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The Geometry of Small Rings.
III.* The Effect of Small-Ring Fusion on the Geometry of Benzene

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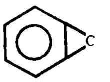
Abstract

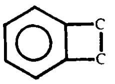
X-ray mean geometries of mono- and dicycloalkenobenzenes with fused-ring sizes $r = 3, 4, 5$ have been obtained by use of the Cambridge Crystallographic Database. The tabulations show no significant variations in aromatic bond lengths. A high proportion of the strain induced in the benzene ring by fusion to small-ring cycloalkenes is reflected in systematic angular deformations. The intra-annular aromatic angle (β) *ortho* to a single fused ring is contracted by 2·2 (2), 4·9 (3) and 10·8 (5)° for $r = 5, 4, 3$; the *ipso* angles (α) expand by *ca* one-half those values. A linear relationship exists between α and β and the cycloalkene angle (ε) at the point of fusion. For monocycloalkenobenzenes with $r = 3$–8 the relationship is $\beta = 96{\cdot}3 + 0{\cdot}20\varepsilon$. Limited data for *p*- and *m*-dicycloalkenobenzenes indicate that angular deformations are approximately additive. Experimental results are compared with simple force-field calculations of angle-bending strain.

Introduction

The idea that small-ring fusion to benzene might cause partial double-bond fixation in the aromatic ring was proposed by Mills & Nixon (1930) to explain anomalous electrophilic substitution results for benzocyclopentene (indan, III). A theoretical study of indan (Longuet-Higgins & Coulson, 1946) favoured fixation in Kekulé structure (IV) by indicating shortening of bond *a*, lengthening of *d* and contraction of angle β. Since that time the two highly strained lower homologues in the series have been isolated: benzocyclobutene (II) (Cava & Napier, 1956) and benzocyclopropene (I) (Anet & Anet, 1964). The series up to benzocyclohexene has been studied by the CNDO/2 method (Cheung, Cooper & Manatt, 1971). Their geometrical results, summarized in Table 1, favour Kekulé structure (V): lengthening of *a* and *c*, shortening of *b*, contraction of β.



(I)



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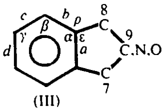

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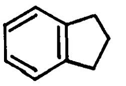
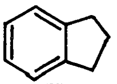
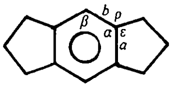


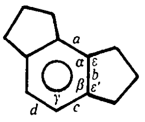
(IV)



(V)



(VI)



(VII)

Early X-ray results on derivatives of (I) (Carstensen-Oeser, Muller & Durr, 1972; Billups *et al.*, 1973) and (II) (Hardgrove, Templeton & Templeton, 1968; Lawrence & MacDonald, 1969; Allen & Trotter, 1970*a*,*b*) indicated severe angular strain in the benzene

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* Part II: Allen (1981).

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Table 1. *CNDO/2 calculated geometries for monocycloalkenobenzenes (from* Cheung, Cooper & Manatt, 1971) *with the nomenclature of* (III)

r	3	4	5	6
a (Å)	1·420	1·421	1·412	1·403
b (Å)	1·365	1·379	1·389	1·392
c (Å)	1·400	1·391	1·386	1·383
d (Å)	1·382	1·381	1·384	1·383
e (Å)	1·458	1·476	1·472	1·470
α (°)	122·6	121·4	119·8	118·7
β (°)	114·8	116·5	119·8	122·0
ε (°)	60·8	91·5	109·7	121·4
$\delta\beta$ (°)	−5·2	−3·5	−0·2	2·0
$\delta\varepsilon$ (°)	−59·2	−28·5	−10·3	1·4
$\partial\beta/\delta\varepsilon$	0·088	0·123	0·019	–

ring, β being contracted by up to 11·7° in (I) (considerably underestimated by the CNDO/2 calculations in Table 1), but revealed no evidence for double-bond fixation. This is in agreement with the explanation of the Mills & Nixon (1930) effect due to Streitweiser, Ziegler, Mowery, Lewis & Lawler (1968). The small-ring C—C bonds of (I)–(III) have unusually high p character (*cf.* Charton, 1970, for cyclopropane), the σ bonds to the benzene *ortho* C atoms thus possessing high s character (Allen, 1981, for cyclopropane). The *ortho* C therefore have enhanced acidity and reduced reactivity towards electrophilic substitution: double-bond fixation is not invoked.

