1.0 ml of the bromine solution was added. Illumination and stirring were continued until the bromine color disappeared. The lengths of time required to decolorize bromine in the competitive brominations p-C_6H_5, H, p-Cl, p-Br, p-I, m-Br, p-CN, and p-NO_2 were approximately 3, 4, 5, 9, 7, 10, 20, and 30 min, respectively.

The Teflon stirring bar was removed, and the flask was placed on a Rotavap to remove excess carbon disulfide solvent. The rate of solvent removal was regulated such that the flask remained cold to the touch throughout the removal of solvent. Solvent removal was terminated when 2–5 ml of the solvent remained in the flask. A sample of the reaction mixture was added to an NMR tube along with 2 drops of 50% tetramethylsilane. A 60-MHz NMR spectrum of the product mixture was taken. All peaks except those in the aromatic region were integrated three times. The integral amplitude was adjusted so that the largest peak grouping integrated nearly full scale on the chart paper.

Each NMR spectrum consisted of the following groupings of peaks: aromatic absorptions δ 8.2–6.8 (A_1); the benzylic proton of the ring-opened dibromide, doublet of doublets, δ 4.9–5.2 (A_2); the methylene protons of p-chlorobenzyl bromide, singlet, δ 4.3–4.4 (A_3); the terminal methylene group of the ring-opened dibromide, δ 3.0–3.7 (A_4); the central methylene protons of the ring-opened dibromide plus a methyl absorption for unreacted p-chlorotoluene plus the benzylic proton of unreacted substituted phenylcyclopropane, δ 3.1–1.4 (A_5); the methylene protons of unreacted substituted phenylcyclopropane, δ 1.3–0.4 (A_6). In the competitive brominations of p-nitrophenylcyclopropane vs. p-chlorotoluene, small amounts of p-chlorobenzal bromide were produced with singlet absorption at δ 6.5–6.6 (A_7).

Values of log (k_2/k_1) were calculated from the relationship

$$\log k_2/k_1 = \log\left[\log\frac{(y-B)}{y}\Big/\log\frac{(x-A)}{x}\right]$$

where k_2 is the rate constant for bromination of the phenylcyclopropane (y) and k_1 is the rate constant for bromination of p-chlorotoluene (x). B and A are the respective amounts of y and x consumed in the reaction. The relative values of the quantities in the equation are related to the NMR integrals by the relations $y - \mathrm{B} = \mathrm{A}_6/4$; $y = \mathrm{A}_6/4 + \mathrm{A}_2$:

$$x - \mathrm{A} = (\mathrm{A}_5 - \mathrm{A}_4 - \mathrm{A}_6/4)/3$$
$$x = (\mathrm{A}_5 - \mathrm{A}_4 - \mathrm{A}_6/4)/3 + \mathrm{A}_7 + \mathrm{A}_3/2$$

Five artificial reaction mixtures were prepared using known quantities and subjected to the analysis. In each case, the calculated log k_2/k_1 was well within the statistical error of the theoretical value.

Competitive Brominations of Substituted Toluenes. The same procedure as used for the competitive brominations of phenylcyclopropanes was employed, with p-cyanophenylcyclopropane as the constant competitor.

Registry No.—**1**, 873-49-4; **2**, 17714-42-0; **3a**, 35076-77-8; **3b**, 1798-84-1; **3c**, 1124-14-7; **3d**, 1798-85-2; **3e**, 57807-27-9; **3f**, 1126-27-8; **3g**, 6921-44-4; **4a**, 58873-50-0; **4b**, 19714-76-2; **4c**, 58873-51-1; **4d**, 58873-52-2; **4e**, 58873-53-3; **4f**, 58873-54-4; **4g**, 58678-85-6; ω-dimethylamino-p-chloropropiophenone hydrochloride, 1798-83-0; ω-dimethylamino-p-phenylpropiophenone hydrochloride, 5409-63-2; dimethylamine hydrochloride, 506-59-2; p-phenylacetophenone, 92-91-1; ω-dimethylamino-m-bromopropiophenone hydrochloride, 2192-15-6; m-bromoacetophenone, 2142-63-4; o-nitrophenylcyclopropane, 10292-65-6; p-chlorotoluene, 106-43-4.

