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Review of the Preferred Rotational Orientation of the Carboxyl and *tert*-Butyl Groups. Structure of *trans*-4-*tert*-Butyl-1-cyclohexanecarboxylic Acid, $C_{11}H_{20}O_2$

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Abstract

$M_r = 184\cdot28$, monoclinic, $P2_1/c$, $a = 12\cdot303\,(3)$, $b = 7\cdot843\,(2)$, $c = 11\cdot854\,(3)$ Å, $\beta = 107\cdot84\,(2)°$, $V = 1088\cdot8$ Å^3, $Z = 4$, $D_x = 1\cdot128$ Mg m^{-3}, Mo $K\alpha$ radiation, $\lambda = 0\cdot71069$ Å, $\mu = 0\cdot081$ mm^{-1}, $F(000) = 408$, $T = 110$ K. Final $R = 0\cdot044$ for 2395 (out of 3161) observed data. A flattening at the *tert*-butyl side and a puckering at the carboxyl side of the ring are observed. The carbonyl O atom of the equatorial carboxyl group is twisted away from the eclipsed position with an α,β bond in the ring by 20·2°, in agreement with the synperiplanar C_β–C_α–C=O arrangement observed for equatorial as well as axial carboxyl groups in several cyclohexanecarboxylic acids and related compounds. The equatorial *tert*-butyl group is twisted away from the perfectly staggered position by about 4°. The off-staggering of the equatorial *tert*-butyl group in several ring structures is described with a Gaussian distribution function $G(\omega, \sigma)$ with $\langle\omega\rangle = 0°$ and $\sigma \simeq 5°$. The broad distribution implies a negligible barrier to rotation of the *tert*-butyl group or a potential energy well with a 'flat' minimum.

Introduction

To explain pK_a differences between variously substituted cyclohexanecarboxylic acids, preferred conformations of the carboxyl group were proposed (Sicher, Tichý & Sipos, 1966*a*, *b*; van Bekkum, Verkade & Wepster, 1966; van Bekkum, 1970): in equatorial and axial carboxyl groups the synperiplanar arrangement H–C_α–C=O and C_β–C_α–C=O should be preferred, respectively. Leiserowitz & Schmidt (1965), Dunitz & Strickler (1968) and Leiserowitz (1976) pointed out that the synperiplanar C_β–C_α–C=O arrangement seems to be a general feature of the molecular shape of α,β-saturated carboxylic acids, whether the carboxyl group is axial or equatorial. However, only two appropriate structures were used to prove this statement with respect to cyclohexanecarboxylic acids. Several crystal structures that bear on this problem have since been studied by X-ray analysis.

The generally accepted perfectly staggered conformation of *tert*-butylcyclohexane is not confirmed by many empirical force-field calculations. Depending on the force field used, the predicted off-staggering is ±17° (Altona & Sundaralingam, 1970), ±15·2° or ±8·4° (van de Graaf, Baas & Wepster, 1978). A recent MM2 force field (Burkert & Allinger, 1982) found the symmetrical geometry (off-staggering = 0°) to be the most stable one. All calculations show anomalous values for the bond angles, bond lengths and torsion angles at the *tert*-butyl side of the ring.

The aim of this investigation was to study the preferred rotational orientation of the carboxyl and *tert*-butyl group by determining the molecular structure of *trans*-4-*tert*-butyl-1-cyclohexanecarboxylic

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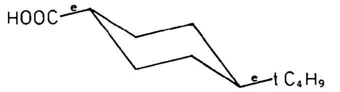
acid (TRANS):



and by comparing the results with data extracted from the literature.