There has been a renewed interest in the properties and chemistry of derivatives of (I) and (II) (Halton, 1973; Santiago, Gandour, Houk, Nutakul, Cravey & Thummel, 1978; Gray, Harruff, Krymowski, Peterson & Boekelheide, 1978, and references therein), because of their recent use as synthetic intermediates. This fact, coupled with current structural interest in substituent-induced deformations of benzene-ring geometry (Domenicano, Vaciago & Coulson, 1975*a*,*b*; Domenicano & Vaciago, 1979; Domenicano, Mazzeo & Vaciago, 1976; Domenicano & Murray-Rust, 1979), has prompted the present review of X-ray results obtained for benzocycloalkenes and their analogues.

Methodology

The May 1980 release of the Cambridge Crystallographic Database has been used for this study. Information retrieval and data analysis was performed with programs described by Allen *et al.* (1979). The complete database was used to locate the low-incidence fragments (I) and (II). For fused-ring sizes of ≥5 a subset (7232 entries, 27% of the total) was prepared, *via BIBSER*, to include only organic compounds (chemical classes 1–60) which did not contain heavy atoms, defined as transition elements, Br and I. For the data analysis raw-data and geometric screens (Murray-Rust & Motherwell, 1978; Allen, 1981) have been employed: structures are only included in this study (unless otherwise stated) if $R \leq 0{\cdot}07$, the mean σ (C—C) $\leq$ 0·01 Å and the coordinate set is error-free. Error estimates for mean parameters ($\bar{x}$) are given by $\sigma(\bar{x}) = [\sum_n (\bar{x} - x_i)^2/n(n-1)]^{1/2}$ for n observations x_i ($i = 1, n$).

Monocycloalkenobenzenes

A variety of mean geometries for monocycloalkenobenzenes with fused-ring sizes (r) = 3–6 are collected in Table 2. For r = 4, 5, 6 the data refer to fragments where the cycloalkene is the sole benzene substituent; substitution was permitted on the fused ring except additional aromatic systems. Mean geometries are presented averaged over exact or imposed m_{ad} symmetry. A simple energy minimization, developed in the Appendix, has been used to provide comparison values for α, β, γ on the basis of the experimental $\delta\varepsilon$.

Benzocyclopropene

Only two derivatives of benzocyclopropene have been studied by X-ray methods; both are derivatives of terphenyl with fusion to the central ring, *viz* dimethyl 2,5-diphenylbenzocyclopropene-1,1-dicarboxylate (Carstensen-Oeser, Muller & Durr, 1972) and 1,1-dichloro-2,5-diphenylbenzocyclopropene (Halton, McLennan & Robinson, 1976). The structure of naphtho[*b*]cyclopropene (Billups *et al.*, 1973) has also been reported.

Equivalent bond lengths in the two terphenyl derivatives differ markedly, as evidenced by the high σ's of Table 2. Bond a is foreshortened (but markedly different) in both compounds; the values of 1·333 for the dimethyl dicarboxylate and 1·351 Å for the dichloride are a reflection of the cyclopropane substituent effect (Allen, 1980) as well as the strain. Neither individual nor mean bond lengths are indicative of bond fixation, a conclusion reinforced by results for the naphthalene derivative (Billups *et al.*, 1973).