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X-Ray Crystal Structure Analysis of Triquinacene at 90 K

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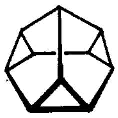
The crystal structure of the $C_{10}H_{10}$ hydrocarbon triquinacene, whose three multiply fused cyclopentene rings adopt an unusual cup-shaped geometry having $p\pi$ orbitals projected toward the center of the concave face, has been determined at 90 K from three-dimensional x-ray counter data. A crystal grown in a stream of cold nitrogen gas was found to have space group $R\bar{3}$ and a (hexagonal) unit cell of $a = 7.272$ (5) Å and $c = 23.557$ (13) Å, with six molecules per cell. The structure was refined using 484 unique reflections with $I > 3\sigma_I$ to a final conventional R factor of 0.052. The molecule has nearly ideal C_{3v} symmetry but, because of packing considerations, only a threefold axis is utilized in the crystalline state.

Homoaromatic character is thought to be present in several cationic and anionic species having one or two homoconjugate linkages.[2,3] Comparable properties have not been uncovered in neutral molecules, presumably because the driving force underlying charge dissipation is no longer present to encourage electronic delocalization, at least to the same extent. As concerns possible neutral six-electron homoaromatic analogues of benzene, the four hydrocarbons **1**–**4** have commanded recent attention. Two of these, *cis,cis,cis*-1,4,7-cyclononatriene (**2**)[4] and triquinacene (**3**),[5] have three double bonds properly disposed for possible interaction, and are potential trishomoaromatic systems.

1

2

3



4

In the case of **2**, it was not possible by x-ray crystallography, ^1H NMR spectroscopy, or heats of hydrogenation to detect any interaction of the double bonds.[4,6] Several chemical and spectroscopic studies have also failed to uncover interaction between the π bonds in **3**.[5] Recent studies by Heilbronner and co-workers using photoelectron spectroscopy have, however, revealed an appreciable interaction of the π bonds in the cyclononatriene.[7] Other photoelectron spectral studies have demonstrated that there exists a much smaller overall interaction of the π levels in **3** relative to **2**.[8]

The geometry of triquinacene is such that the three double bonds occupy fixed positions having one lobe of their pπ orbitals projected toward the midpoint of the concave surface. Comparable rigidity is not seen in **2** which possesses the ability for facile conformational inversion of its crown-to-crown structure in the liquid phase.[6] Modified through space interaction of the π levels in **3** is therefore expected. Such interaction is related not only to the degree of overlap of the orbitals involved, but also to their energy separation.[9] The observed very small split in the e(π) and $a_1(\pi)$ levels in **3**[8] can be attributed either to decreased through space interaction relative to **2** or to large through bond contributions involving the $a_1(\pi)$ and $a_1(\sigma)$ levels. In an effort to gain additional three-dimensional information about triquinacene, its x-ray crystal structure has now been determined. The molecular structure of **2**, obtained previously,[6] was available for direct comparison.

Experimental Section

Preparation. Triquinacene was prepared by previously described procedures[5d,e] and purified by preparative VPC on a 6 ft × 0.25 in. column packed with 5% SE-30 on Chromosorb P at 130 °C. The ^1H NMR spectrum of **3** (in $CDCl_3$) shows two sharp signals at δ 5.63 and 3.71. Its ^{13}C NMR spectrum (in $CDCl_3$) is characterized by peaks at 132.89, 47.96, and 29.24 ppm.

Crystallographic Data. Because of the low melting point of **3** (18–19 °C), the hydrocarbon was handled as a liquid and a small drop was sealed in a 0.2-mm glass capillary and mounted on a Picker FACS-I automated diffractometer. The crystal was obtained by slowly translating a stream of cold nitrogen gas onto the sample. The cold stream was generated using a modified Enraf Nonius gas flow system. After many attempts, it was possible to grow the entire sample into a single crystal, as confirmed with x-ray oscillation photographs. The temperature of the gas stream was maintained at 90 K within ±2 K as measured with a copper–constantan thermocouple.

