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Rotational Conformation of the Phenyl Moiety in Geminally Substituted Phenylcyclohexanes with Equatorial Phenyl

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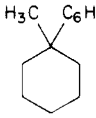
The conformations of *t*-3,4-dimethyl-*r*-4-phenylcyclohexanone (**2**), *r*-1-phenyl-1-methyl-*c*-2-(*p*-nitrobenzoxy)cyclohexane (**3**), and *c*-4-methyl-1-phenylcyclohexan-*r*-1-ol (**8**) in the solid state have been determined by X-ray crystallography and compared to those of the promedols (**4, 5**) and prodine salts (**6, 7**). Crystals of **2** are monoclinic, space group $P2_1/c$, with four molecules in a cell of dimensions a = 14.810 (4) Å, b = 6.316 (4) Å, c = 13.187 (5) Å, β = 110.17 (3)°. The structure was refined to a final value of the weighted R factor of 0.035 based on 1399 intensities. Crystals of **3** are also monoclinic, space group $P2_1/a$, with four molecules in a cell of dimensions a = 14.950 (4) Å, b = 7.457 (4) Å, c = 16.759 (3) Å, β = 111.51 (2)°; the structure was refined to a weighted R factor of 0.057 using 1264 independent intensities. Crystals of **8** are triclinic, $P\bar{1}$, with four molecules in a cell of dimensions a = 11.069 (4) Å, b = 11.142 (3) Å, c = 9.630 (4) Å, α = 107.57 (3)°, β = 97.66 (3)°, γ = 86.59 (2)°. The final weighted R factor is 0.064 on 1672 intensities. In **2** the phenyl group is within 3.4° of the bisector plane of the cyclohexane ring, in **3** it is at 47° to the plane, and in **8** there are two independent molecules in the unit cell with values of 15.5° and 25.3° for the torsion angle in question. Force-field calculations show that in 1-phenyl-1-methylcyclohexane (**1**) (equatorial phenyl conformer) the optimal torsional angle is 68° rather than 90° but that the phenyl ring is likely to librate about the perpendicular (90°) conformation, since the energy barrier at 90° is very low. This finding may explain the discrepancy between the previously calculated and experimental free energy diference between the Ph-equatorial and Ph-axial conformers of **1**. Calculations for **2**, the formate analogue of **3**, and **8** show that the energy well in **2** is relatively steep, that in **3** it is somewhat shallow, and that in **8** it is extremely shallow. When the energy minimum is shallow, conformation in solution will be variable and may or may not correspond to that in the crystal.

In 1971 Allinger and Tribble[1] carried out force-field calculations (MM1 force field) on phenylcyclohexane and 1-methyl-1-phenylcyclohexane (**1**). The results of these calculations plus some later revisions based on the MM2 force field[2a] are summarized in Chart I. Phenylcyclohexane, as expected, is most stable in the conformation with equatorial phenyl. In this conformation, in turn, the most stable rotational arrangement is that in which the plane of the phenyl ring is in the symmetry plane of the cyclohexane chair ("bisecting" or "parallel" conformation). In the less stable axial conformer, on the other hand, the optimal rotational conformation is that with the phenyl ring at right angles to the bisector plane of the chair ("perpendicular" conformation). The reason for this is that in the bisecting conformation, one of the ortho hydrogens of the phenyl would clash with two of the axial hydrogen atoms of the cyclohexane ring. An interesting consequence is that the major source of the conformational energy (i.e., excess energy of axial over equatorial conformation) of the phenyl substituent is the van der Waals interaction of the two ortho hydrogens of the phenyl ring and the two equatorial hydrogens of the cyclohexane chair in positions 2 and 6. The calculated difference in energy between axial and equatorial phenyl (3.45 kcal/mol by MM2[2b]) is somewhat larger than the experimental value[3] of 2.87 kcal/mol.



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When a geminal methyl substituent is introduced in phenylcyclohexane, the situation changes substantially. The difference between equatorial and axial methyl is 1.74 kcal/mol[4] and so, on the basis of additivity, one might have expected equatorial phenyl to be preferred over axial in **1** by 2.87–1.74 or 1.13 kcal/mol. Instead, one observed an *axial* preference for phenyl of 0.32[3] to 0.34[5] kcal/mol.

This discrepancy is anticipated by the molecular mechanics calculations[1] in the following way. When the phenyl is axial and perpendicular, introduction of an equatorial geminal methyl group introduces no unfavorable mutual interactions. But when the phenyl is equatorial and bisecting, introduction of the axial geminal methyl substituent introduces not only the normal axial interaction of methyl but also a mutual interaction between the methyl substituent and one of the ortho hydrogen atoms of the phenyl group. The molecule either must sustain this extra interaction or the phenyl group must rotate into the perpendicular orientation (chart I). In the latter case, it will encounter the same unfavorable ortho-H/eq-H interactions which occur in the perpendicular conformation of axial phenyl. The result is a substantial destabilization, in **1**, of the equatorial phenyl/axial methyl conformer, to the point where it is less stable than the axial phenyl/equatorial methyl one. The original calculations (MM1) suggested that, for equatorial phenyl, axial methyl, the phenyl-perpendicular conformer was more stable than the bisecting one by 1.16 kcal/mol, but in the MM2 calculation, this difference was reduced to 0.36 kcal/mol. The latter value is small enough to raise questions as to the actual situation, especially in the solid state where packing forces might affect the energy of various conformers by a few tenths of a kcal/mol.

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(1) Allinger, N. L.; Tribble, M. T. *Tetrahedron Lett.* **1971**, 3259.

(2) (a) Allinger, N. L., personal communication, 1981, (b) Present work: the optimum conformation for "perpendicular" axial phenyl is actually not at a 90° torsional angle but at a 65.5° one (see Scheme I); the entropy of mixing between this conformation and the bisecting one contributes 0.04 kcal/mol (at −100 °C) to the axial conformer. An additional entropy contribution no doubt comes from extensive libration of the axial phenyl across the shallow (0.23 kcal/mol) energy barrier at 90°.

(3) Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959.

