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Rotation Barriers of Interacting Axial Methyl Groups

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A molecular dynamics study on some podocarpane derivatives is described. The ^{13}C NMR relaxation times lead to the diffusion constants of various methyl groups in diaxial interaction. Molecular deformations are shown to be responsible for the rotational barrier values of these methyl groups calculated by the force field method (FFM). A correlation between the two methods is proposed.

The methyl group is a widely encountered substituent in organic chemistry and the steric effects associated with its presence at some place in a molecule have been the subject of numerous studies. For a long time, this group has been assigned a globular shape, but more recently its intimate nature as a three-pronged substituent has been shown to be of importance, from both theoretical and experimental points of view.[1-4]

Recognizing the polyhedral nature of the methyl group raises the question of its dynamic behavior. C_{3v} symmetry implies that the rotational process can be characterized by a single energy term, i.e. the barrier to internal rotation. The measurement of the H_1 or C_{13} NMR relaxation time is a powerful method for the determination of this barrier and numerous studies have used such techniques.[5-25] Interpretation of the relaxation data is simpler in carbon[7,9-11,15,17-25] than in proton[5,6,8,12,13,16,17] or fluorine[14] (in the case of a trifluoromethyl group) NMR and therefore the carbon nucleus has been used, whenever possible, to probe the molecular dynamics of the CH_3 top.

TABLE I: ^{13}C Chemical Shifts of Compounds 1–5[a]

carbon	1	2	3	4	5
1	39.1	39.5	40.1	38.9	39.8
2	19.0	21.5	18.7	21.1	18.5
3	42.4	36.6	42.2	36.3	42.1
4	33.3	30.7	33.3	30.4	33.2
5	55.5	54.6	56.8	54.4	56.8
6	21.8	20.8	18.5	20.1	
7	35.9	40.8	41.6	41.2	41.2
8	36.8	37.5	37.7	37.3	37.8
9	56.3	57.3	59.1	58.5	
10	36.9	37.3	37.7	36.9	37.5
11	25.1	20.8	20.5	16.2	16.2
12	27.1	35.6	35.5	33.9	34.0
13	26.4	29.8	29.8	31.1	31.1
14	35.5			59.5	60.5
Me-4 ax	22.0		21.5		21.4
Me-4 eq	33.6	20.5	33.4	20.3	33.3
Me-8		15.5	15.5	17.1	17.2
Me-10	14.3	14.2	16.4	13.8	16.2
Me-13		20.8	20.8	17.0	17.0
COO*Me*		50.6	50.6	50.6	50.5

[a] δ values downfield from Me_4Si, $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$.

This paper reports on a study of the rotational barrier of interacting axial methyl group on backbones formed by fused cyclohexane rings. There are various natural or snythetic organic compounds in which a di- or multiaxial interaction exists, but the structures chosen for the present study all bear a common perhydrophenanthrene skeleton.

The mechanistic details of methyl group rotation are studied by force field calculations and the net energy barriers derived from these calculations are compared with results obtained by NMR C_{13} relaxation analysis.

The compounds used to gather this experimental data are presented in Figure 1. **1** was prepared from podocarp-8,14-en-13-one[26] by standard methods. The other compounds were prepared by hydrogenation of the corresponding olefins, which are of synthetic[27] or natural origin.[28]

NMR Relaxation Times

Prior to relaxation time analysis, the ^{13}C spectra of compounds **1–5** was analyzed. Results are presented in Table I. The assignment of most of the carbon resonances was done by comparison with other models[29-31] and by use of common additive substituent effects. However, since this study is directed toward methyl

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(1) Roussel, C.; Balaban, A. T.; Berg, U.; Chanon, M.; Gallo, R.; Klatte, G.; Memiaghe, J. A.; Metzger, J.; Oniciu, D.; Pierrot-Sanders, J. *Tetrahedron* **1983**, *39*, 4209.

(2) Burgi, H. B.; Hounshell, W. D.; Nachbar, R. B.; Mislow, K. *J. Am. Chem. Soc.* **1983**, *105*, 1427.

(3) Hounshell, W. D.; Iroff, L. D.; Iverson, D. J.; Wroczynski, R. J.; Mislow, K. *Isr. J. Chem.* **1980**, *20*, 65.