Experimental section

The title compound was kindly provided by Professor H. van Bekkum, Laboratory of Organic Chemistry, Delft University of Technology. Crystals from petroleum ether (80–100°C) at 278 K, colourless crystal, D_m not measured, approximate size $0{\cdot}4\times0{\cdot}3\times0{\cdot}3$ mm, crystal enclosed in glass capillary. 1967 reflections measured with Cu $K\alpha$ at 300 K of which 1379 had $I>2\sigma(I)$; crystal cooled to 110 K with a modified low-temperature Enraf–Nonius device; systematic absences $h0l$ for l odd and $0k0$ for k odd; cell parameters from diffractometer angular settings of 25 centred reflections with $20°<2\theta(\mathrm{Mo})<40°$; data collected for $h, k, \pm l$ (h 0 to 17; k 0 to 11; l −16 to 15) in $\omega/2\theta$ scan mode with $\theta_{max}=30°$ on an Enraf–Nonius CAD-4 diffractometer (graphite-monochromated Mo $K\alpha$ radiation); 3161 independent reflections of which 2395 reflections had $I>\sigma(I)$; standard reflections showed no significant changes; no correction for absorption or extinction. Structure solution by direct methods; with data at 300 K: anisotropic refinement, H not located, $R=0{\cdot}13$; large librational motion was observed around an axis passing through the carbonyl C atom and the quaternary C atom of the *tert*-butyl group – no further convergence achieved; with data at 110 K: anisotropic full-matrix least-squares refinement based on F using unit weights, H (from difference map) included with fixed isotropic values; maximum shift of parameters in the last cycle $0{\cdot}1\sigma$, final $R=0{\cdot}0438$, $S=0{\cdot}93$; final $|\Delta\rho|$ peaks of $0{\cdot}35$ e Å^{-3}, about half-way between bonded C atoms. Atomic scattering factors from Cromer & Mann (1968) for C and O and from Stewart, Davidson & Simpson (1965) for H; calculations performed with *XRAY*72 (Stewart, Kruger, Ammon, Dickinson & Hall, 1972).

Discussion

The molecular structure and atom numbering of TRANS are given in Fig. 1. Table 1 lists the final atomic parameters.* Bond lengths, bond angles and relevant torsion angles are listed in Table 2.

* Lists of structure factors, anisotropic thermal parameters, distances and angles involving H atoms and a full bibliography concerning Fig. 2, Fig. 3 and Fig. 5 have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 39267 (34 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Fractional atomic coordinates and their e.s.d.'s* ($\times10^4$, *for* H $\times10^3$) *and* U_{eq} (Å$^2\times10^4$)

U_{iso}(Å$^2\times10^4$) for H atoms were held fixed. $U_{eq}=\frac{1}{3}\sum_i U_{ii}$.

	x	y	z	U_{eq}/U_{iso}
C(1)	1624 (1)	6711 (2)	9513 (1)	154 (5)
C(2)	894 (1)	5638 (2)	8475 (1)	179 (6)
C(3)	1555 (1)	4076 (2)	8279 (1)	179 (6)
C(4)	2692 (1)	4538 (2)	8074 (1)	137 (5)
C(5)	3385 (1)	5691 (2)	9082 (1)	177 (6)
C(6)	2722 (1)	7258 (2)	9270 (1)	196 (6)
C(7)	3373 (1)	2959 (2)	7872 (1)	160 (6)
C(8)	3784 (1)	1823 (2)	8974 (1)	211 (7)
C(9)	4415 (1)	3550 (2)	7521 (2)	249 (7)
C(10)	2630 (1)	1876 (2)	6852 (2)	273 (8)
C(11)	948 (1)	8203 (2)	9734 (1)	155 (5)
O(1)	199 (1)	7759 (2)	10273 (1)	293 (6)
O(2)	1055 (1)	9660 (1)	9429 (1)	261 (5)
H(11)	180 (2)	593 (2)	1021 (2)	228
H(21)	69 (2)	639 (3)	778 (2)	228
H(22)	18 (2)	531 (2)	858 (2)	228
H(31)	167 (2)	327 (2)	896 (2)	228
H(32)	109 (2)	345 (2)	759 (2)	228
H(41)	251 (1)	530 (3)	734 (2)	228
H(51)	362 (2)	497 (3)	983 (2)	228
H(52)	409 (2)	609 (2)	894 (2)	228
H(61)	252 (2)	809 (2)	856 (2)	228
H(62)	321 (2)	795 (2)	995 (2)	228
H(81)	435 (2)	244 (3)	966 (2)	291
H(82)	414 (2)	76 (3)	881 (2)	291
H(83)	315 (2)	136 (3)	923 (2)	291
H(91)	479 (2)	251 (3)	731 (2)	291
H(92)	498 (2)	422 (3)	817 (2)	291
H(93)	419 (2)	441 (3)	683 (2)	291
H(101)	230 (2)	265 (3)	613 (2)	291
H(102)	200 (2)	128 (3)	703 (2)	291
H(103)	304 (2)	91 (3)	662 (2)	291
H(O1)	−14 (2)	864 (3)	1036 (2)	355