(4) Booth, H.; Everett, J. R. *J. Chem. Soc., Chem. Commun.* **1976**, 278.

(5) DeBeule, H.; Tavernier, D.; Anteunis, M. *Tetrahedron* **1974**, *30*, 3573.

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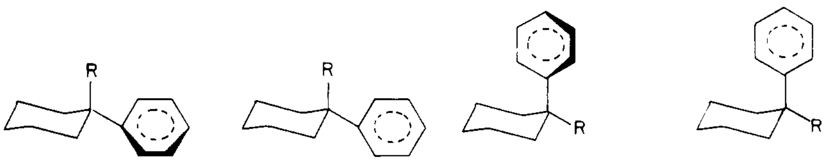
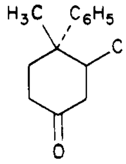
Chart I. Phenyl Group Orientations and the Calculated Energy Values (kcal/mol)



R		equatorial perpendicular	equatorial parallel (bisectional)	axial perpendicular	axial parallel (bisectional)
H	MM1[a]	3.92	0.00	3.66	5.22
H	MM2[b]	2.99	0.00	3.72 (3.49[c,d])	4.80
Me	MM1[a]	0.90	2.06	0.00	6.43
Me	MM2[b]	0.96	1.32	0.00	5.27
Me	MM2[c]	0.95 (0.61[e])	1.31	0.00	5.22

[a] Reference 1. [b] Reference 2. [c] Present work. [d] At 65.5° torsion angle (rather than 90°). [e] At 68.1° torsion angle (rather than 90°).

For the present crystallographic study it was necessary to have available compounds which would crystallize in the equatorial-phenyl conformation (i.e., the one which is less stable in 1) and which would form satisfactory crystals. This requirement led to the study of two compounds with equatorial and axial substituents, respectively, in the adjacent 2-position: *r*-4-phenyl-*t*-3,4-dimethylcyclohexanone (**2**) and *r*-1-phenyl-1-methyl-*c*-2-(*p*-nitrobenzoxy)cyclohexane (**3**). While the presence of a substituent in the position adjacent to the geminal one might be considered a disadvantage, it is, on the other hand, of interest in its own right, since a number of substituted six-membered rings (mostly piperidines) of pharmacological interest have this kind of substitution pattern. In fact the α- (**4**[6]) and γ-promedols (**5**[7]) and two of the isomeric prodine salts (**6**[8], **7**[9]) have been studied crystallographically before. These compounds have geminal hydroxy or propionoxy groups in lieu of methyl; in the present investigation, we studied the related 1-phenyl-*c*-4-methylcyclohexan-*r*-1-ol (**8**) which is devoid of vicinal substituents. (In 1-phenylcyclohexanol the conformer with equatorial phenyl is preferred because the energy advantage of equatorial over axial OH is much less than that for methyl and also because the bisecting phenyl/geminal OH interaction is less than the corresponding Ph/Me interaction.[10])



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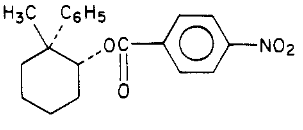

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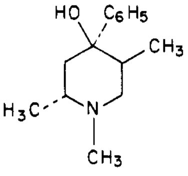

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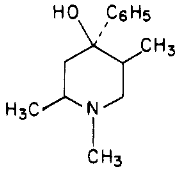

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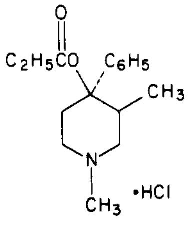

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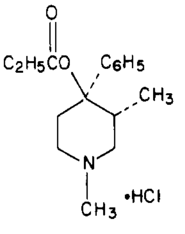

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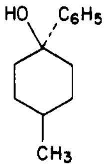
In addition to the crystallography, we also carried out MM2 calculations[11] on **2**, an analogue of **3**, viz., the formate of *t*-2-methyl-*c*-2-phenyl-*r*-1-cyclohexanol (**9**, formate instead of *p*-nitrobenzoate **3**) and **8**.



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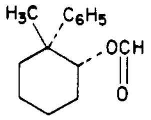

9

Experimental Section

1-Phenyl-*c*-4-methylcyclohexan-*r*-1-ol (8). Alcohol **8** was prepared as described,[12] mp 62–64 °C (lit.[12] mp 63.5 °C; the nomenclature[12] is opposite to that used here): ^{1}H NMR δ ($CDCl_3$) 0.97–0.99 (d, J = 5.6 Hz, 3 H), 1.58 (br s, OH), 1.43–1.49, 1.54–1.59, 1.62–1.66, 1.77–1.85 (m, 9 H), 7.21–7.26 (tt, $J_{1,2}$ = 7.3 Hz, $J_{1,3}$ = 1.3 Hz, 1 H), 7.32–7.37 (dd, J = 7.8 Hz, 7.2 Hz, 2 H), 7.49–7.52 (m, 2 H); ^{13}C NMR δ ($CDCl_3$) 22.4_9 (Me), 30.7_1 (C-3), 32.0_5 (C-4), 38.9_1 (C-2), 72.7_4 (C-1), 124.5_6 (C-*o*), 126.6_7 (C-*p*), 128.2_1 (C-*m*), 149.6_7 (C-*i*).

***t*-3,4-Dimethyl-*r*-4-phenylcyclohexanone (2) and Its Cis Isomer.** Methylmagnesium iodide was prepared in ether (200 mL) from 37 g (0.24 mol) of iodomethane and 4.8 g (0.2 mol) of magnesium turnings under nitrogen. The resulting grey solution was cooled to −5 °C with an ice–salt bath and dry copper(I) iodide (2 g; ca. 0.01 mol) was added with stirring. To the resulting suspension was added 4-methyl-4-phenylcyclohexenone[13] (18.6 g, 0.1 mol) in anhydrous ether (50 mL) dropwise over a period of 1 h with stirring at −5 °C. When the addition was complete, the cooling bath was removed, and stirring was continued overnight. Saturated ammonium chloride solution (50 mL) was then added carefully with external cooling, and the ether layer was separated. The aqueous layer was washed (4 × 50 mL) with ether

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and then with saturated sodium thiosulfate solution and dried ($MgSO_4$). After concentration, the resulting yellow oil (54%) (a 3:1:1 mixture of **2**, the cis isomer, and the 1,2-addition product) was separated by HPLC (10% ethyl acetate + hexane). Compound **2** was crystallized from pentane (mp 67 °C), whereas the cis isomer remained as an oil.