Valence angles in the two terphenyl derivatives are more consistent (Table 2) and the 10·8° contraction in β is very marked. The resultant expansion of α,γ is not symmetric. It is predicted that the overall effect of 2,5-diphenyl substitution on benzocyclopropene would be to contract β by 3·2° and increase α,γ by 1·6° (Domenicano & Murray-Rust, 1979). Similar work by Norrestam & Schepper (1978) predicts β contraction of 2·6°, α,γ expansion by 1·3°. Insufficient data exist to enable a separation of substituent and fusion-strain effects for benzocyclopropene individually. Nevertheless, a comparison of experimental and energy-minimization results (Table 2, and see below) indicates that

Table 2. *Mean geometries for monocycloalkenobenzenes with the nomenclature of* (III) *and averaged over* m_{ad} *symmetry* (r *= fused-ring size*; n = *number of contributors*; σ*'s in parentheses*)

Experimental data

r	3	4	$5A^{(a)}$	$5B^{(a)}$	$5C^{(a)}$	$5D^{(a)}$	6
n	2	13	80	21	59	34	84
a (Å)	1·342 (13)	1·383 (3)	1·391 (3)	1·393 (4)	1·390 (3)	1·386 (3)	1·399 (3)
b (Å)	1·394 (17)	1·391 (4)	1·384 (2)	1·382 (3)	1·385 (2)	1·384 (2)	1·393 (2)
c (Å)	1·407 (17)	1·395 (5)	1·387 (2)	1·391 (3)	1·386 (3)	1·386 (2)	1·384 (2)
d (Å)	1·390 (4)	1·392 (5)	1·385 (3)	1·381 (3)	1·386 (3)	1·385 (3)	1·383 (2)
D (Å)$^{(b)}$	1·389 (15)	1·391 (4)	1·386 (2)	1·387 (3)	1·386 (3)	1·385 (3)	1·389 (2)
$\delta a^{(b)}$	−47	−8	5	6	4	1	10
δb	5	0	−2	−5	−1	−1	4
δc	18	4	1	4	0	−1	−5
δd	1	1	−1	−6	0	0	−6
e (Å)	1·49 (4)	1·509 (5)	1·489 (5)	1·508 (5)	1·483 (5)	1·483 (3)	1·495 (6)
α (°)	126·0 (10)	122·6 (2)	121·1 (2)	120·8 (2)	121·2 (2)	121·4 (2)	119·6 (2)
β (°)	109·2 (5)	115·1 (3)	117·8 (2)	118·2 (2)	117·6 (3)	117·3 (2)	120·1 (2)
γ (°)	124·5 (7)	122·3 (3)	121·1 (3)	120·9 (2)	121·2 (3)	121·3 (3)	120·2 (3)
ε (°)	63·2 (7)	93·8 (3)	108·5 (4)	108·0 (5)	108·7 (5)	109·1 (2)	117·2 (9)
$\delta\alpha^{(c)}$	6·0 (10)	2·6 (2)	1·1 (2)	0·8 (2)	1·2 (2)	1·4 (2)	−0·4 (2)
$\delta\beta$	−10·8 (5)	−4·9 (3)	−2·2 (2)	−1·8 (2)	−2·4 (3)	−2·7 (2)	0·1 (2)
$\delta\gamma$	4·5 (7)	2·3 (3)	1·1 (2)	0·9 (2)	1·2 (3)	1·3 (3)	0·2 (3)
$\delta\varepsilon$	−56·8 (7)	−26·2 (3)	−11·5 (4)	−12·0 (5)	−11·3 (5)	−10·9 (2)	−2·8 (9)
$\delta\beta/\delta\varepsilon$	0·190	0·187	0·191	(0·150)	(0·212)	(0·248)	–
$\delta\gamma/\delta\alpha$	0·750	0·885	1·000	(1·125)	(1·000)	(0·929)	–
$\delta\alpha_{1\cdot0}{}^{(d)}$	5·1	2·4	1·0	–	–	–	0·3
$\delta\beta_{1\cdot0}$	−10·2	−4·8	−2·0	–	–	–	−0·6
$\delta\gamma_{1\cdot0}$	5·1	2·4	1·0	–	–	–	0·3
$\delta\alpha_{0\cdot9}$	5·7	2·6	1·2	–	–	–	0·3
$\delta\beta_{0\cdot9}$	−10·8	−4·9	−2·3	–	–	–	−0·6
$\delta\gamma_{0\cdot9}$	5·1	2·3	1·1	–	–	–	0·3
$\delta\alpha_{0\cdot8}$	6·2	2·9	1·3	–	–	–	0·3
$\delta\beta_{0\cdot8}$	−11·2	−5·2	−2·3	–	–	–	−0·5
$\delta\gamma_{0\cdot8}$	5·0	2·3	1·0	–	–	–	0·2