(4) Nakamura, M.; Oki, M.; Nakanishi, H. *J. am. Chem. Soc.* **1973**, *95*, 7169.

(5) Imashiro, F.; Takegoshi, K.; Okazawa, S.; Furukawa, J.; Terao, T.; Saika, A.; Kawamori, A. *J. Chem. Phys.* **1983**, *78*, 1104.

(6) Imashiro, F.; Takegoshi, K.; Terao, T.; Saika, A. *J. Phys. Chem.* **1982**, *86*, 3306.

(7) Beirbeck, H.; Easton, J. W.; Saunders, J. K.; Bell, R. A. *Can. J. Chem.* **1982**, *60*, 1173.

(8) Imashiro, F.; Takegoshi, K.; Terao, T.; Saika, A. *J. Am. Chem. Soc.* **1982**, *104*, 2247.

(9) Aksnes, D. W.; Holak, T. A. *Org. Magn. Reson.* **1981**, *17*, 285.

(10) Mellink, W. A.; Kaptein, R. *Org. Magn. Reson.* **1980**, *13*, 279.

(11) Ericsson, A.; Kowalewski, J.; Liljefors, T.; Stilbs, P. *J. Magn. Reson.* **1980**, *38*, 9.

(12) Lubianez, R. P.; Jones, A. A. *J. Magn. Reson.* **1980**, *38*, 331.

(13) Haslinger, E.; Robien, W. *J. Am. Chem. Soc.* **1980**, *102*, 1237.

(14) Gerig, J. T.; Loehr, D. T.; Luk, K. F. S.; Roe, D. C. *J. Am. Chem. Soc.* **1979**, *101*, 7482.

(15) Jordan, R. F.; Norton, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 4853.

(16) Haslinger, E.; Lynden-Bell, R. M. *J. Magn. Reson.* **1978**, *31*, 33.

(17) London, R. E.; Eastman, M. P.; Matwlyoff, N. A. *J. Phys. Chem.* **1977**, *81*, 884.

(18) Axelson, D. E.; Holloway, C. E. *Can. J. Chem.* **1976**, *54*, 2820.

(19) Ladner, K. H.; Dalling, D. K.; Grant, D. M. *J. Phys. Chem.* **1976**, *80*, 1780.

(20) Apsimon, J. W.; Beierbeck, H.; Saunders, J. K. *Can. J. Chem.* **1975**, *53*, 338.

(21) Collins, S. W.; Alger, T. D.; Grant, D. M.; Kuhlmann, K. F.; Smith, J. C. *J. Phys. Chem.* **1975**, *79*, 2031.

(22) Gray, G. A.; Cremer, S. E. *J. Magn. Reson.* **1973**, *12*, 5.

(23) Lyerla, J. R.; Grant, D. M. *J. Phys. Chem.* **1972**, *76*, 3213.

(24) Lyerla, J. R.; Grant, D. M.; Harris, R. K. *J. Phys. Chem.* **1971**, *75*, 585.

(25) Kuhlmann, K. F.; Grant, D. M. *J. Chem. Phys.* **1971**, *55*, 2998.

(26) Do Khac Manh, D.; Fetizon, M.; Flament, J. P. *Tetrahedron* **1975**, *31*, 1897.

(27) Bory, S.; Do Khac Manh, D.; Feitzon, M.; Kone, M.; Anh, Nguyen Trong *Bull. Soc. Chim.* **1975**, 2347.

(28) Bastard, J.; Do Khac Manh, D.; Fetizon, M. *Phytochemistry* **1979**, *18*, 1839.

(29) Wahlberg, I.; Almqvist, S. O.; Nishida, T.; Enzell, C. R. *Acta Chem. Scand., Ser. B* **1975**, *29*, 1047.

(30) De Miranda, D. S.; Brendolan, G.; Imamura, P. M.; Sierra, M. G.; Marsaioli, A.; Ruveda, E. A. *J. Org. Chem.* **1981**, *46*, 4851.

(31) Imamura, P. M.; Ruveda, E. A. *J. Org. Chem.* **1980**, *45*, 510.