Cell dimensions were obtained from least-squares refinement of the setting angles of 17 carefully centered high-order reflections. From searches for reflections using the diffractometer, only systematic absences (hkl: $-h + k + l = 3n$) consistent with space groups $R3$, $R32$, $R\bar{3}$, $R3m$, and $R\bar{3}m$ were observed. The additional observation that $I_{hkl} \neq I_{\bar{h}kl}$ implies that the space group must be $R3$ or $R\bar{3}$. Crystallographic data for **3** are given in Table I.

X-Ray Data Collection. All reflections in the sphere $2\theta < 55°$ were measured with Nb-filtered Mo Kα radiation using a θ–2θ step scan technique. A total scan range of [2.5° + 0.7° tan θ] was used with a step size of 0.03°2θ and a count time of 1.00 s per step. The intensities of three standard reflections measured after every 50 reflections did not change significantly during data collection. Integrated intensities were obtained from analysis of the step scan profiles[10] and corrected for absorption (μ = 0.63 cm^{-1}) assuming the crystal to be a cylinder of length 0.3 mm and diameter 0.2 mm. Standard deviations were assigned according to the expression

$$\sigma_I = (\sigma^2_{count} + (0.03\, I)^2)^{1/2}$$

where σ_{count} was calculated from counting statistics.

Table I. Crystallographic Data for Triquinacene (3)

Mol wt	130.2	Space group	$R\bar{3}$
a, Å	7.272 (5)	ρ_{calcd}, g/cm^3	1.202 for $Z = 6$
c, Å	23.557 (13) (hexagonal cell)	Volume, Å^3	1078.8

Table II. Final Fractional Atomic Coordinates and Isotropic Thermal Parameters[a]

Atom	x	y	z	U_{iso},[b] Å^2
C1	0.29350 (23)	0.05699 (23)	0.23908 (7)	
C2	0.21398 (24)	0.17736 (24)	0.27398 (7)	
C3	0.14964 (24)	0.31032 (21)	0.23895 (7)	
C4	0.0	0.0	0.29904 (13)	
H1	0.4221 (25)	0.1266 (25)	0.2180 (7)	0.0361 (42)
H2	0.3164 (22)	0.2685 (24)	0.3029 (7)	0.0315 (38)
H3	0.2470 (22)	0.4293 (24)	0.2176 (7)	0.0329 (42)
H4	0.0	0.0	0.3404 (13)	0.0337 (74)

[a] Standard deviations in parentheses. [b] Isotropic thermal parameters expressed as $\exp(-2\pi^2\, U_{iso} \sin^2\theta/\lambda^2)$.

Averaging of the symmetry equivalent forms reduced the total of 2942 measured reflections to 597 independent ones. The average discrepancy between symmetry related forms of the 120 strongest unique reflections was 3.6%. A total of 484 unique reflections with $I > 3\sigma_I$ was used in solution and refinement of the structure.

Solution and Refinement of the Structure. The statistical distribution of normalized structure amplitudes (E's) indicated a centrosymmetric structure. The space group was taken to be $R\bar{3}$. The structure was solved using Long's[11] sign predicting program. The 100 E's above 1.3 were used with a starting set of four permutable signs in addition to one sign determining the origin. The carbon atoms skeleton was easily identified in the E map from the solution set with the highest consistency index (0.59). However, large disagreement between F_o and F_c for low-order 00l reflections in an initial structure factor calculation indicated that the placement of the molecule along the c axis was incorrect. A translation of the molecule by c/6 gave the correct solution.