(*a*) For precise fragment definitions and description of $r = 5$ variants see text.
(*b*) $D = a + 2b + 2c + d/6$; $a = (D - a) \times 10^3$ *etc.*
(*c*) Angular deviations from 120°.
(*d*) See Appendix; subscripts refer to the parameter x ($=\delta\gamma/\delta\alpha$).

the observed data for $r = 3$ are well reproduced by equation (4) of the Appendix. Further, the $\delta\beta/\delta\varepsilon$ ratio for $r = 3$ is in excellent agreement with values for $r = 4$, $5A$. The tentative conclusion must be that deformation due to fusion strain is the predominant influence.

Benzocyclobutene

A more complete and consistent set of data is available for $r = 4$ (Table 2). Bond length a is minimally shortened, but no distance deviates significantly from the mean D. The pattern of angular deformation in the benzene ring noted for $r = 3$ is again observed, giving an almost identical $\delta\beta/\delta\varepsilon$ ratio. Only two of the 21 independent values for β lie outside the narrow range of 114·5–116·0°; all ε values are between 92·5 and 96·5°. The R limit was increased to 0·085 for $r = 4$.

Benzocyclopentene

Data for benzene rings having a five-membered ring (carbocyclic or heterocyclic) as sole substituent occur frequently in the X-ray literature. To preserve the analogy between fragments (I), (II), (III) only rings having C at positions 7 and 8 in (III) were included in this analysis; position 9 was restricted to C,N,O. Four sets of results are given in Table 2. The mean geometry averaged over all datasets ($5A$) is split into two subgroups: $5B$ includes structures without multiple bonding to positions 7 and 8 [*i.e.* C(7) = C(8) = C(sp^3) and there is no possibility of conjugation with benzene], while $5C$ has C(7) and/or C(8) = C(sp^2) and conjugation of the aromatic system with intra- or extra-annular bonds of the fused system is possible. $5D$ is a subset of $5C$ corresponding to anhydride rings (7 = 8 = carbonyl; 9 = O).

There is little variation in bond lengths $a-d$ for $5A-5D$. In all cases a tends to be the longer bond in contrast to $r = 3$, 4, but the trend is not significant. Bond length e in $5C$, $5D$ is foreshortened in comparison with $5B$ by some 0·025 Å, reflecting changes in hybridization at C(7) and/or C(8) and probable conjugative interaction(s).

The expected pattern of angular distortions is observed; β is significantly and consistently $<120°$, while the near equality of α and γ imparts almost exact *mm* symmetry to the benzene ring. The overall $\delta\beta/\delta\varepsilon$ ratio ($5A$) is in close agreement for $r = 3$, 4 (0·19) although values for subsets vary from 0·15 to 0·25. There appears to be a slight additional contraction of β for the conjugated subsets $5C$, $5D$, but this may be an artifact. The conjugated samples are dominated by carbonyl interactions and it has been shown (Domenicano, Mazzeo & Vaciago, 1976; Domenicano & Murray-Rust, 1979) that –COOH substitution has little effect on the internal angles. There appears to be some justification for treating benzocyclopentenes as a homogenous sample and all further discussion is in terms of the overall means of $5A$ (Table 2).

Fused rings with $r \geq 6$

Mean geometry was calculated for substructural analogues of (III) having $r = 6$, 7, 8. Fragment positions of type 9 in (III) were restricted to C,N,O and benzoquinones were excluded for $r = 6$. Results for benzocyclohexenes are included in Table 2. Mean values of α, β, γ conform to an undistorted hexagon, which is to be expected from the minimal fusion strain generated by a mean ε of 117·2 (9)°. The high $\sigma(\varepsilon)$ exemplifies the very wide spread of ε for $r = 6$, 7, 8 where individual values range from 107·0 to 126·8° for structures having $R \leq 0{\cdot}07$. Structures where ε values differ significantly (*i.e.* by > *ca* 3·5°) from 120° do show the expected deformations in α, β, γ and the complete data for $r = 6$, 7, 8 are included in the regression analysis discussed below.