0022-3654/86/2090-3936$01.50/0

TABLE II: ^{13}C Longitudinal Relaxation Times of Compounds 1–5[a]

carbon	1	2	3	4	5
1	2.28 (0.05)	1.29 (0.02)	0.79 (0.02)	1.01 (0.06)	0.79 (0.03)
2	2.25 (0.09)	1.27 (0.02)	0.72 (0.03)	0.91 (0.05)	0.73 (0.03)
3	1.65 (0.06)	1.13 (0.02)	0.65 (0.01)	0.88 (0.08)	0.65 (0.04)
4		2.42 (0.02)		1.37 (0.04)	
5	4.03 (0.13)	2.43 (0.03)	1.46 (0.02)	1.77 (0.13)	1.45 (0.06)
6	2.18 (0.08)	1.33 (0.03)	0.76 (0.02)	1.05 (0.08)	0.79 (0.02)
7	2.22 (0.09)	1.25 (0.02)	0.70 (0.02)	0.81 (0.07)	0.75 (0.04)
8	3.95 (0.18)				
9	3.96 (0.14)	2.53 (0.03)	1.36 (0.04)	1.83 (0.09)	1.49 (0.09)
11	2.29 (0.03)	1.21 (0.03)	0.71 (0.03)	0.84 (0.05)	0.73 (0.02)
12	2.14 (0.05)	1.26 (0.02)	0.74 (0.01)	0.89 (0.05)	0.78 (0.04)
13	1.82 (0.04)	2.28 (0.02)	1.35 (0.04)	1.45 (0.08)	1.17 (0.04)
14	2.27 (0.03)		1.30 (0.05)	1.68 (0.14)	1.48 (0.08)
Me-4 ax	2.43 (0.06)		1.09 (0.06)		1.23
Me-4 eq	1.59 (0.04)	1.38 (0.04)	0.69 (0.03)	0.95 (0.07)	0.89 (0.08)
Me-8		4.21 (0.03)	2.59 (0.13)	1.86 (0.16)	1.82 (0.05)
Me-10	6.09 (0.18)	4.28 (0.04)	1.70 (0.07)	2.99 (0.21)	1.31 (0.04)
Me-13		1.54 (0.02)	0.97 (0.03)	1.54 (0.11)	1.62 (0.05)
COO*Me*		5.00 (0.02)	2.93 (0.11)	3.30 (0.17)	3.15 (0.24)

[a] The values and the errors in parentheses are given in seconds.

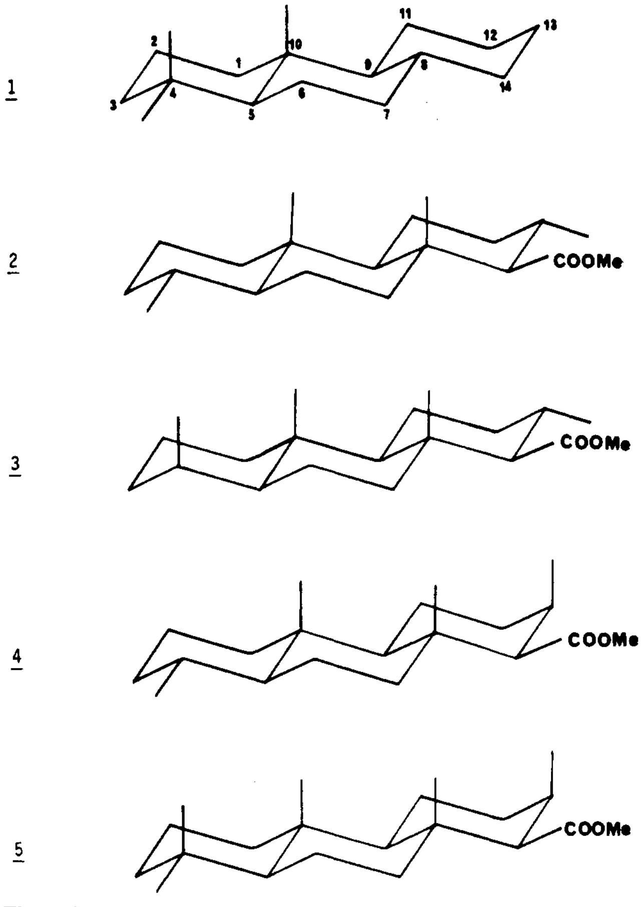

Figure 1.

