C<sub>1</sub>C<sub>2</sub>C<sub>3</sub>; the prow-keto boat of phase O and dihedral angle 41° is shown in Fig 1. For any form of non-zero phase, substituents are denoted e' (quasiequatorial) or a' (quasiaxial), depending on whether they become equatorial or axial at phase O. We use symbols such as e<sub>3</sub>' to denote an e'-substituent at position 3, etc.

or our previous data<sup>1</sup> (flexible ring). Group moments were as follows: C-phenyl, 0.4D, C—OH, 1.65, C-*p*-chlorophenyl and C—F, 1.9, C=O, 2.9 D.\*

### Structural studies

Dipole moments, measured and computed, are recorded in Table 1. *cis*-3,5-Diphenylcyclohexanone (Ia) is obviously diequatorial, although some deviation from regular geometry cannot be completely excluded (difference of *ca.* 0.2 D between the computed and experimental values). As for 3-*p*-chlorophenyl-5-phenylcyclohexanone (Ib), the comparison indicates a *trans*-geometry ( $e_3a_5$ ); indeed, the similarity of the NMR of Ia and Ib renders alternative interpretations (e.g., flexible ring) unlikely. In contrast with these compounds, the dipole moment of 3,5-di(*p*-chlorophenyl)cyclohexanone (Ic) fits none of the values computed for rigid or "reversed chair"<sup>13</sup> conformations, and its substantial difference (1 D or more) from all computed values excludes also irregular varieties<sup>14</sup> of these geometries. Equally, Ic is quite dissimilar in NMR to Ia or Ib.

TABLE I. EXPERIMENTAL AND COMPUTED DIPOLE MOMENTS

Compound	Computed values (Debye)				Exptl.
	$e_3e_5$	$a_3a_5$	$e_3a_5$	$a_3e_5$	
Ia. chair	2.46	3.27	2.86		2.69
Ib. chair (3-Cl- $\phi$ , 5- $\phi$ )	1.99	3.18	2.44	3.79	2.44
Ic. chair	0.84	5.54	3.28		2.32
Ic. "reversed chair"	0.42	6.00	3.23		
IIIc. hydroxyl equatorial	0.76	4.62	2.48		2.35
IIIc. hydroxyl axial	1.83	5.45	3.42		

The carbonyl-reduction of Ic with aluminium isopropoxide in 2-propanol (as pointed out, a non-stereospecific reagent; see Experimental) provides only one alcohol (IIIc) with equatorial OH.†

The *trans*-Ar. Ar relationship, thus suggested, is confirmed by the dipole moment which identifies IIIc as *cis*, *trans*-3e,5a-di(*p*-chlorophenyl)-le-cyclohexanol, so that the ketone Ic is *trans*-3,5-di(*p*-chlorophenyl)cyclohexanone. The nearest alternative (still off by *ca.* 0.5 D) is  $a_1e_3e_5$ , not in line with the equatorial assignment for the OH. Moreover, an  $a_1e_3e_5$ -alcohol implies that Ic is *cis* and therefore expected<sup>3</sup> to furnish 1:1 mixture of two alcohols,  $a_1e_3e_5$  and  $e_1e_3e_5$ . Let us add that the *cis*,*trans*-alcohol is obtainable directly from IIc, but its low yield and the large bulk of by-products in the process (Experimental) rob this reaction of much of its stereochemical interest.

Having discarded, for Ic, chair-like conformations, we examine now the flexible

\* Reduced moments<sup>10</sup> of the following one-dipole molecules: toluene,<sup>11</sup> 0.43 D. MeOH,<sup>11</sup> 1.70 D. *p*-chlorophenylcyclohexane,<sup>12</sup> 1.96 D. cyclohexanone,<sup>11</sup> 3.08 D.

† The assignment is based upon the NMR spectrum of the proton, geminal to the OH:  $\delta$  (CDCl<sub>3</sub>, 60 MHz) 4.33–3.66 ppm from TMS, width at half-height 22 c/s. It rests upon the observation<sup>15</sup> that the coupling constant between neighbouring axial hydrogens is larger than between hydrogens in other orientations, from which it follows<sup>16, 17</sup> that multiplets corresponding to highly-coupled axial protons are wider than others. Relevant references<sup>16</sup> are the two isomers of 5-phenyl-2-cyclohexen-1-ol: the compound of *e*-OH and *a*-H (geminal to OH) has  $\delta$  4.35 (CCl<sub>4</sub>), width at half-height 18 c/s, against 4.20 and 8 for the other.

forms, characterizing each<sup>1</sup> by the angle  $\theta$  between the planes  $C_6C_1C_2$  and  $C_1C_2C_3$  (Fig 1). Fig 2 (full curves) displays the dependence of the computed dipole moments\* upon  $\theta$ , and selects  $a'_3e'_3$  at  $\theta \approx 35^\circ$  (a somewhat distorted "prow-keto"<sup>1</sup> form) as the most probable structure for Ic. The nearest alternative ( $\mu \approx 2.0$  D) is  $e'_3a'_3$  at  $\theta \approx 41^\circ$ . A choice between these two, based upon quantum-chemical grounds, is deferred to the next section.