The ε–β relationship

The consistency of $\delta\beta/\delta\varepsilon$ for $r = 3$, 4, 5 (Table 2) indicates a linear relationship of the form $\beta = \beta_o + y\varepsilon$ where $y = 0{\cdot}19$ and $\beta_o = 97{\cdot}2°$. Linear regression of β on ε based on a scattergram of the 243 symmetry-independent individual values for $r = 3$–8 gives $\beta_o = 93{\cdot}7°$ and $y = 0{\cdot}22$. Such an analysis is very heavily weighted towards ε values in the narrow range 104–127° (228 values). To reduce this bias the ε for $r = 5$, 6, 7, 8 were divided into six intervals of 3° each covering the range 104–121° plus a final open interval for $\varepsilon \geq 122°$ (13 values). The mean ε and β for these seven groups are plotted in Fig. 1, together with the mean values for $r = 3$, 4 from Table 2. Linear regression on nine points gives $\beta = 96{\cdot}3 + 0{\cdot}20\varepsilon$. Also indicated on Fig. 1 are the lines $\beta = 97{\cdot}2 + 0{\cdot}19\varepsilon$ given by $r = 3$, 4, 5 (Table 2) and $\beta = 91{\cdot}7 + 0{\cdot}24\varepsilon$ given by regression on the seven intervals for $r = 5$–8.

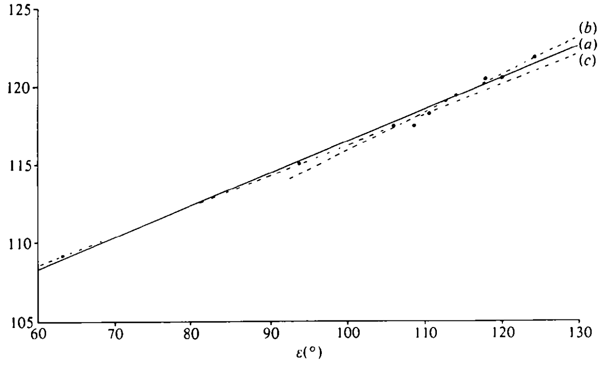

Fig. 1. The ε–β relationship (see text). The lines have the following equations: (a) $\beta = 96{\cdot}3 + 0{\cdot}20\varepsilon$; ($b$) $\beta = 91{\cdot}7 + 0{\cdot}24\varepsilon$; ($c$) $\beta = 97{\cdot}2 + 0{\cdot}19\varepsilon$.

Simple energy minimization (Appendix), based only on angle-bending strain with neglect of anharmonicity terms, predicts a linear ε–β relationship with $y = 0{\cdot}18$, 0·19, 0·20 for x ($= \delta\gamma/\delta\alpha$) = 1·0, 0·9, 0·8 respectively, in agreement with experiment. The differing values of y for $r = 3$, 4, 5 (0·19) and $r = 5$–8 (seven groups, $y = 0{\cdot}24$) might suggest a slight non-linearity in the relationship in agreement with energy calculations by Hazell & Hazell (1977). Experimental results are however, somewhat inconclusive since there is a paucity of $\varepsilon \geq 122°$. It appears that the relationship $\beta = 96{\cdot}3 + 0{\cdot}20$ provides highly accurate estimates of β (and hence α,γ) for ranges of ε which are likely to occur experimentally.