Trans isomer 2: ^1H NMR δ (100 MHz, $CDCl_3$) 0.7–0.76 (d, J = 6.2 Hz, 3 H, 2-CH_3), 1.4 (s, 3 H, 1-CH_3), 1.64–2.6 (m, 7 H), 7.2–7.48 (m, 5 H, Ph); IR 1717 cm^{-1} (CCl_4); ^{13}C NMR δ ($CDCl_3$) 16.6$_4$ and 18.1$_4$ (Me-1 and Me-2 or vice versa), 38.5$_1$ (C-6), 39.0$_5$ (C-5), 40.3$_9$ (C-3), 40.4$_9$ (C-4), 46.1$_4$ (C-2), 125.6$_9$ (C-*o*), 126.1$_4$ (C-*p*), 128.4$_8$ (C-*m*), 147.6$_7$ (C-*i*), 210.5$_1$ (C-1); MS, *m/e* 202 (M^+), 131, 118 (100%), 117, and 91. Anal. Calcd for $C_{14}H_{18}O$: C, 83.15; H, 8.98; Found: C, 83.03; H, 9.13.

Cis isomer 2: ^1H NMR δ ($CDCl_3$, 250 MHz) 0.54–0.58 (d, J = 7 Hz, 3 H, 2-CH_3), 1.52 (s, 3 H, 1-CH_3), a series of multiplets 1.96–2.06 (1 H), 2.1–2.2 (1 H), 2.2–2.5 (3 H), 2.5–2.6 (m, 1 H), 2.8–2.9 (dd, J = 12 Hz and J = 4 Hz, 3 H), 7.2–7.45 (m, 5 H); ^{13}C NMR δ ($CDCl_3$) 16.8$_9$ (Me-2), 27.3$_6$ (Me-1), 30.8$_4$ (C-5), 37.8$_8$ (C-6), 39.5$_8$ (C-4), 41.2$_5$ (C-3), 45.0$_1$ (C-2), 125.6$_2$ (C-*o*), 125.9$_5$ (C-*p*), 128.4$_4$ (C-*m*), 148.3$_4$ (C-*i*), 211.5$_7$ (C-1).

***t*-2-Methyl-*c*-2-phenylcyclohexan-1-*r*-ol. Epoxidation of 4-Methyl-4-phenyl-2-cyclohexenone.** This reaction was carried out by using the procedure of Hoehn.[14] To a solution of the enone[13] (4 g) in methanol (400 mL) cooled in ice water (5 °C) was added 2 M NaOH (16 mL), followed immediately by 30% H_2O_2 (16 mL). This mixture was left in the refrigerator for 48 h and then added to 200 mL of water, and the product was extracted with ether (4 × 50 mL). The ether solution was washed with saturated NaCl solution and dried over $MgSO_4$. Distillation of the ether left the α-epoxy ketone as a yellow oil.

***c*- and *t*-6-Methyl-6-phenyl-2-cyclohexen-1-*r*-ol.** To the above α-epoxy ketone in 100 mL of methanol was added, at room temperature in an atmosphere of nitrogen with stirring, 3 g of 98% hydrazine in 10 mL of methanol followed by 1 mL of acetic acid in 10 mL of methanol. The pale yellow solution turned immediately deep yellow, and gas evolution commenced which persisted for about 20 min. The mixture was stirred overnight. Dilution with water (200 mL), extraction with ether (4 × 50 mL), washing the ether solution successively with 2 M HCl (10 mL), saturated sodium bicarbonate (20 mL), and finally with saturated sodium chloride solution, drying over anhydrous sodium sulfate, and concentration yielded a mixture of the allylic alcohols (2:1 ratio). Distillation in a Kugelrohr apparatus gave a low-melting, waxy solid: ^1H NMR of mixture δ ($CDCl_3$, 250 MHz), 1.04 (s, CH_3 of *t*), 1.24 (s, CH_3 of *c*), 1.4–2.2 (m, 2 × 4 H), 2.22 (br s 2 × OH), 4.10–4.14 (br t C*H*OH-*t*), 4.48–4.52 (br, C*H*OH in *c*), 5.74–5.78 (m, olefinic in *c*), 5.90–5.94 (m, olefinic in *t*), 7.20–7.45 (m, 2 × 5 H, Ph); ^{13}C δ ($CDCl_3$), *c*-6-Me 18.63$_2$ (Me), 23.3$_8$ (C-4), 33.4$_5$ (C-5), 41.4$_5$ (C-6), 72.7$_8$ (C-1), 125.9$_3$ (C-*p*), 126.0$_3$ (C-*o*), 128.1$_3$ (C-*m*), 128.4$_1$ (C-3), 129.9$_1$ (C-2), 147.7$_8$ (C-*i*); *t*-6-Me 23.2$_6$ (C-4), 23.9$_2$ (Me), 26.2$_0$ (C-5), 41.1$_5$ (C-6), 71.4$_8$ (C-1), 125.9$_3$ (C-*p*), 126.2$_2$ (C-*o*), 126.9$_3$ (C-3), 128.3$_1$ (C-*m*), 130.1$_2$ (C-2), 146.8$_1$ (C-*i*).