Scattering factors for carbon and for a "spherical bonded" hydrogen atom were taken from Vol. IV of the International Tables.[12] Least-squares refinement with anisotropic temperature factors for the carbon atoms and isotropic temperature factors for the hydrogens gave a final R of 0.052 and R_w of 0.032.[13] The quantity minimized in the refinement was $\Sigma w(|F_o| - |F_c|)^2$ with weights $w = 1/\sigma_F{}^2$. An isotropic extinction parameter was included as a variable in the refinement. All programs used for data reduction and refinement are part of the Integrated Crystallographic Computing Library at the State University of New York at Buffalo. A table of observed and calculated structure factors is available.[14]

Results and Discussion

The final positional and isotropic thermal parameters are given in Table II. The anisotropic thermal parameters are presented in Table III. Although the molecule has a crystallographically imposed threefold rotation axis parallel to the c axis, the individual units have nearly ideal C_{3v} symmetry. Atoms labeled with ′ and ″ are generated by rotations about the threefold axis of 120 and 240°, respectively (Figure 1). The more important intramolecular bond distances and bond angles are given in Figure 1. Full details are given in the supplementary material. Standard deviations in distances and

Table III. Anisotropic Thermal Parameters[a,b] (Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C1	0.0236 (8)	0.0321 (8)	0.0322 (9)	0.0146 (7)	0.0004 (7)	0.0024 (7)
C2	0.0244 (8)	0.0271 (8)	0.0316 (9)	0.0097 (7)	−0.0050 (7)	−0.0037 (7)
C3	0.0322 (9)	0.0214 (8)	0.0326 (9)	0.0117 (7)	0.0022 (7)	−0.0006 (7)
C4	0.0298 (9)	0.0298[c]	0.0246 (16)	0.0149[c]	0.0	0.0

[a] Anisotropic thermal parameters expressed as $\exp -2\pi^2(U_{11}a^{*2}h^2 + U_{22}b^{*2}k^2 + U_{33}c^{*2}l^2 + U_{12}a^*b^*hk + U_{13}a^*c^*hl + U_{23}b^*c^*kl)$. [b] Standard deviations in parentheses. [c] From symmetry $U_{11} = U_{22} = 2U_{12}$.

Table IV. Intermolecular Contacts of <3.0 Å

Atoms		Distance	No.
H3 . . . H3′	$(1 + X, 1 + Y, Z)$	2.62	6
. . . H3″	$(X, 1 + Y, Z)$		
H2 . . . H2′	$(\frac{1}{3} - X, \frac{2}{3} - Y, \frac{2}{3} - Z)$	2.75	6
. . . H2″	$(\frac{1}{3} - X, -\frac{1}{3} - Y, \frac{2}{3} - Z)$		
H3 . . . H3′	$(-\frac{1}{3} - X, \frac{1}{3} - Y, \frac{1}{3} - Z)$	2.84	6
. . . H3″	$(\frac{2}{3} - X, \frac{1}{3} - Y, \frac{1}{3} - Z)$		
H1 . . . H1′	$(1 + X, Y, Z)$	2.87	6
. . . H1″	$(1 + X, 1 + Y, Z)$		
H2 . . . H4	$(\frac{1}{3} - X, \frac{2}{3} - Y, \frac{2}{3} - Z)$	2.89	3
H4 . . . H2	$(\frac{1}{3} - X, \frac{2}{3} - Y, \frac{2}{3} - Z)$	2.89	3
. . . H2′	$(-\frac{2}{3} - X, -\frac{1}{3} - Y, \frac{2}{3} - Z)$		
. . . H2″	$(\frac{1}{3} - X, -\frac{1}{3} - Y, \frac{2}{3} - Z)$		
H1 . . . H3	$(\frac{2}{3} - X, \frac{1}{3} - Y, \frac{1}{3} - Z)$	2.90	6
H1 . . . H1	$(\frac{2}{3} - X, \frac{1}{3} - Y, \frac{1}{3} - Z)$	2.93	3
H1 . . . H3′	$(1 + X, Y, Z)$	2.94	6

angles were calculated from the full variance–covariance matrix obtained from the last cycle of refinement.

Corrections to the bond distances due to librational thermal motion were calculated using the rigid-body TLS analysis.[15] The negligible corrections reflect the small degree of thermal motion at 90 K.

The five-membered rings in the molecule are slightly nonplanar. The deviations from the least-squares plane ($4.337x - 2.782y + 18.769z = 5.594$) through atoms C1, C2, C4, C2″, and C3″ are 0.008, −0.017, 0.005, −0.015, and 0.019 Å, respectively. A better least-squares plane ($4.246x - 2.724y + 18.992z = 5.630$) is obtained through atoms C1, C2, C2″, and C3″ giving deviations of 0.002, −0.001, −0.002, and 0.001 Å, respectively, with atom C4 0.049 Å above the plane. Atoms H1 and H3″ are −0.024 and −0.031 Å from the first plane and −0.043 and −0.050 Å from the second plane, respectively.