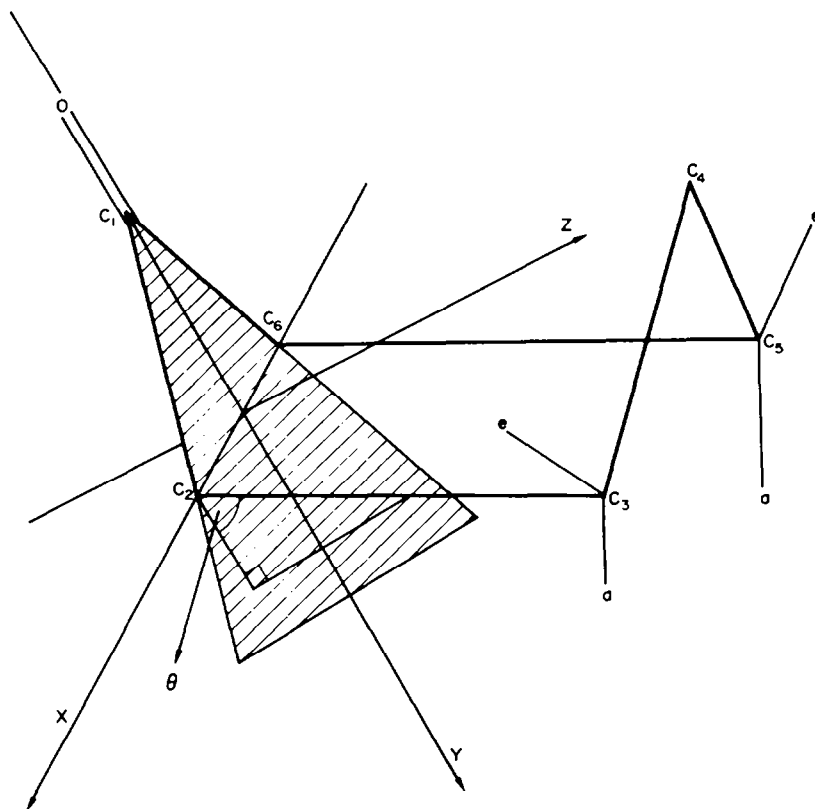


FIG 1. Geometry of the flexible-cyclohexanone structure: coordinate system [xyz] and the distortional angle  $\theta$  ( $\theta = 41^\circ$  shown)

Ib and Ic have substituents of similar steric bulk so that their conformational difference stems most probably from dipole-dipole repulsion.<sup>18</sup> A rough estimate of this factor may be obtained by approximating the total interaction in the three-dipole molecules as sum of the three two-dipole contributions (CO-Ar<sub>1</sub>, CO-Ar<sub>2</sub>, Ar<sub>1</sub>-Ar<sub>2</sub>), given each by<sup>19</sup>

$$E = \mu_1\mu_2 (\cos \chi - 3 \cos \alpha_1\alpha_2)/r^3$$

Here,  $r$  is the length of a vector  $\mathbf{R}$  connecting the dipoles  $\mu_1$  and  $\mu_2$ ,  $\chi$  the dipolar angle,  $\alpha_1$  and  $\alpha_2$  the angles  $(\mu_1, \mathbf{R})$  and  $(\mu_2, \mathbf{R})$ , respectively. It is seen immediately

\* Owing to the particular geometrical construction,  $a'_3e'_3$  and  $e'_3a'_3$  are identical only at  $\theta = 41^\circ$  ("regular boat")

that the interaction in Ic, which carries two strong dipoles, is more pronounced than in Ib, containing only one. In order to verify that the *pro*-keto boat represents less repulsion than the chair, we disregard  $E(\text{Ar}_1-\text{Ar}_2)$  and the term in  $(\alpha_1, \alpha_2)$ —these being almost identical in the two conformations—and note that the cosines of the dipolar angles  $\chi(\text{CO}-\text{Ar})$  are lower in the first, than in the second possibility: boat,  $\chi_a 150^\circ 20'$  ( $\cos \chi_a = -0.87$ ),  $\chi_e 89^\circ 39'$  (0.01), chair  $\chi_e 121^\circ 35'$  ( $-0.52$ ),  $\chi_a 68^\circ 58'$  (0.36).