***c*-2- and *t*-2-Methyl-2-phenylcyclohexan-*r*-1-ols.** This mixture was obtained by the catalytic reduction of 500 mg of the above allylic alcohol mixture in 10 mL methanol over 100 mg of 5% rhodium on alumina at room temperature and atmospheric pressure (3 h). The products were separated by using HPLC with EtOAC:hexane (1:9) eluent. **cis**: mp 34–36 °C; ^1H NMR δ ($CDCl_3$, 250 MHz), 1.35 (s, 3 H, CH_3), 1.50 (br s OH), 1.50–1.89 (m, 8 H), 3.89–3.95 (dd, J = 12 Hz and J = 4 Hz, 1 H, C*H*OH), 7.18–7.28 (br t, 1 H), 7.30–7.50 (m, 4 H); ^{13}C δ ($CDCl_3$) 16.7$_5$ (Me), 21.6$_5$ (C-4), 24.5$_4$ (C-5), 29.6$_3$ (C-6), 38.2$_9$ (C-3), 43.4$_3$ (C-2), 75.6$_4$ (C-1), 126.0$_8$ (C-*p*), 126.2$_2$ (C-*o*), 128.4$_1$ (C-*m*), 148.2$_8$ (C-*i*). **trans**: mp 49–50 °C; ^1H NMR δ ($CDCl_3$, 250 MHz) 1.28 (s, 3 H, CH_3), 1.34–1.74 (m, 7 H), 1.80–1.86 (m, 1 H, probably OH), 2.12–2.26 (m, 1 H), 4.00–4.04 (unresolved t, 1 H, C*H*OH), 7.20–7.28 (br t, 1 H), 7.30–7.50 (m, 4 H); ^{13}C NMR δ ($CDCl_3$) 19.9 (C-5), 21.6$_2$ (C-4), 25.5$_7$ (C-Me), 28.2$_7$ (C-6), 30.1$_1$ (C-3), 42.0$_6$ (C-2), 74.2$_6$ (C-1), 126.1$_9$ (C-*o*, C-*p*), 128.6$_5$ (C-*m*), 148.1$_0$ (C-*i*). The *p*-nitrobenzoate[15] (**3**) melted at 112–113 °C. The compounds were analyzed as acetates. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: cis isomer C, 77.89; H, 8.76; trans isomer C, 77.94; H, 8.89.

Table I. Atomic Positional Parameters for 2

atom	*x*	*y*	*z*	*B*(A^2)
O	−0.55974 (7)	0.2104 (2)	0.3899 (1)	
C1	−0.4753 (1)	0.1762 (3)	0.4097 (1)	
C2	−0.3991 (1)	0.2689 (3)	0.5059 (1)	
C3	−0.3122 (1)	0.3554 (2)	0.4811 (1)	
C4	−0.2704 (1)	0.1915 (3)	0.4213 (1)	
C5	−0.3525 (1)	0.1211 (3)	0.3187 (1)	
C6	−0.4403 (1)	0.0330 (3)	0.3401 (1)	
C7	−0.2388 (1)	0.4422 (3)	0.5840 (1)	
C8	−0.2314 (1)	−0.0006 (3)	0.4936 (1)	
CP1	−0.1926 (1)	0.2973 (3)	0.3864 (1)	
CP2	−0.1007 (1)	0.2179 (3)	0.4133 (1)	
CP3	−0.0316 (1)	0.3160 (4)	0.3817 (1)	
CP4	−0.0513 (1)	0.4986 (3)	0.3237 (1)	
CP5	−0.1417 (1)	0.5808 (3)	0.2955 (1)	
CP6	−0.2117 (1)	0.4812 (3)	0.3255 (1)	
H2A	−0.3772 (9)	0.148 (2)	0.5627 (10)	5.5 (4)
H2B	−0.4257 (9)	0.389 (2)	0.5387 (10)	5.0 (4)
H3	−0.3349 (7)	0.478 (2)	0.4318 (9)	2.9 (3)
H5A	−0.3283 (8)	0.009 (2)	0.2816 (10)	4.1 (3)
H5B	−0.3715 (8)	0.250 (2)	0.2725 (10)	4.2 (3)
H6A	−0.4215 (9)	−0.106 (3)	0.3781 (11)	6.3 (4)
H6B	−0.4946 (9)	0.005 (2)	0.2748 (11)	6.1 (4)
H7A	−0.1816 (9)	0.504 (2)	0.5737 (10)	5.1 (4)
H7B	−0.2658 (9)	0.561 (3)	0.6135 (10)	5.6 (4)
H7C	−0.2164 (10)	0.326 (3)	0.6389 (12)	7.4 (5)
H8A	−0.2078 (9)	−0.106 (2)	0.4544 (10)	5.4 (4)
H8B	−0.1700 (10)	0.036 (2)	0.5592 (11)	6.7 (4)
H8C	−0.2822 (9)	−0.070 (3)	0.5172 (11)	6.1 (4)
H2P	−0.0833 (9)	0.087 (3)	0.4543 (11)	5.5 (4)
H3P	0.0300 (11)	0.254 (3)	0.4006 (13)	7.2 (5)
H4P	−0.0012 (9)	0.573 (3)	0.3052 (10)	6.1 (4)
H5P	−0.1595 (9)	0.706 (2)	0.2582 (10)	5.3 (4)
H6P	−0.2744 (8)	0.541 (2)	0.3047 (9)	3.5 (3)

Crystallography. A colorless crystal of *t*-3,4-dimethyl-*r*-4-phenylcyclohexan-1-one (**2**) was found to be monoclinic, space group $P2_1/c$, a = 14.810 (4) Å, b = 6.316 (4) Å, c = 13.187 (5) Å, β = 110.17 (3)°, volume = 1158 (2) A^3, Z = 4, D_{calcd} = 1.160, D_{obsd} = 1.15 (2) g cm^{-3} (flotation in aqueous potassium iodide). A colorless crystal of 4-*c*-methyl-1-phenylcyclohexan-*r*-1-ol (**8**) was triclinic, space group $P\bar{1}$, a = 11.069 (4) Å, b = 11.142 (3) Å, c = 9.630 (4) Å, α = 107.57 (3), β = 97.66 (3), γ = 86.59 (2)°, volume = 1122 (1) $Å^3$, Z = 4 (2 independent molecules), D_{calcd} = 1.30, D_{obsd} = 1.29 (2) g cm^{-3}. A colorless crystal of *t*-1-methyl-*c*-1-phenyl-*r*-2-[(*p*-nitrobenzoyl)oxy]cyclohexane (**3**) was monoclinic, space group $P2_1/a$, a = 14.950 (4) Å, b = 7.457 (4) Å, c = 16.759 (3) Å, β = 111.41 (2)°, volume = 1739 (2) $Å^3$, Z = 4, D_{calcd} = 1.30, D_{obsd} = 1.32 (2) g cm^{-3}. All data collected on Enraf-Nonius CAD-4/SDP diffractometer using Mo Kα radiation and a graphite monochromator. Absorption corrections were not applied.