The cyclohexane ring

The mean C–C–C bond angle, mean C–C bond length and mean torsion angle in the ring are 110·9°, 1·530 Å and 55·9°, respectively. The corresponding values in *cis*-4-*tert*-butyl-1-cyclohexanecarboxylic acid (CIS; van Koningsveld, 1972) are 111·5°, 1·529 Å and 54·8°. Force-field calculations on equatorial *tert*-butylcyclohexane (Altona & Sundaralingam, 1970) gave 111·2°, 1·533 Å and 55·4°. Using another force field the calculated mean torsion angle is 55·9° (van de Graaf, Baas & Wepster, 1978). The ring in TRANS (with an equatorial carboxyl group) relaxes just in

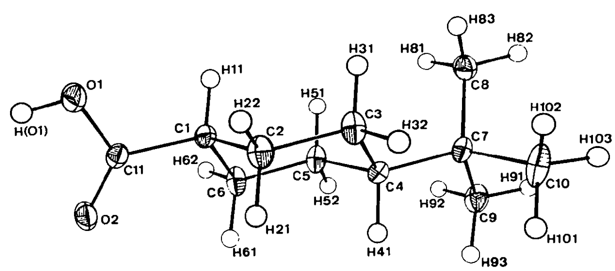


Fig. 1. *ORTEP* plot (Johnson, 1965) of TRANS showing the molecular structure and atom numbering. Boundary surfaces for C and O are drawn at the 50% probability level and for H arbitrarily.

the reverse order compared to the ring in CIS (with an axial carboxyl group): puckering at C(1) and flattening at C(4) occurs (Table 2). The flattening at C(4) is in excellent agreement with the calculations of Altona & Sundaralingam {relevant torsion angles: 52·7° [C(2)C(3)C(4)C(5)] and 54·8° [C(3)C(4)C(5)C(6)]}, but differs considerably from the calculations of van de Graaf, Baas & Wepster (corresponding values: 54·8° and 55·4°).

Rotational orientations of the carboxyl and *tert*-butyl groups

The carboxyl group

The carbonyl O atom in TRANS is twisted away from the C(6)-eclipsed position by 20·2°. The observed conformation, therefore, deviates by about 20° from the 'generally preferred' conformation of carboxylic acids (Leiserowitz & Schmidt, 1965; Dunitz & Strickler, 1968; Leiserowitz, 1976) and 140° from the proposed conformation for an equatorial carboxyl group (Sicher, Tichý & Sipos, 1966*a*, *b*; van Bekkum, Verkade & Wepster, 1966; van Bekkum, 1970).

Fig. 2* summarizes the C_β–C_α–C=O torsion angles in substituted cyclohexanecarboxylic acids and in some related compounds retrieved from the Cambridge Structural Data Base (CSDB: Allen *et al.*, 1979). Structures, in which mutual interaction between the carboxyl group and a C_β substituent (*e.g.* a second carboxyl group) might influence the τ value, are included in Fig. 2 unless the authors explicitly stated this interaction to be present.

The structures used in Fig. 2(*a*) and (*b*), including several bearing a substituent on C_β, show that there is no difference between the preferred rotational position of an axial and an equatorial carboxyl group: both prefer the synperiplanar C_β–C_α–C=O arrangement ($\tau = 0 \pm 30°$). The outliers in Fig. 2(*b*) originate from an equatorial carboxyl group in all-*cis*-1,2,3,4,5,6-cyclohexanehexacarboxylic acid (τ = 36·6°) and from a bowsprit carboxylic group in bicyclo[3.3.1]nonane-3α-monocarboxylic acid (τ = −49·0°). Fig. 2 (*c*) and (*d*) illustrate that, when the H atom on C_α is replaced by a methyl group, or when C_α is a bridgehead atom of fused saturated six-membered rings, that synperiplanar C_β–C_α–C=O arrangement seems to be preferred in which C_α–C_β is a ring bond or the common bond of the fused rings, respectively. The only exception is 3-oxo-*cis*-bicyclo[4.4.0]decane-1-carboxylic acid where C=O is synperiplanar with the C_α–C_β bond not common to both rings. The outlier in Fig. 2(*c*) is from the axial

* See deposition footnote. Figs. 2(*a*) and 2(*b*) include data with *R* factors <0·08; data in Figs. 2(*c*) and 2(*d*) have *R* < 0·10, except for AXOLAC [Fig. 2(*d*)], which has *R* = 0·12.