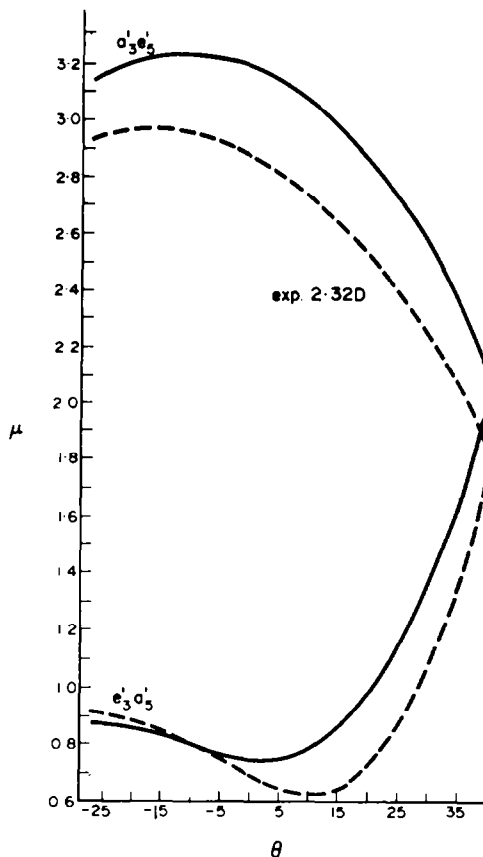


FIG. 2. Calculated dipole moment of 3,5-di(*p*-chlorophenyl)cyclohexanone (in Debye units) as function of the distortional angle. Bold curves: group-moment summation. Dashed curves: quantum-chemical evaluation

For later reference, we show in Fig 3 the trends of the three-dipole mutual interaction, approximated as sum of three two-dipole contributions. A hypothetical flexible form of 3,5-difluorocyclohexanone serves as a model, with vector  $\mathbf{R}$  assumed to connect the mid-points of  $\text{C}_3\text{-F}$  and  $\text{C}_5\text{-F}$ . Let us remark, in anticipation of the subsequent discussion, that the *trans*-structure represents indeed less interaction than the *cis*, although the conformation of least dipole-dipole repulsion is not the

one we suggest for Ic, but rather  $a'_3e'_5$  at  $\theta = -20^\circ$  (we shall show that this latter form is destabilized by severe steric interaction). An interesting result, concerning the *cis*-configuration, is that the repulsive forces are lower in the diaxial, than in the diequatorial conformation.

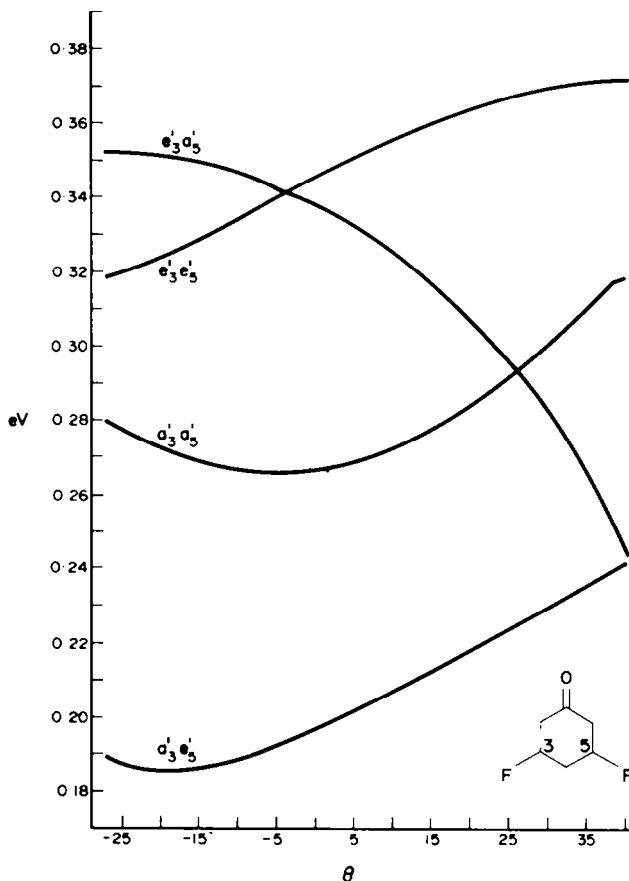


FIG 3. Computed dipole-dipole repulsion as function of the distortional angle, in four stereochemical varieties (hypothetical) of 3,5-difluorocyclohexanone

#### All valence-electron results

In view of the unusual shape assigned to 3,5-di(*p*-chlorophenyl)cyclohexanone (Ic), and its configurational dissimilarity with the diphenyl and phenyl-*p*-chlorophenyl compounds (Ia, b), it was of some interest to carry out "all valence-electron" analyses of flexible cyclohexanones that carry electron-attracting substituents at positions 3 and 5. Because of computer-capacity limitations, we had to content ourselves with the simplest model, namely, 3,5-difluorocyclohexanone, which represents correctly the effects of the two C-Hal bonds in Ic, but not the steric requirements of its two aryl