All structures were solved by direct methods using MULTAN.[16] In the structure of **2**, all 18 hydrogen atoms were clearly located in a difference Fourier map phased by the carbon and oxygen atoms, and in the final refinement all hydrogen atoms were refined isotropically. In **8** and **3**, however, for which the crystals were of much poorer quality, hydrogen atoms were placed in calculated positions and not refined; the hydrogen atom associated with the hydroxy group could not be located in either of the two crystallographically independent molecules of **8** and were not included in the refinement. A correction for secondary extinction was included in **2**, the value of the extinction coefficient being 1.14 (6) × 10^{-6}. The atomic positional parameters of **2**, **3**, and **8**, derived from the final least-squares refinements are listed in Tables I, II, and III, respectively.

Calculations. The molecular mechanics calculations were performed by the MM2 force field[11] explicitly taking into account lone pairs. In each case, after the energy minimum and corresponding geometry were found, the phenyl group was rotated by "dihedral driving" to find additional minima. In the case of **9**,

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(14) Hoehn, W. H. *J. Org. Chem.* **1958**, *23*, 929.

(15) Shriner, R. K.; Fuson, R. C.; Curtin, D. Y. "The Systematic Identification of Organic Compounds", 5th Ed.; John Wiley & Sons: New York, 1964; p 246, proc.(a).

(16) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A: Cryst. Phys., Diffr., Theor. Gen. Crystallogr.* **1971**, *A27*, 368.

Table II. Atomic Positional Parameters for 3

atom	x	y	z
O1	0.4629 (2)	0.1339 (4)	0.7615 (2)
O2	0.6044 (2)	0.0560 (5)	0.8597 (2)
O3	0.4412 (2)	0.4156 (6)	1.1623 (2)
O4	0.2991 (2)	0.4079 (7)	1.0712 (2)
N	0.3843 (3)	0.3830 (7)	1.0915 (2)
C1	0.3883 (3)	0.0034 (7)	0.6229 (3)
C2	0.4887 (3)	0.0463 (7)	0.6957 (2)
C3	0.5476 (3)	0.1771 (7)	0.6646 (3)
C4	0.4956 (3)	0.3419 (7)	0.6214 (3)
C5	0.4003 (3)	0.2999 (8)	0.5511 (3)
C6	0.3388 (3)	0.1767 (7)	0.5829 (3)
C7	0.4089 (3)	−0.1114 (8)	0.5539 (3)
C8	0.3303 (3)	−0.1082 (7)	0.6627 (2)
C9	0.2515 (3)	−0.0432 (8)	0.6776 (3)
C10	0.2044 (3)	−0.1450 (9)	0.7180 (3)
C11	0.2334 (3)	−0.3140 (9)	0.7442 (3)
C12	0.3106 (4)	−0.3853 (8)	0.7295 (3)
C13	0.3577 (3)	−0.2804 (8)	0.6887 (3)
C14	0.5257 (3)	0.1194 (7)	0.8416 (3)
C15	0.4869 (3)	0.1860 (7)	0.9050 (3)
C16	0.3895 (3)	0.2177 (7)	0.8843 (3)
C17	0.3547 (3)	0.2776 (8)	0.9451 (3)
C18	0.4193 (3)	0.3089 (7)	1.0261 (3)
C19	0.5153 (3)	0.2784 (7)	1.0497 (3)
C20	0.5489 (3)	0.2169 (7)	0.9880 (3)

Table III. Atomic Positional Parameters for 8

atom	x	y	z
O	−0.4736 (3)	0.0881 (3)	0.4267 (3)
O′	0.3981 (3)	−0.0209 (3)	0.8809 (3)
C1	−0.4372 (4)	0.2124 (4)	0.5201 (5)
C2	−0.5069 (4)	0.2448 (4)	0.6536 (5)
C3	−0.6443 (4)	0.2572 (4)	0.6193 (5)
C4	−0.6785 (4)	0.3508 (4)	0.5313 (5)
C5	−0.6140 (4)	0.3144 (4)	0.3961 (5)
C6	−0.4763 (4)	0.3050 (4)	0.4305 (5)
C7	−0.3020 (4)	0.2124 (4)	0.5688 (5)
C8	−0.2401 (4)	0.1035 (4)	0.5756 (5)
C9	−0.1182 (5)	0.1000 (4)	0.6209 (5)
C10	−0.0517 (4)	0.2085 (5)	0.6618 (5)
C11	−0.1121 (5)	0.3212 (5)	0.6592 (6)
C12	−0.2344 (4)	0.3213 (4)	0.6133 (6)
C13	−0.8151 (5)	0.3590 (5)	0.4942 (6)
C1′	0.2860 (4)	0.0372 (4)	0.9320 (5)
C2′	0.2645 (4)	−0.0054 (4)	1.0631 (5)
C3′	0.2417 (4)	−0.1465 (4)	1.0208 (5)
C4′	0.1374 (4)	−0.1881 (4)	0.8986 (5)
C5′	0.1614 (4)	−0.1478 (4)	0.7679 (5)
C6′	0.1831 (4)	−0.0070 (4)	0.8074 (5)
C7′	0.2963 (4)	0.1804 (4)	0.9771 (4)
C8′	0.4064 (4)	0.2388 (4)	1.0001 (5)
C9′	0.4150 (4)	0.3670 (4)	1.0377 (5)
C10′	0.3131 (5)	0.4438 (4)	1.0545 (5)
C11′	0.2033 (5)	0.3900 (5)	1.0352 (6)
C12′	0.1942 (4)	0.2598 (4)	0.9987 (5)
C13′	0.1172 (5)	−0.3280 (5)	0.8575 (6)

rotation was also performed around the two bonds leading to the ester oxygen.