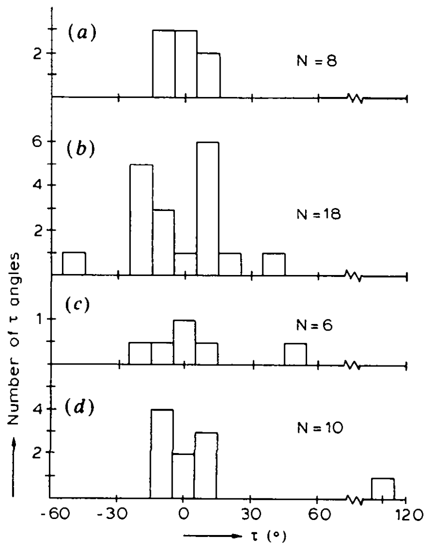


Fig. 2. C_β–C_α–C=O torsion angles (τ) in (substituted) cyclohexanecarboxylic acids and some related compounds with (*a*) axial COOH and H on C_α, (*b*) equatorial COOH and H on C_α, (*c*) ax./eq. COOH and CH_3 on C_α, (*d*) ax./eq. COOH and C_α is a bridgehead atom in fused six-ring systems. τ is defined with respect to a ring C_β atom and is restricted to $-60° \le \tau \le 120°$; τ is given a minus sign when, in a Newman projection along the C_α–C(OOH) bond, the carbonyl O atom projects 'within' the $C_\beta C_\alpha C_\beta$ angle; τ = 0°: perfect eclipsing of C=O with C_α–C_β.

Table 2. *Molecular geometry*

Averaged e.s.d.'s are 0·002 Å for bond lengths, 0·1° for bond angles and somewhat larger for torsion angles. All C–H bond distances are equal to 1·00 Å within 2σ [σ(C–H) = 0·02 Å]; maximum e.s.d. for angles involving H atoms is 2°; σ(O–H) = 0·02 Å.

Bond distances (Å)

C(1)–C(2)	1·533	C(7)–C(8)	1·533
C(2)–C(3)	1·527	C(7)–C(9)	1·536
C(3)–C(4)	1·535	C(7)–C(10)	1·530
C(4)–C(5)	1·532	C(1)–C(11)	1·504
C(5)–C(6)	1·529	C(11)–O(1)	1·321
C(6)–C(1)	1·526	C(11)–O(2)	1·218
C(4)–C(7)	1·554	O(1)–H(O1)	0·82

Bond angles (°)

C(2)–C(1)–C(6)	109·7	C(4)–C(7)–C(8)	112·6
C(2)–C(1)–C(11)	110·3	C(4)–C(7)–C(9)	109·6
C(6)–C(1)–C(11)	112·5	C(4)–C(7)–C(10)	110.1
C(1)–C(2)–C(3)	110·7	C(8)–C(7)–C(9)	108·8
C(2)–C(3)–C(4)	112·8	C(8)–C(7)–C(10)	108·2
C(3)–C(4)–C(5)	109·4	C(9)–C(7)–C(10)	107·4
C(3)–C(4)–C(7)	113·3	C(1)–C(11)–O(1)	112·6
C(5)–C(4)–C(7)	113·2	C(1)–C(11)–O(2)	124·3
C(4)–C(5)–C(6)	113·2	O(1)–C(11)–O(2)	123·1
C(5)–C(6)–C(1)	110·1		

Selected torsion angles (°)