TABLE III: Overall Diffusion Results[a,b]

	1	2	3	4	5
D_{xx}	2.89 (4)	1.13 (7)	0.70 (13)	0.90 (17)	0.78 (3)
D_{yy}	0.44 (8)	0.57 (8)	0.27 (18)	0.32 (21)	0.27 (4)
D_{zz}	1.24 (4)	0.70 (6)	0.47 (11)	0.56 (15)	0.42 (3)
β	5.6 (2)	14.7 (1)	9 (1)	*c*	7.6 (1)
D_{xx}/D_{yy}, D_{zz}/D_{yy}	6.6, 2.8	2.0, 1.2	2.6, 1.7	2.8, 1.8	2.9, 1.6

[a] Diffusion coefficients are given in 10^{10} radian^2 s^{-1}. The second Euler angle β is given in degrees. [b] Relative standard marginal deviations are given in percent and in parentheses. [c] Not optimized.

groups, their firm assignment was mandatory. Selective proton–carbon decoupled spectra were thus recorded in order to correlate the proton and carbon spectra. For instance, methyl 8 and 13 of **5** have very close carbon resonances. However, methyl 13 is a doublet in the proton domain, whereas methyl 8 is a singlet. They are therefore easily distinguished.

Upon modification of the stereochemistry of the methyl groups the backbone carbons undergo the expected chemical changes. More interestingly the angular methyl groups 8 and 10, which experience a varible steric compression due to their axial neighbors, are deshielded by ca. 1.5 ppm for each diaxial interaction. For instance, methyl 10 resonates at 12.3 ppm in 5α-androstane,[32] at ca. 14.0 ppm in **1**, **2**, and **4**, and at ca. 16.3 ppm in **3** and **5**.

The relaxation times were measured by the inversion recovery sequence[33,34] and the results are presented in Table II. In order to ascertain the relaxation mechanism of the protonated carbons, ^1H–^{13}C NOE spectra were recorded. The enhancements were found to be 2.98 ± 0.1, thus establishing the dipole–dipole mechanism as the sole relaxation mechanism.

From the T_1's of the backbone resonances, overall diffusion parameters can be extracted.[35-37] In the most general case, the diffusion of a molecule should be specified by six variables, i.e. the three diffusion coefficients and three Euler angles referencing the principal diffusion frame in a fixed molecular frame and in the present case and the principal inertial frame. During the optimization procedure however, we found that the first and third Euler angles were always very loosely defined, i.e., letting them free in the least-square fit would not decrease the sum of squares of the differences between observed and computed T_1's. These two variables were thus set to zero and not optimized.

On the other hand, the second Euler angle, which is the angle between the two z axes of the diffusion and inertial frames, was in most cases well determined by the fitting process. Table III summarizes the results obtained and presents the values of the diffusion constants together with one Euler angle. Figure 2 gives a definition of the molecular coordinate system.

The results of Table III show some general trends. Firstly, the diffusion coefficients are fairly well defined. However, the correlation matrix shows that D_{xx} and D_{yy} are always highly correlated (<-0.9), showing their sum to be well defined. Secondly, the Euler angle β is in most cases close to 10°, showing that the diffusion

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(32) Blunt, J. W.; Stothers, J. B. *Org. Magn. Reson.* **1977**, *9*, 439.

(33) Canet, D.; Levy, G. C.; Peat, I. R. *J. Magn. Reson.* **1975**, *18*, 199.

(34) Bernassau, J. M.; Hyafil, F. *J. Magn. Reson.* **1980**, *40*, 245.

(35) Berger, S.; Kreissl, F. R.; Grant, D. M.; Roberts, J. D. *J. Am. Chem. Soc.* **1975**, *97*, 1805.

(36) Levy, G. C.; Kumar, A.; Wang, D. *J. Am. Chem. Soc.* **1983**, *105*, 7536.

(37) Bernassau, J. M.; Fetizon, M.; Pinheiro, J. A. *J. Phys. Chem.*, accepted for publication.