Results and Discussion

Repetition of the force-field calculations of 1-methyl-1-phenylcyclohexane (1) by means of the MM2 force field[11] confirmed Allinger's data[2] for the parallel and perpendicular conformations with equatorial phenyl and the perpendicular conformation for axial phenyl but disclosed that the minimum-energy conformation for equatorial phenyl corresponds to a 68° torsion angle (taking the angle of the bisecting conformer as 0° and that of the perpendicular one as 90°) rather than 90°. The energy difference between the global minimum torsion angle ($\tau = 68°$) and the bisecting conformer ($\tau = 0°$) is 0.7 kcal/mol. The energy difference between 68° and 90° amounts to only 0.34 kcal/mol, so that the ring will, in fact, librate rapidly about the perpendicular (90°) position.[17] However, the change reduces the energy difference between axial and equatorial phenyl geminal to methyl from 0.96 to 0.61 kcal/mol. Moreover, for the equatorial-phenyl conformer, there will not only be an entropy of mixing of the bisecting and perpendicular conformers (about 0.7 G) but also a sizable vibrational entropy because of the libration. This may well bring the free-energy difference between equatorial and axial phenyl conformers down to the observed[3] 0.32 kcal/mol at −100 °C.[18]

Table IV. Torsion Angles in the Cyclohexyl Moieties

atoms	2	3	8A	8B
C(1)–C(2)–C(3)–C(4)	−51.4	49.6	−53.8	−55.1
C(2)–C(3)–C(4)–C(5)	55.5	−50.9	54.1	55.0
C(3)–C(4)–C(5)–C(6)	−55.7	51.7	−56.3	−55.1
C(4)–C(5)–C(6)–C(1)	50.6	−55.0	56.1	55.4
C(5)–C(6)–C(1)–C(2)	−44.1	53.2	−51.3	−52.4
C(6)–C(1)–C(2)–C(3)	45.1	−49.2	51.3	52.2
C(1)–C(2)–C(3)–E[a]	−179.1			
C(5)–C(4)–C(3)–E	−179.2			
A[c]–C(4)–C(3)–E	61.4			
Ph[b]–C(4)–C(3)–E	−61.9			
C(3)–C(2)–C(1)–O	−136.3			
C(5)–C(6)–C(1)–O	137.3			
C(2)–C(3)–C(4)–A	−63.9			
C(2)–C(3)–C(4)–Ph	172.8			
C(6)–C(5)–C(4)–A	64.1			
C(6)–C(5)–C(4)–Ph	−174.0			
C(3)–C(4)–Ph–Ph′[d]	125.7			
C(3)–C(4)–Ph–Ph″	−54.1			
C(5)–C(4)–Ph–Ph′[d]	−117.1			
C(5)–C(4)–Ph–Ph″	63.1			
A–C(4)–Ph–Ph′	3.4			
A–C(4)–Ph–Ph″	−176.4			
C(3)–C(2)–C(1)–A		69.9	−64.5	−65.6
C(3)–C(2)–C(1)–Ph		−173.1	175.7	174.7
C(5)–C(6)–C(1)–A		−64.3	65.1	65.5
C(5)–C(6)–C(1)–Ph		173.2	−173.9	−174.7
C(2)–C(1)–Ph–Ph′		−68.9	93.2	103.4
C(2)–C(1)–Ph–Ph″		108.7	−84.7	−76.0
C(6)–C(1)–Ph–Ph′		169.3	−144.5	−134.4
C(6)–C(1)–Ph–Ph″		−13.1	37.7	46.1
A–C(1)–Ph–Ph′		47.0	−25.3	−15.5
A–C(1)–Ph–Ph″		−135.5	156.8	165.1
C(2)–C(3)–C(4)–C(13)			178.3	179.4
C(6)–C(5)–C(4)–C(13)			−179.8	−179.5
C(4)–C(3)–C(2)–O		−64.1		
C(6)–C(1)–C(2)–O		67.4		
A–C(1)–C(2)–O		−173.4		
Ph–C(1)–C(2)–O		−56.4		

[a] E = equatorial substituent [C(7) in **1**]. [b] Ph = phenyl ipso carbon atom. [c] A = axial substituent [C(8) in **1**, OH in **2**, C(7) in **3**]. [d] Ph′, Ph″ = phenyl ortho carbon atoms.

Introduction of an equatorial vicinal methyl group, however, produces an unfavorable interaction at high τ values between the ortho hydrogen atoms of the phenyl group and the vicinal equatorial substituent. Consequently, in 2 the phenyl ring is almost in the bisecting conformation, the exocyclic torsion angle C(8)–C(4)–CP(1)–CP(2) being only 3.4 (1)° in the solid state; a view of the structure of 2 in the crystals is presented in Figure 1 and torsion angles in the cyclohexyl moieties of all four crystallographically independent molecules are tabulated in Table IV. The force-field calculation for 2 is in excellent agreement with this observation, showing a fairly sharp minimum for a value of 0–1° for the torsion angle. As the

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[17] Eliel, E. L. *Isr. J. Chem.* **1976**, *15*, 7.

[18] The energy minimum for the axial-Ph/equatorial-Me isomer, while indeed located at a 90° torsion angle, is also shallow in the 75–105° region (varying by less than 0.1 kcal/mol). Thus its vibrational entropy might be sizeable also, although probably less than that of the equatorial-phenyl/axial-methyl conformer with its double minimum.

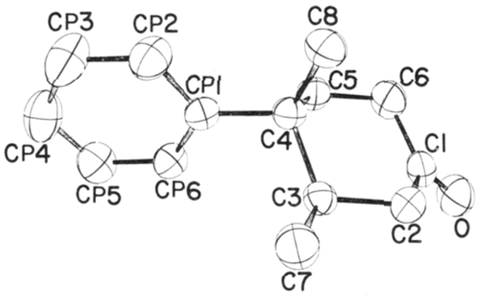

Figure 1. View of one molecule of **2**. Thermal ellipsoids are drawn at the 40% probability level; hydrogen atoms are omitted for clarity.