Along C(11)–C(1)		Endocyclic torsions	
O(2)–C(11)–C(1)–C(6)	20·2	C(6)–C(1)–C(2)–C(3)	58·1
O(2)–C(11)–C(1)–C(2)	−102·7	C(1)–C(2)–C(3)–C(4)	−56·2
O(2)–C(11)–C(1)–H(11)	143	C(2)–C(3)–C(4)–C(5)	52·7
O(1)–C(11)–C(1)–C(2)	75·7	C(3)–C(4)–C(5)–C(6)	−53·3
O(1)–C(11)–C(1)–H(11)	−39	C(4)–C(5)–C(6)–C(1)	57·2
		C(5)–C(6)–C(1)–C(2)	−58·1
Along C(7)–C(4)			
C(8)–C(7)–C(4)–H(41)	175		
C(9)–C(7)–C(4)–C(3)	172·8		
C(10)–C(7)–C(4)–C(5)	−179·7		

Hydrogen-bond geometry (A and deg)

O(1)···O(2')	2·633	O(1)–H(O1)···O(2')	171
H(O1)···O(2')	1·82	Atom (i) at −x, −y + 1, −z + 1	

carboxyl group in *ent*-9,15α-dihydroxyatis-16-en-19-oic acid ($\tau = 47{\cdot}1°$).

Some 40 cyclic carboxylic acids are not included in Fig. 2. In these structures, of which the majority contain four-membered, five-membered, and/or six-membered boat rings* one can challenge the use of 'axial' and 'equatorial' in defining the position of the ring substituents. The C_β–C_α–C=O torsion angles in these compounds are summarized in the histogram in Fig. 3.† The figure again shows (whether the substituent on C_α is H or C) the synperiplanar C_β–C_α–C=O arrangement to be a general feature, as in a whole series of straight-chain carboxylic acids (Kanters, Kroon, Peerdeman & Schoone, 1967).

The tert-butyl group

The angle ω, defined in Fig. 4, measures the deviation of the *tert*-butyl group from the perfectly staggered position. In TRANS $\omega = 3{\cdot}9°$. The data on (substituted) ring systems with an equatorial *tert*-butyl group, retrieved from the CSDB, were subdivided into two groups depending upon the fact whether *in principle* the molecules could possess *m* symmetry or not. To avoid structure-hits in which the orientation of the *tert*-butyl group might be influenced by steric factors, the C_α and C_β ring atoms bear, besides the *tert*-butyl on C_α, only H atoms. In two structures, where H atoms were not located, ω was calculated using the formula $|\omega| = |(1+5)-(4+6)|/4$.

Fig. 5(*a*) and (*b*)* give the distribution of ω in asymmetrically and symmetrically substituted molecules, respectively. The Gaussian distributions are not essentially different: σ is about 5° in both cases. This is not surprising when the actual symmetry is taken into account. In the crystal, twisting of the ring system and different rotational positions of the substituents are observed. There are only two symmetrically substituted structures where the symmetry of the space group demands $\omega = 0°$. The distribution does not show a maximum for $8{\cdot}4° < |\omega| < 17°$ as might be expected from force-field calculations. A very broad distribution for $|\omega| < 15°$ is observed instead. Neither a relation between ω and the angle between the two β,γ bonds (measuring the ring twist) nor one between ω and the average of the torsion angles around the α,β bonds (measuring the local ring puckering/flattening) could be established for the structures studied. Therefore the actual value of ω seems to be determined by the packing of the molecules. The broadening of the distribution must follow from a negligible barrier to rotation of the *tert*-butyl group within the region $|\omega| < 15°$. Or, in other words, the potential-energy well must have a 'flat' minimum. This is in agreement with the negligibly small – compared to the zero-point energy – calculated steric-energy difference of only $0{\cdot}05\,\mathrm{kJ\,mol^{-1}}$ between the conformations of equatorial *tert*-butylcyclohexane with $\omega = 0°$ and $\omega = 8{\cdot}4°$, respectively (Baas, van de Graaf, van Veen &

* Three-membered rings are omitted because of overcrowding; conjugation between C=O and ring orbitals in cyclopropanecarboxylic acids leads to the 'bisecting' conformation as the preferred arrangement (Allen, 1980).

† See deposition footnote; 35 entries have $R < 0{\cdot}10$ and 4 (EXBACX, HKGIBB, IONDEC and NPHPTA) have $0{\cdot}12 < R < 0{\cdot}16$.