Table 3. *Mean geometries for p-dicycloalkenobenzenes with the nomenclature of* (IV) *and averaged over mm symmetry* (*r = fused-ring size*; *n = number of contributors*; *σ's in parentheses*)

Experimental data		
r	4, 4	5, 5
n	2	7
a	1·385 (38) Å	1·388 (5) Å
b	1·392 (37)	1·381 (5)
D	1·389 (37)	1·385 (5)
δa	−4	+3
δb	+3	−4
α	125·6 (5)°	123·0 (4)°
β	108·8 (2)	114·0 (5)
ε	92·8 (17)	107·7 (4)
$\delta\alpha$	5·6	3·0
$\delta\beta$	−11·2	−6·0
$\delta\varepsilon$	−27·2	−12·3
$\delta\beta/\delta\varepsilon$	0·41	0·49
$\delta\beta_2/\delta\beta_1$	2·28	2·72
Energy-minimization results		
$\delta\alpha$	4·7	2·1
$\delta\beta$	−9·4	−4·2

Dicycloalkenobenzenes

X-ray results for simple dicycloalkenobenzenes are sparse. There are no examples for r = 3,3 and the available data (irrespective of raw-data screens) for *para*-fused 4,4 and 5,5 systems are collected in Table 3, averaged over *mm* symmetry with the nomenclature of (VI).

Bond lengths in the two *p*-4,4 derivatives [benzo[1,2:4,5]dicyclobutene (R = 0·139; Lawrence & MacDonald, 1969) and a highly substituted derivative of 1,6-di-*tert*-butylbenzo[1,2:4,5]dicyclobutene (R = 0·088; Tsukada, Shimanouchi & Sasada, 1978)] differ widely, as shown by the very high $\sigma(a)$, $\sigma(b)$ values of Table 3. The angular agreement, however, is quite remarkable; the resultant $\delta\beta/\delta\varepsilon$ ratio of 0·41 is 2·2 times the corresponding monocyclo value.

Geometric parameters for the seven *p*-5,5 structures ($R \leq$ 0·10) are much more consistent. The independent bond lengths a and b do not differ significantly from the mean d, or from each other. The expected trend of angular deformation is observed with a mean contraction in α of 6·0° for an ε of 107·7°. The $\delta\beta/\delta\varepsilon$ ratio of 0·49 is some 2·55 times the corresponding monocyclo value.

The simple energy minimization (Appendix) predicts that $\delta\alpha,\delta\beta$ for *p*-di-fusion should be greater than the mono-fused value by a factor of 1·9. The ratios $\delta\beta_2/\delta\beta_1$ are somewhat higher than this, especially for the *p*-5,5 data; consequently, $\delta\alpha,\delta\beta$ are underestimated (by a factor of 0·7–0·8) by equation (5) of the Appendix. It may be noted that the C(ar)–C(ar)–C(sp^3) angle bending force constant k_2 appears as the numerator of equations (4), (5); small changes in k_2 have a more significant effect on $\delta\alpha$ estimates than do changes in k_1,k_3. A case could be made for increasing k_2 to a value close to k_1 [the C(ar)–C(ar)–C(ar) constant] since annular C(sp^2) substituents tend to dominate the structural subsets. While this is questionable, in view of the many approximations of the Appendix and the small size of the subsets in Table 3, it is worth noting that better overall $\delta\alpha$ estimates for both mono- and di-fusion can be obtained with $k_2 \sim$ 0·8–0·9 and $x = 1$.

Table 4. *The mean geometry of m-dicyclopentenobenzene with the nomenclature of* (V) *and averaged over m_{ad} symmetry* (*three contributors*; *distances in* Å; *angles in degrees*; *σ's in parentheses*)

	Experimental	Estimated$^{(a)}$
a	1·372 (5)	–
b	1·389 (9)	–
c	1·378 (6)	–
d	1·395 (9)	–
D	1·384 (7)	–
α	119·0 (8)	118·9
β	122·4 (8)	122·2
γ	118·7 (6)	118·9
ε	110·7 (8)	–
ε'	109·4 (8)	–
$\delta\alpha$	−1·0	−1·1
$\delta\beta$	+2·4	+2·2
$\delta\gamma$	−1·3	−1·1
$\delta\varepsilon$	−9·3	–
$\delta\varepsilon'$	−10·6	–

(a) Using simple additivity with the results for 5*A* of Table 2.