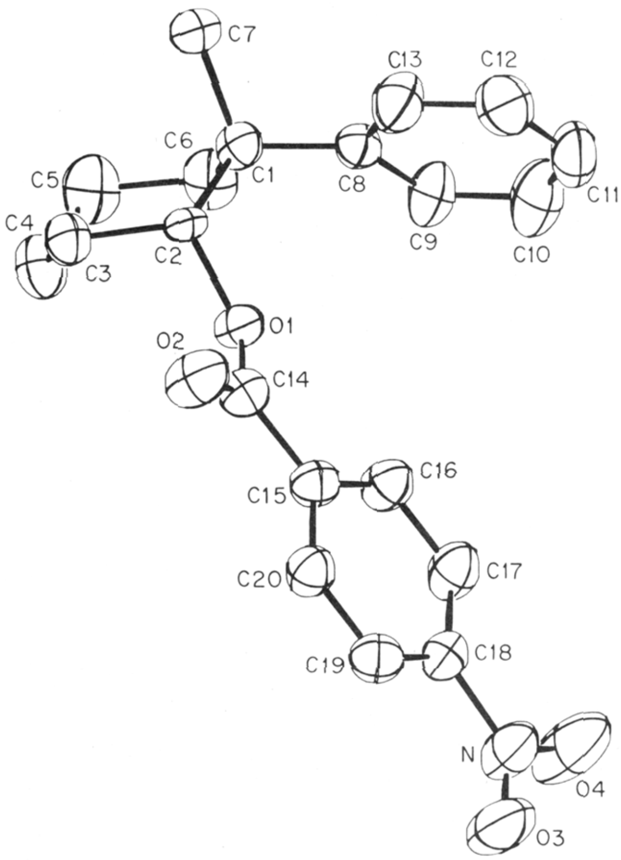

Figure 2. View of one molecule of **3**. Drawn as in Figure 1.

phenyl group is rotated (in either direction) one of its ortho hydrogen atoms encounters an increasingly unfavorable interaction with the equatorial methyl group, the energy rising to 6.5 kcal/mol above the minimum in the perpendicular conformation. Ring inversion of **2** converts it to the conformer with axial phenyl and axial 2-methyl, which is calculated to be 1.02 kcal/mol higher in energy than the conformer which has these two groups equatorial. Thus, the observation of the equatorial phenyl conformer in the crystals of **2** with a near zero torsional angle is not surprising.

The observation and calculation of approximately zero values for τ in **2** deserve further comment in light of the results calculated above for **1**. The unfavorable interaction between the equatorial phenyl and geminal axial methyl group calculated for **1** is still present in **2**, but the crystal structure determination of **2** reveals that this steric interaction is relieved by two structural features. Firstly the exocyclic C(4)–CP(1) bond length of 1.533 (1) Å in **2** is considerably greater than a normal sp^3-sp^2 C–C bond and is greater than the corresponding bond length in **3** or **8**. Secondly, the exocyclic bond angle C(8)–C(4)–CP(1) is enlarged to a value of 111.8 (1)°, thereby reducing any interaction between the axial methyl group and the equatorial phenyl ring. Consequently, the interaction with C(7) dominates, and the observed τ value of 3.4° is near zero. The same pattern is observed in the structures of α- (**4**) and γ-promedol (**5**) alcohols.[6,7] In the α-isomer, which has a very small torsion angle of 1.8°, the exocyclic bond length and angle are 1.530 (4) Å and 111.6 (2)°, which are insignificantly different from the values in **2**; in the γ-isomer, which has an intermediate torsion angle of 16.2°, the corresponding values are smaller, 1.517 (3) Å and 110.3 (1)°, respectively, and are very similar to the average values of 1.518 Å and 109.8° in **3**. Similarly, the force-field calculations on **2** suggest a lengthened exocyclic bond (1.541 Å) and an enhanced bond angle (111.7°); these calculated values are in encouraging and remarkable agreement with the crystallographic results.

An axial vicinal substituent, however, has minimal interaction with the phenyl group. Consequently, force-field calculations for the formate analogue **9** of the *p*-nitrobenzoate **3** give no indication that the axial formate group affects the conformation of 1-phenyl-1-methylcyclohexane (equatorial phenyl) in the least; the calculated torsional minimum is still near 70° (at 66.9° to be precise). Although this minimum is rather flat in the 55–80° region the potential energy climbs appreciably above and below these values. The solid state structure of **3**, shown in Figure 2, is in qualitative agreement with the calculation, the τ value of 47.0° being large and positive. Similar values of 43.4° and 37.9° were observed[9] in the hydrochloride and hydrobromide salts, respectively, of β-prodine (**7**). It is noteworthy, however, that the calculated energy for **9** at the observed (for **3**) torsion angle of 47° is approximately 0.9 kcal/mol above the calculated minimum. The source of this quantitative discrepancy is not readily apparent. It evidently does not stem from problems resulting from the availability of both s-cis and s-trans conformers for the ester moiety since, as expected,[19] the formate **9** is most stable (by 3.8 kcal/mol) in the *Z* conformation [O=C on the side of C(2)] which is also the observed conformation of the *p*-nitrobenzoate (see Figure 2); moreover, a change to the *E* conformation in **9** does not change interactions involving the phenyl moiety. The alternate conformation (axial phenyl, equatorial formate) is destabilized by a sizeable ortho-hydrogen/formate oxygen interaction.

Agreement between calculation and experiment is more satisfactory for compound **8**. The calculations for **8** show that the hydroxyl conformation with the *H*-O outward ($\tau = \pm 48.6°$) is more stable, by 1.2 kcal/mol, than that with OH inward. In this conformation the near bisecting phenyl ($\tau = 5°$) is at an energy minimum, though not at the global one. In fact there is a very broad, low energy region in the potential curve between −15° and +65° torsion angles, with an energy variation of no more than 0.35 kcal/mol. Within this low energy region, minima are calculated at +50° as well as +5°, with a barrier of only 0.35 kcal/mol between them, so, by the definition given by one of us,[17] this whole region may be considered as pertaining to a single molecule. The +5° minimum is only 0.11 kcal/mol above the +50° one; a third minimum, 0.30 kcal/mol above the global one, is found at −55° but is separated by a somewhat higher energy barrier from the other two. The crystal structure of **8**, shown in Figure 3, is entirely compatible with the calculations, the corresponding torsion angles in the two independent molecules in the unit cell being 15.5° and 25.3°.