* See deposition footnote. All structures have an R factor $< 0{\cdot}10$, except MEBNON, which has $R = 0{\cdot}12$. The deposited material lists $\omega(1), \ldots, \omega(6)$ separately. No significant changes in the ω distribution occur when the definition of ω is changed to $|\omega| = |(1+5)-(4+6)|/4$.

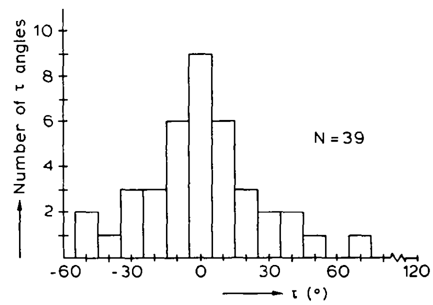
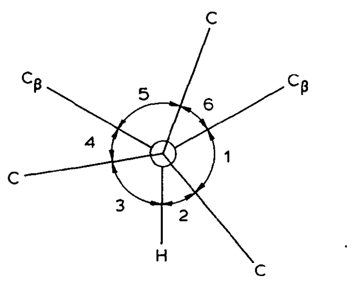


Fig. 3. Histogram of τ in various cyclic carboxylic acids. (For definition of τ: see caption to Fig. 2.)



$$|\omega| = \frac{|\Sigma(1+3+5) - \Sigma(2+4+6)|}{6}$$

Fig. 4. Newman projection along C(t-Bu)–C_α; definition of ω.

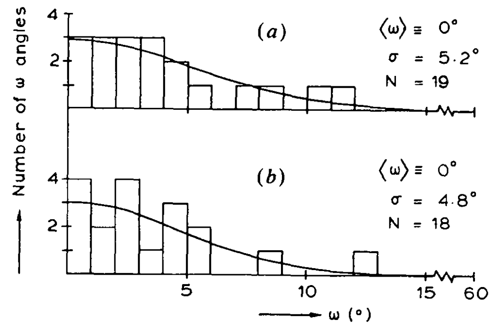


Fig. 5. Distribution of ω in (*a*) asymmetrically and (*b*) symmetrically substituted saturated ring systems with an equatorial *tert*-butyl group.

Wepster, 1980). A more recent MM2 force field found the symmetrical geometry ($\omega = 0°$) to be the more stable one (Burkert & Allinger, 1982), and it would appear that the twisted *tert*-butyl group is an artefact of the earlier force fields.

Packing

The packing of TRANS in the crystal is illustrated in Fig. 6. Two carboxyl groups form the well-known eight-membered ring around a centre of symmetry. The geometry of the hydrogen-bonding scheme is added in Table 2.

The authors are indebted to Professors B. M. Wepster and H. van Bekkum, Dr J. M. A. Baas and Dr A. J. van den Berg for their critical reading and discussion of the manuscript.

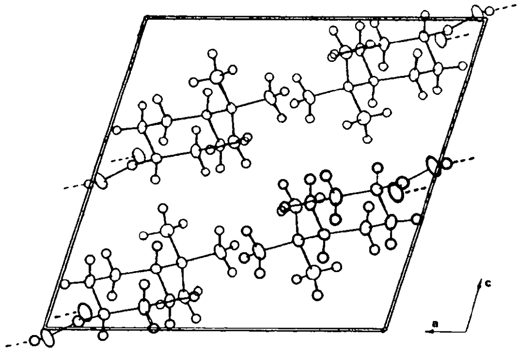


Fig. 6. Drawing of the unit-cell contents viewed down **b**. Hydrogen bonds are indicated by broken lines.

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Nucleic Acid Binding Drugs. X.* A Theoretical Study of Proflavine Intercalation into RNA and DNA Fragments: Comparison with Crystallographic Results

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Abstract

The minimum-energy structure for the interactions of the intercalation drug proflavine with the dinucleoside phosphates cytidylyl-3′,5′-guanosine and deoxycytidylyl-3′,5′-deoxyguanosine have been found by means of a combination of computer graphics and empirical energy calculations. The minimum-energy positions for the drug, given the crystallographically observed nucleotide backbone conformations as starting points, are very close to the positions in the crystal structures of the complexes, with the intercalated proflavine molecule inserted from the major-groove direction in each case. Alternative orientations for the drug were found to be much less stable. NMR studies in solution [Patel (1979). *Biopolymers*, **16**,

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