There are three *meta*-dicyclopentenobenzenes (VII) with $R \leq$ 0·07 and no additional benzene substituents. The available data are collected in Table 4, together with values of α, β, γ derived by simple additivity from the monocyclopentenobenzene results of Table 2. The spread of individual values in the three structures is quite variable; nevertheless the resultant means do indicate an approximate additivity of angular deformations.

Conclusions

The available X-ray geometries of mono- and dicycloalkenobenzenes with fused-ring sizes r = 3, 4, 5 have been tabulated and examined. There is no evidence for significant bond-length variation in the benzene ring caused by fusion to strained small-ring cycloalkenes, although there is a paucity of available data for the most highly strained systems involving cyclopropene. There is, therefore, no evidence for partial double-bond fixation in these systems (Mills & Nixon, 1930). The bond-length variations observed here would also indicate that the variations obtained by CNDO/2 calculations (Cheung, Cooper & Manatt, 1971) are somewhat overestimated (Table 1).

The strain in the benzene ring due to small-ring mono-fusion (III) and *p*-di-fusion (VI) is consistently reflected in significant expansion of angles α and γ, with a corresponding contraction of β (by $\alpha + \gamma$). Although the benzene rings in mono-fused situations approximate *mm* symmetry there is a tendency for the expansion $\delta\gamma$ to be less than $\delta\alpha$, and the ratio $\delta\gamma/\delta\alpha$ decreases with decreasing fused-ring size r (Table 2). The ratios $\delta\beta/\delta\varepsilon$, $\delta\alpha/\delta\varepsilon$ are almost identical for r = 3, 4, 5 indicating linear relationships between ε and α or β. A regression analysis of a ε–β plot for ε in the range 60–130° (derived from r = 3–8) yields the relationship $\beta = 96{\cdot}3 + 0{\cdot}20\varepsilon$ for monocycloalkenobenzenes. An analysis of the few available dicycloalkenobenzenes indicates the approximate additivity of benzene-ring deformations.

Simple force-field calculations (Appendix), based solely on angle-bending strain, give values of $\delta\alpha$, $\delta\beta$, $\delta\gamma$ which agree closely with the experimental results. This agreement indicates that a high proportion of the strain in the fused systems is reflected by the angular deformations noted above. It is interesting to note that the CNDO/2 results of Cheung, Cooper & Manatt (1971) seriously underestimate the angular deformation (Table 1).

APPENDIX

Here it is assumed that the strain in the benzene ring caused by fusion to a small-ring cycloalkene is reflected entirely by valence-angle deformations in the planar aromatic system. Bond-stretching, non-bonded interactions *etc.*, are ignored. The general expression (neglecting anharmonicity terms) for the strain energy due to angle bending is $2E_a = \sum k(\theta - \theta_o)^2$, where θ_o is the unstrained angle and k is a force constant. With the nomenclature of (III), and assuming that deformation of C—C—H angles is one-half the corresponding internal-angle deformation (and of opposite sign), we obtain:

$$\begin{aligned} 2E_a = {} & k_1[2(\delta\alpha)^2 + 2(\delta\beta)^2 + 2(\delta\gamma)^2] \\ & + k_2[2(\delta\varepsilon)^2 + 2(\delta\rho)^2] \\ & + k_3[4(\delta\beta/2)^2 + 4(\delta\gamma/2)^2], \end{aligned} \qquad (1)$$

where k_1, k_2, k_3 are force constants for C(ar)—C(ar)—C(ar), C(ar)—C(ar)—C(sp^3) and C(ar)—C(ar)—H angles respectively.