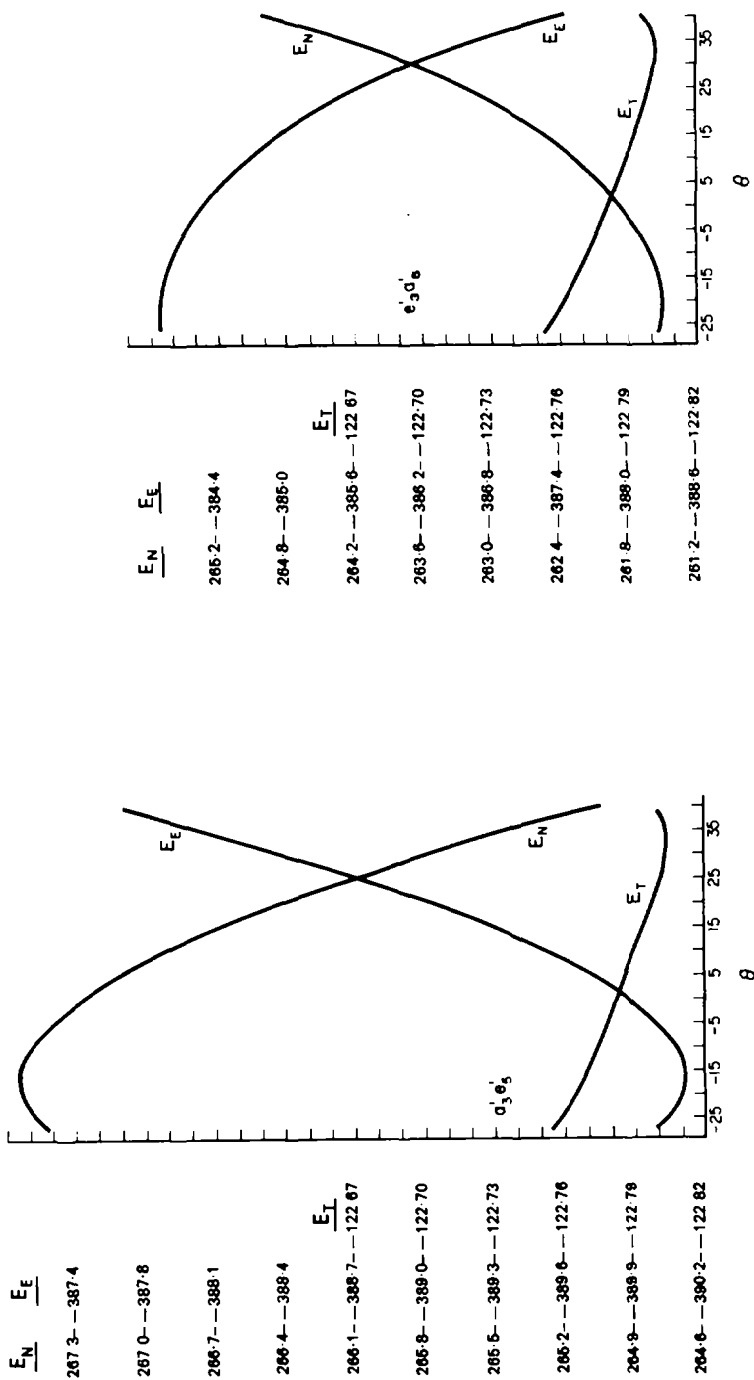


FIG. 5

FIG. 4

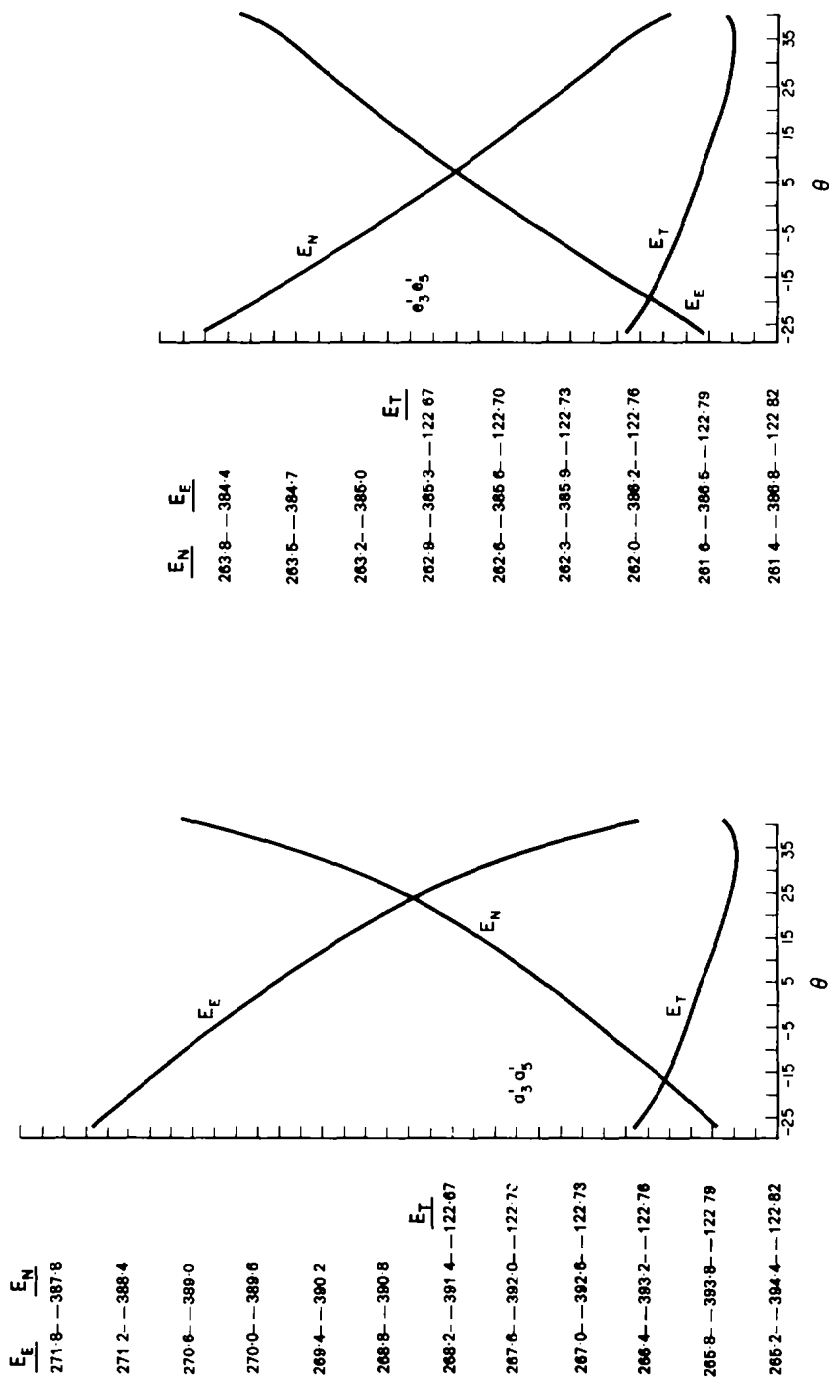


FIG. 7

FIG. 6

FIGS 4-7. Computed energy and energy-components (in atomic units) as function of the distortional angle, in four stereochemical varieties (hypothetical) of 3,5-difluorocyclohexanone