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[19] Curl, R. F. *J. Chem. Phys.* **1959**, *30*, 1529.

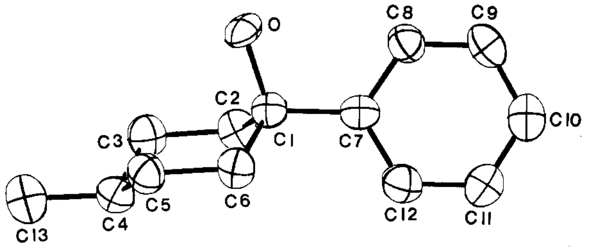

Figure 3. View of one molecule of **8**; the molecule shown is molecule B, but the difference between A and B is very small. Drawn as in Figure 1.

The torsion angles of 1.8° and 16.2° in the promedols **4** and **5**, alluded to earlier, are entirely in agreement with the calculations for the related compounds **2** and **3**. The calculations for **2** support a small torsion angle for a compound with a vicinal equatorial methyl, and those for **3** indicate insensitivity of the potential energy to the torsional angle as long as it is less than 65°. The latter finding is also in accord with the relatively large torsion angle of 38–44° in the prodine salts **7** in which the axial vicinal methyl group probably makes little difference. On the other hand, the relatively large torsion angle (28°) in **6** is surprising, in view of the presence of an equatorial vicinal methyl group in this compound. The combined data for **6** and **7** (which, it must be recalled, are propionates, not free alcohols) suggest that torsion angles near zero may be less well-tolerated in the esters than in their alcohol precursors.

The geometry of the cyclohexyl group is also markedly influenced by substitutions. In **2**, the chair is considerably flattened, the average endocyclic torsion angle being only 50.4°. The main effect is at C(1), where the torsion angles C(3)–C(2)–C(1)–C(6) and C(2)–C(1)–C(6)–C(5) are only 45.1 (1)° and −44.1 (1)°. This average value of 50.4° can be compared with the value of 49.4° in 4,4-dimethylcyclohexan-1-one.[20] In **3** there is also significant flattening, although the average torsion angle of 51.6° demonstrates that the effect is smaller than that in **2**. Moreover, in **3** the principal flattening is at C(2), with torsion angles of −49.2 (4)° and 49.6 (4)°; this flattening associated with axial substitution has been predicted on theoretical grounds.[21]

In the two independent molecules of **8**, the distortion from idealized chairs is much smaller, the average torsion angles being 53.8° and 54.2° in the A and B molecules, respectively. These values are close to the value of 54.7° theoretically predicted for cyclohexane itself by Bixon and Lifson[22] and also approach the values of 55.3 (9)° and 55.9 (4)° determined from electron diffraction studies on methylcyclohexane and cyclohexane, respectively.[23]

The endocyclic bond lengths within the cyclohexane rings in **2** and **3** each show that the longest bonds are associated with the fully substituted carbon atoms [C(4) in **1**, C(1) in **3**]. Thus, the C(4)–C(3) and C(4)–C(5) distances of 1.553 (1) and 1.540 (2) Å in **2** are longer than the other values of 1.497 (2)–1.533 (2) Å, the longer bond being that to the substituted carbon atom C(3). In **3**, the bond between C(1) and the substituted carbon atom C(2) is extremely long, 1.583 (4) Å.

Conclusion

Both the crystallographic data and the force-field calculations indicate that the torsion angle of an equatorial phenyl moiety in geminally substituted phenylcyclohexanes varies considerably from one case to the other, depending on the nature of the geminal substituent, on whether there is a vicinal substituent, and, if so, whether it is equatorial or axial. In some cases quite shallow potential wells are encountered; in such cases changes in rotational attitude of the phenyl moiety are obviously quite facile. In view of the importance of compounds of this type in pharmacology, it is well to keep in mind that in such cases the conformation found in the crystal may be changed in solution with input of little energy and may thus not be the conformation in contact with the pharmacological receptor. Force-field calculations, which are easy to carry out, will indicate whether the molecule finds itself in a deep potential well or whether the well is shallow and rotation of the phenyl correspondingly facile.

Acknowledgment. This work was supported by NSF Grant CHE80-20388 and Army Research Office Contract DAAG29-82-K-0184. The high-field NMR spectra were recorded by Dr. David Harris.

Registry No. **2**, 98688-67-6; **2** (cis isomer), 98688-70-1; **3**, 98688-68-7; **8**, 30689-83-9; **9**, 98688-69-8; 4-methyl-4-phenyl-2-cyclohexenone, 17429-36-6; 2,3,4-trimethyl-4-phenylcyclohexanone, 98688-71-2; *cis*-6-methyl-6-phenyl-2-cyclohexen-1-ol, 98688-72-3; *trans*-6-methyl-6-phenyl-2-cyclohexen-1-ol, 98688-73-4; 5-methyl-2-oxo-2-phenyl-7-oxabicyclo[4.1.0]heptane, 98757-35-8; *cis*-2-methyl-2-phenylcyclohexan-1-ol, 98757-36-9; *trans*-2-methyl-2-phenylcyclohexan-1-ol, 98757-37-0; *cis*-1-(acetyloxy)-2-methyl-2-phenylcyclohexane, 98688-74-5; *trans*-1-(acetyloxy)-2-methyl-2-phenylcyclohexane, 98688-75-6.

Supplementary Material Available: Tables S1, S2, and S3 (bond lengths in **2**, **3**, and **8**, respectively), S4, S5, and S6 (bond angles in **2**, **3**, and **8**, respectively), S7, S8, and S9 (anisotropic thermal parameters in **2**, **3**, and **8**, respectively), and S10, S11, and S12 (observed and calculated structure amplitudes for **2**, **3**, and **8**, respectively (44 pages). Ordering information is given on any current masthead page.

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