The molecules in the crystal structure are arranged in layers perpendicular to the *c* axis. Contacts between molecules are top to top and bottom to bottom in alternate layers (Figure 2). The closest intermolecular contacts are listed in Table IV. Contacts between hydrogens apparently prevent the compound from crystallizing in a structure which utilizes the full C_{3v} symmetry of the molecule. In contrast, the C_{3v} symmetry of **2** is incorporated in its crystal structure.[6]

The nonbonded intraannular methylene hydrogen interactions in **2** have the effect of denying close approach of one CH_2 group to another. Notwithstanding, the degree of pucker in the cyclononatriene (defined as the vertical distance of CH_2 group from the basal plane adopted by the trigonal carbons) is expected to be more accentuated than that in triquinacene, particularly since an apical carbon and multiple cyclopentene ring formation need not be accommodated. In actuality, the angle defined by atoms C3″–C1–C2 in **2** (124°) is approximately 11° wider than the corresponding angle in **3** (112.8°). As a result, the allylic carbons in triquinacene (e.g., C2 and C2″) are separated by 2.497 Å and the C1–C2–C3 angle is enlarged to 113.8°. For **2**, this angle is significantly smaller (108°). It follows that the nonbonded C1 . . . C3 distance adopted by **3** (2.533 Å) is necessarily larger than that in **2** (2.46 Å). Both distances are too long for normal π–π bonding overlap from the convex direction and deny the possibility for conventional peripheral delocalization in both systems.

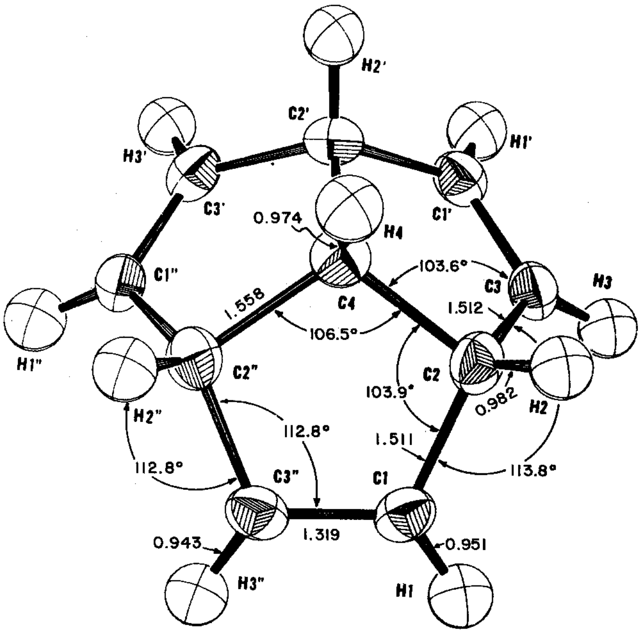


Figure 1. Numbering scheme for the triquinacene molecule. The threefold axis is along the C4–H4 bond. Thermal ellipsoids are drawn at 50% probability.

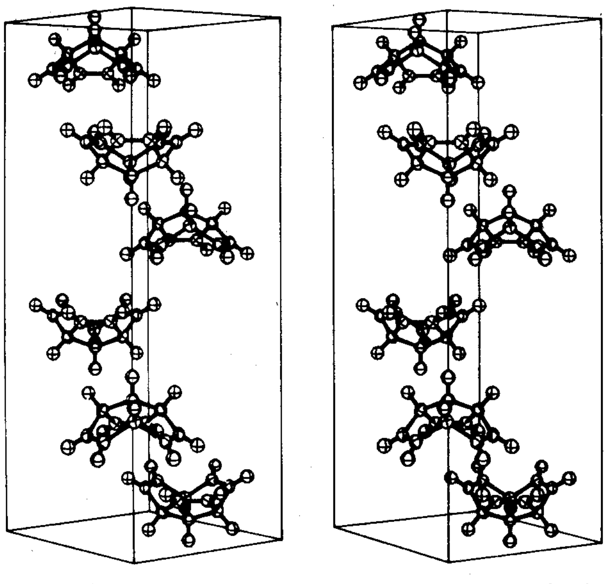


Figure 2. Stereoscopic view of the packing in the hexagonal unit of triquinacene molecules.