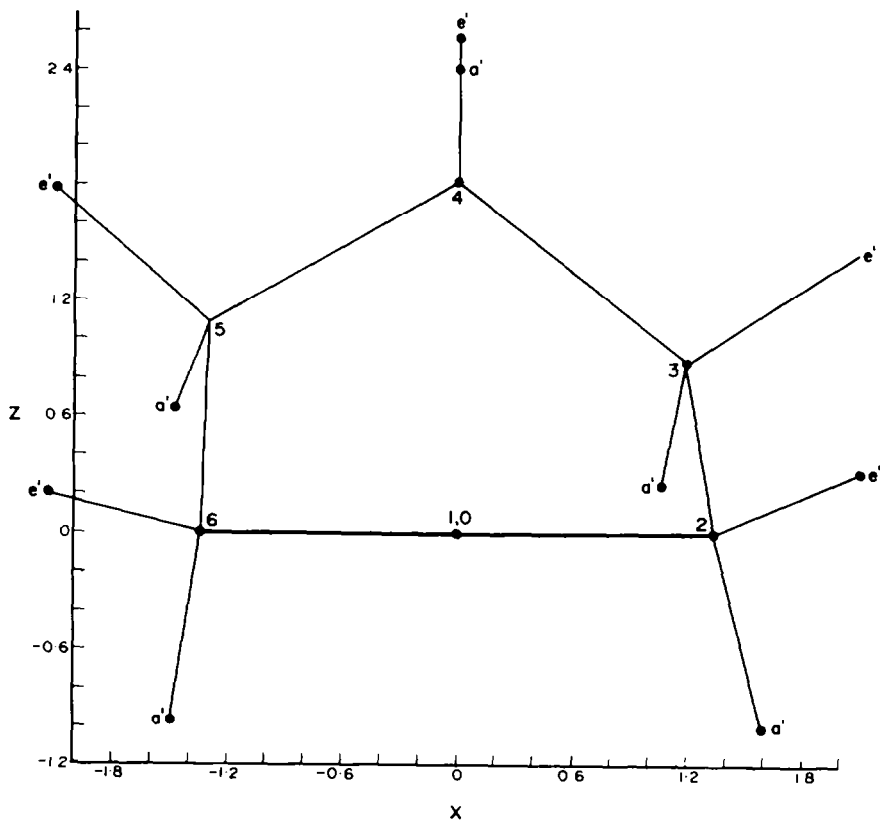


FIG. 8a



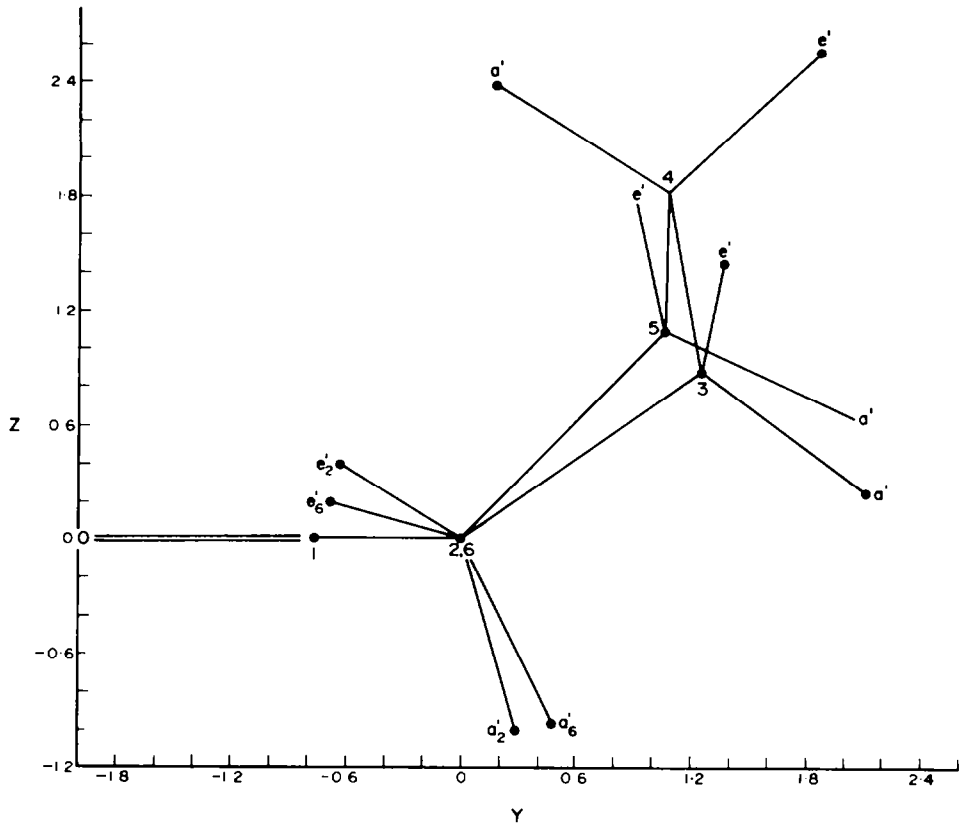


FIG. 8b

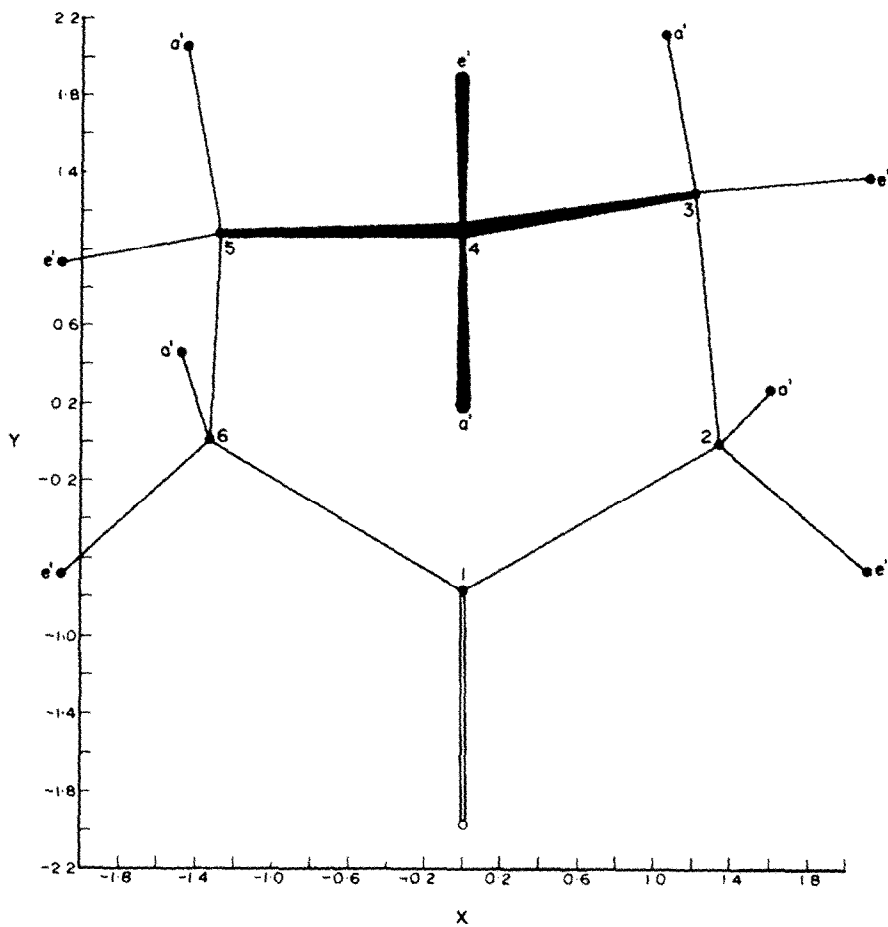


FIG. 8c

FIGS 8a-c. Projections on the  $xz$ ,  $yz$  and  $xy$  planes of a flexible cyclohexanone, distorted at  $\theta = +35^\circ$

substituents. Still, we do not consider the latter factor as decisive, in view of the observed conformational differences between Ib and Ic.