Equation (1) can be simplified by the following approximations: (i) $\delta\gamma = x\delta\alpha$ ($x \to 1$); (ii) $\delta\beta = -(\delta\alpha + x\delta\alpha)$, assuming $x \to 1$ hence the benzene ring has approximate *mm* symmetry (Britton, 1977); (iii) $\delta\alpha + \delta\rho = -\delta\varepsilon$ (~60, 30, 12° for r = 3, 4, 5). Making substitutions and simplifying we obtain an equation of the form:

$$E_2 = K_1(\delta\alpha)^2 + 2k_2(\delta\varepsilon)(\delta\alpha) + 2k_2(\delta\varepsilon)^2, \qquad (2)$$

where

$$K_1 = [(2k_1 + k_3)(x + x^2) + 2k_1 + k_2 + k_3/2].$$

For minimal strain energy:

$$\partial E_a/\partial(\delta\alpha) = 2K_1(\delta\alpha) + 2k_2(\delta\varepsilon) = 0, \qquad (3)$$

whence

$$\delta\alpha = k_2/K_1(\delta\varepsilon) = M_1(\delta\varepsilon). \qquad (4)$$

A similar treatment for *p*-dicycloalkenobenzenes, with strict *mm* symmetry in the nomenclature of (VI), gives

$$\delta\alpha = k_2/K_2(\delta\varepsilon) = M_2(\delta\varepsilon), \qquad (5)$$

where

$$K_2 = 3k_1 + k_2 + k_3.$$

Force constants k_1, k_2, k_3 of 1·0, 0·70, 0·50 × 10^{-18} J rad^{-1} are given by Boyd, Sanwal, Shary-Tehrany & McNally (1971); k_3 is modified to 0·40 × 10^{-18} J rad^{-1} by Andose & Mislow (1974). Thus we have M_1 = 0·09, 0·10, 0·11 for x = 1·0, 0·9, 0·8 and M_2 = 0·17.

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Structures of the Neuroleptic Drugs α- and β-Clopenthixol

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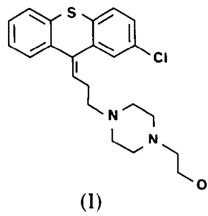
Abstract

The tricyclic neuroleptic drug α-clopenthixol ($C_{22}H_{25}ClN_2OS$) is monoclinic, $P2_1/n$, with a = 11·549 (4), b = 15·739 (6), c = 11·627 (5) Å, β = 109·47 (2)°, U = 1992·6 Å^3, Z = 4. Its less potent β isomer is triclinic, $P\bar{1}$, with a = 6·493 (2), b = 7·758 (3), c = 21·881 (8) Å, α = 90·11 (2), β = 91·48 (2), γ = 92·81 (2)°, U = 1100·5 Å^3, Z = 2, and crystallizes as a dihydrate. The structures have been refined to R = 0·051 for 2503 reflexions (α) and 0·039 for 3170 reflexions (β). Various structural features of these drugs and those of the closely related α- and β-flupenthixol are compared.

Introduction

The thioxanthenes are an important group of neuroleptic drugs used in the treatment of psychotic patients. A member of this class which has recently been receiving increasing clinical interest is clopenthixol, which can exist as α and β isomers differing in their conformation about the exocyclic double bond. The α (*cis*) isomer is shown here (I). Pharmacological (Petersen, Moller-Nielsen, Pedersen, Jorgensen & Lassen, 1977) and clinical (Gravem, Engstrand & Guleng, 1978) studies have shown that this isomer is much more potent than the β form. One reason for this X-ray study was to establish the geometry of these two isomers.



(I)

There has also been increasing interest in the structural and conformational factors responsible for

Table 1. *Additional crystal data and data-collection and refinement details*

	α Isomer	β Isomer
Formula	$C_{22}H_{25}ClN_2OS$	$C_{22}H_{25}ClN_2OS.2H_2O$
M_r	400·97	437·01
D_x (Mg m^{-3})	1·337	1·319
μ(Mo $K\alpha$) (mm^{-1})	0·3	0·3
Crystal size (mm)	0·4 × 0·35 × 0·2	0·75 × 0·4 × 0·25
Crystal form	Colourless blocks, elongated along [101]	Pale-yellow blocks, elongated along **a**
Data collection		
2θ limits (°)	7–50	7–50
Reflexions measured	3497	4166
Unique reflexions	3496	3881
Observed reflexions [$F > 4\sigma(F)$]	2503	3174
Refinement		
Final R	0·051	0·039
Final R'	0·049	0·042
Weighting: g =	0·0005	0·0004
Largest difference peak (e Å^{-3})	0·22	0·18

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