That neither **2** nor **3** can partake of homoallylic participation on their exo surfaces due to the excessively long gaps between the individual π bonds is consistent with their chemical reactivity. The answer to the critical question of whether stabilization is made possible from such a π-orbital arrangement on the concave underside is decidely negative. That homoconjugative interaction is entirely prohibited is evidenced further by the complete lack of anchimeric assistance to ionization in *exo*-2,3-dihydrotriquinacen-2-ol tosylate[16] and the electronic properties of 2,3-dihydrotriquinacen-2-one.[17]

The increased nonbonded distance separating the allylic carbons in *cis,cis,cis*-1,4,7-cyclononatriene will result in a somewhat more favorable canting of the π orbitals in the molecular interior. It seems reasonable to assume therefore that **2** will be capable of better through space interaction than **3** and that the photoelectron spectroscopic results[18] provide a quantitative measure of these effects. In other words, through space interaction between the three π-bond segments increases with increased molecular puckering. For bridged bicyclic dienes of the Dewar benzene, norbornadiene, bicyclo[2.2.2]octadiene, etc., type, the same is true. In this series, through space interaction falls off as the length of the saturated bridge increases from 0 to 4.[18] This comparable behavior points up convincingly the somewhat analogous orbital alignments which characterize these two groups of molecules.

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Registry No.—**3**, 6053-74-3.

Supplementary Material Available. A complete listing of intramolecular bond distances and bond angles (4 pages). Ordering information is given on any current masthead page.

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Quantitative Structure–Activity Relationships of D- and L-*N*-Acyl-α-aminoamide Ligands Binding to Chymotrypsin. On the Problem of Combined Treatment of Stereoisomers[1a]

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The binding of D- and L-*N*-acyl-α-aminoamides [RCH(NHCOR′)CONH$_2$] to chymotrypsin is correlated with the molar refractivity (MR) of R and NHCOR′. The group with the largest MR value appears to bind in the so-called hydrophobic cleft (ρ_2 area); the smaller group binds in ρ_1 space. Working from this premise, the K_m values for 23 L amides and the K_i values for 22 D amides can be correlated in a single equation. This appears to be the first instance where the structure–activity relationship of optical isomers has been correlated in a single equation.

One of the challenges facing those interested in the formulation of quantitative structure–activity relationships (QSAR) is the problem of including different stereoisomers in a single equation. Sometimes there is little difference in the biological activity of, say, D and L isomers and sometimes there is vast difference between high activity and complete inactivity. An excellent system with which this problem can be explored is α-chymotrypsin and the various ligands with which it interacts. The structure and mechanism of action of this enzyme are probably better understood than those of any other enzyme.

Over the years many studies of substituent effects on ligand interactions with enzymes have been made but attempts to formulate linear free-energy relationships of the Hammett type correlating structure with activity have been limited to sets with small numbers of congeners. Until recently, these correlation studies have tried to rationalize substituent effects using a single electronic parameter such as σ or σ⁻. With the development[2] of the hydrophobic parameter π, analogous to σ, it has been shown that taking hydrophobic effects as well as steric effects (E_s) of substituents into account enables one to formulate much more comprehensive QSAR for chymotrypsin.[3] Various groups have begun to test the use of hydrophobic parameters in the formulation of structure–activity relationships with chymotrypsin.[4–10]

The parameter π is defined as $\pi_X = \log P_X - \log P_H$ where P_X is the octanol/water partition coefficient of a derivative and P_H that of the parent compound. Considerable evidence has accumulated to indicate that π models the hydrophobic interaction of substituents with lipophilic portions of enzymes[11] as well as other macromolecules.[12]

While much attention has been focused on the interaction