We used the CNDO/2 technique<sup>20</sup> and the program authored by Segal;<sup>21</sup> geometries were defined in terms of  $\theta$ , calculations being performed in steps of 5°.

Dipole moments, computed for  $e'_3a'_5$  and  $a'_3e'_5$  (Fig 2, dashed lines) as well as for  $a'_3a'_5$  and  $e'_3e'_5$  are close to the group-moment values (full curves). In Table 2 we compare the charge distribution of flexible cyclohexanone and 3,5-difluorocyclohexanone, both deformed at  $\theta = +35^\circ$ . The reported values indicate that the dipoles are almost fully localized at C=O, C<sub>3</sub>-F and C<sub>5</sub>-F, the perturbation at other centres being small. This obviously provides an *a posteriori* justification for the group-moment approach.

TABLE 2. CHARGE DISTRIBUTION AT DISTORTION  $\theta = 35^\circ$

	cyclohexanone electron units		$a_3e_5$ -difluorocyclohexanone electron units	
C <sub>1</sub>	+0.245	} -0.021	+0.250	} -0.006
O	-0.266		-0.256	
C <sub>2</sub>	-0.043	} -0.003	-0.085	} -0.006
H <sub>2</sub> (e')	+0.020		+0.032	
H <sub>2</sub> (a')	+0.020		+0.047	
C <sub>3</sub>	+0.021	} +0.012	+0.247	} +0.013
H <sub>3</sub> , F <sub>3</sub> (a')	-0.003		-0.208	
H <sub>3</sub> (e')	-0.006		-0.026	
C <sub>4</sub>	+0.019	} +0.001	-0.057	} -0.018
H <sub>4</sub> (e')	-0.015		+0.015	
H <sub>4</sub> (a')	-0.003		+0.024	
C <sub>5</sub>	+0.031	} +0.015	+0.257	} +0.023
H <sub>5</sub> , F <sub>5</sub> (e')	-0.009		-0.211	
H <sub>5</sub> (a')	-0.007		-0.023	
C <sub>6</sub>	-0.043	} +0.006	-0.084	} -0.007
H <sub>6</sub> (e')	+0.018		+0.045	
H <sub>6</sub> (a')	+0.019		+0.032	

The  $\theta$ -dependence of the nuclear-repulsion ( $E_N$ ), electronic ( $E_E$ ) and total energies ( $E_T = E_N + E_E$ ) for the four possible patterns of substitution ( $a'_3e'_5$ ,  $e'_3a'_5$ ,  $a'_3a'_5$ ,  $e'_3e'_5$ ) are displayed in Figs 4–7 in atomic energy units (1 a.u. = 627 kcal/mol). We first note that, whereas  $E_N$  and  $E_E$  depend strongly upon the pattern, the total energy is almost unaffected, achieving its minimum, for all cases, at  $\theta = +35^\circ$ . The minimal-energy values are as follows:  $a'_3e'_5$ , -122.8122 a.u.,  $e'_3a'_5$ , -122.8119,  $a'_3a'_5$ , -122.8116,  $e'_3e'_5$ , -122.8107 a.u. True, the differences are rather small, but it is significant that the ordering, at  $\theta = 35^\circ$ , parallels exactly the trend in dipole-dipole repulsion energies (Fig 3):  $a'_3e'_5$ , 0.234 eV,  $e'_3a'_5$ , 0.268,  $a'_3a'_5$ , 0.310, and  $e'_3e'_5$ , 0.371 eV.

As to relative stabilities, we now note that the *trans*-configuration is more stable than the *cis*, and that the form  $a'_3e'_5$  represents, at  $\theta = 35^\circ$ , the lowest attainable energy. This may settle the ambiguity regarding the dipole moment of Ic, which

could indicate both  $a_3'e'_5$  at  $35^\circ$  and regular  $e'_3a'_5$  (Fig 2); the former of the two possibilities is more plausible.

For completeness, we show in Figs 8a-c the projections of the lowest-energy structure ( $a_3'e'_5$ ,  $35^\circ$ ) upon the planes  $xz$ ,  $yz$  and  $xy$ ; the coordinate system was given in Fig 1.

### EXPERIMENTAL

Dipole moments were calculated according to Halverstadt and Kumler,<sup>22</sup> from measurements carried out at  $30.0 = 0.1$  in  $C_6H_6$  (AnalaR, dried over Na). Dielectric constants were determined by the heterodyne beat method (500 kHz), specific volumes-- with an Oswald-Sprengel type pycnometer, and the refractive indices with a sodium-lamp Bellingham and Stanley Pulfrich refractometer. We are indebted to Dr. H. Weiler-Feilchenfeld for these measurements.

*Meerwein-Ponndorf-Verley reduction of 3.5-di(p-chlorophenyl)cyclohexanone (Ic).* Compound Ic (1 g) was treated with the reducing agent, prepared<sup>23</sup> from 0.37 g aluminium and 13.5 ml 2-propanol, for 3 hr.<sup>24</sup> The solvent was evaporated and the residue kept overnight with a soln of conc HCl (10 ml) in water (35 ml). The solid precipitate was filtered, dissolved in a small quantity of  $C_6H_6$  and chromatographed<sup>3</sup> on a column of 35 g alumina. Light petroleum eluted some impure starting material ( $\bar{\nu}$  neat  $1720\text{ cm}^{-1}$ ); further elution, with a mixture of light petroleum and  $C_6H_6$ , yielded 0.6 g of 3.5-di(p-chlorophenyl)-1-cyclohexanol (IIIc), m.p. 131 (from cyclohexane),  $\bar{\nu}$   $CCl_4$  (dilute solution)  $3605\text{ cm}^{-1}$  (unassociated sec OH<sup>25</sup>). (Found: C, 67.39; H, 5.73; Cl, 22.20.  $C_{18}H_{18}Cl_2O$  requires: C, 67.30; H, 5.61; Cl, 22.12%).

*Catalytic reduction of 3.5-di(p-chlorophenyl)-2-cyclohexen-1-one (IIc).* To 2.5 g of IIc, dissolved in  $C_6H_6$  (100 ml), 0.3 g Pd/C (10%) was added and the mixture hydrogenated for 5 hr at 3.4 atm. Work-up and three recrystallizations from cyclohexane left 0.6 g of IIIc, m.p. 131°.

### REFERENCES

- 1 Part II. A. Y. Meyer, J. Schlesinger and E. D. Bergmann, *J. Chim. Phys.* **68**, 668 (1971)
- 2 Part I. A. Y. Meyer and J. Schlesinger, *Israel J. Chem.* **8**, 671 (1970)
- 3 M. Balasubramanian and A. D'Souza, *Tetrahedron* **24**, 5399 (1968)
- 4 A. Y. Meyer and E. D. Bergmann, *Israel J. Chem.* **6**, 735 (1968)
- 5 E. D. Bergmann and A. Weizmann, *Chem. Rev.* **29**, 553 (1941)
- 6 C. P. Smyth, *Dielectric Behavior and Structure*, McGraw-Hill, New York (1955)
- 7 E. J. Corey and R. A. Sneed, *J. Am. Chem. Soc.* **77**, 2505 (1955)
- 8 J. D. Dunitz, *J. Chem. Ed.* **47**, 488 (1970)
- 9 N. L. Allinger, J. Allinger and M. A. DaRooge, *J. Am. Chem. Soc.* **86**, 4061 (1964)
- 10 J. Cantacuzène, *J. Chim. Phys.* **59**, 186 (1962)
- 11 A. L. McClellan, *Tables of Experimental Dipole Moments*, W. H. Freeman, San Francisco (1963)
- 12 A. Y. Meyer, unpublished measurement (benzene,  $30^\circ$ )
- 13 L. C. G. Goaman and D. F. Grant, *Tetrahedron* **19**, 1531 (1963)
- 14 J. B. Lambert, R. E. Carhart and P. W. R. Corfield, *J. Am. Chem. Soc.* **91**, 3567 (1969)
- 15 R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, *J. Am. Chem. Soc.* **80**, 6098 (1958)
- 16 R. Levene, M.Sc. Thesis, Jerusalem (1969); cf. J. Klein and R. Levene, *Tetrahedron Letters* 4833 (1969)
- 17 J. Cantacuzène and R. Jantzen, *Tetrahedron* **26**, 2429 (1970)
- 18 E. L. Eliel, N. L. Allinger, S. J. Angyal and G. A. Morrison, *Conformational Analysis*, Interscience, New York (1965)
- 19 J. M. Lehn and G. Ourisson, *Bull. Soc. Chim. Fr.* 1113 (1963)
- 20 J. A. Pople, D. P. Santry and G. A. Segal, *J. Chem. Phys.* **43**, S129 (1965); J. A. Pople and G. A. Segal, *Ibid.* **43**, S136 (1965); *eid.*, *Ibid.* **44**, 3289 (1966)
- 21 G. A. Segal, CNDO II, QCPE 91 (1966)
- 22 I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.* **64**, 2988 (1942)
- 23 A. L. Wilds, in R. Adams, Ed., *Organic Reactions*, Vol. II, p. 198, Wiley, New York (1944)
- 24 M. Balasubramanian and N. Padma, *Tetrahedron* **19**, 2135 (1963)
- 25 C. N. R. Rao, *Chemical Applications of Infrared Spectroscopy*, Academic Press, New York (1963)