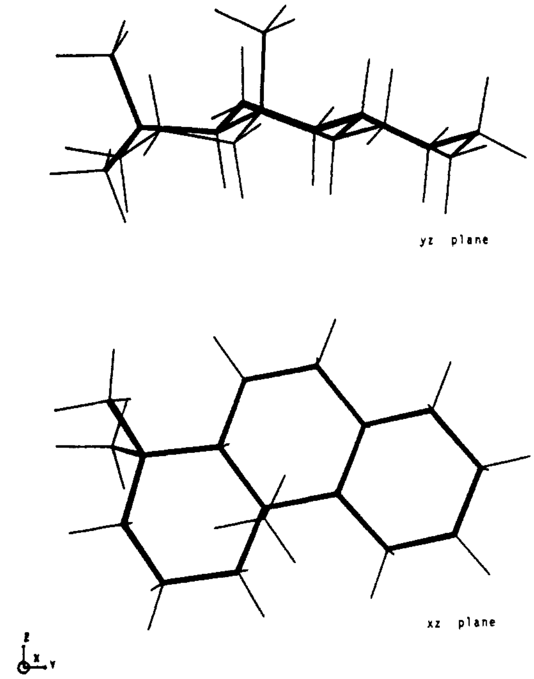

Figure 2. Projection of the molecule **1** on two of the planes of the molecular coordinate system.

TABLE IV: Diffusion Constants[a,b] and Rotational Barriers[c] (RB) from NMR Measurements and Force Field Calculations[d]

	1	2	3	4	5
Me-4 ax	2.9 (3)		2.0 (6)		2.4 (3)
	3.15		3.45		3.30
	2.66		3.03		2.73
Me-4 eq	0.5 (12)	1.9 (6)	0.5 (11)	0.9 (17)	1.09 (16)
	4.55	3.73	4.55	4.08	4.79
	4.15	4.23	4.43	4.21	4.35
Me-8		16.2 (1)	11.0 (7)	4.7 (10)	5.3 (4)
		1.77	2.08	2.76	2.67
		2.48	2.78	2.42	2.24
Me-10	20.5 (4)	17.3 (1)	4.9 (6)	11.8 (7)	2.8 (3)
	1.58	1.72	2.73	2.03	3.18
	2.41	2.05	2.57	2.84	3.02
Me-13		2.1 (3)	1.6 (6)	3.2 (9)	4.4 (3)
		3.41	3.62	3.07	2.81
		3.17	3.19	2.95	2.66
COOMe		33.6 (1)	18.4 (8)	19.6 (5)	28.0 (7)
		1.19	1.67	1.62	1.33
		1.3	1.3	1.3	1.3

[a] In 10^{10} radian^2/s. [b] The estimated error in percent is given in parentheses. [c] In kcal/mol. [d] Table gives successively for each methyl group its rotational diffusion constant, its energy barrier computed from NMR measurements, and its barrier computed from force field calculation.

tensor is slighly tilted with respect to the inertial frame. Thirdly, all compounds have a similar shape and this is clearly evidenced by the ratio of the diffusion constants. Except for **1** which does not bear a carbomethoxy group in position 14, the ratio D_{xx}/D_{yy} and D_{zz}/D_{yy} are fairly constant for compounds **2**–**5**. With respect to **1**, introduction of a polar group in the y axis direction decreases expectedly the rotational diffusion coefficient around the x axis.

The consistency of the overall diffusion data is therefore very satisfactory and gives fair confidence in the results obtained.

Once the overall diffusion parameters have been determined, it is possible to extract the internal diffusion constant for each methyl group of the molecule. The results, presented in Table IV, show that the four axial methyl groups and the methoxy group are consistently the slowest and fastest spinning groups of the molecule, respectively. Of course, comparison between different molecules is better achieved, if ones computes an energetic barrier from the equation obtained in ref 37

$$V = 3.93 - 0.58 \ln (Dr/10^{10})$$

TABLE V: Partitioning of the Energy of the Rotational Barrier of Methyl-10 in Some Representative Compounds[a]

	total	STR	BND	1,4	vdW	TOR
A[b]	3.20	0.09	0.04	0.65	0.00	2.42
2	2.05	0.07	−0.26	0.54	−0.23	1.93
A−2	1.15	0.02	0.30	0.11	0.23	0.49
3	2.57	0.21	0.56	0.49	0.21	1.08
2–3	−0.52	−0.14	−0.82	0.05	−0.44	0.85
5	3.02	0.24	0.70	0.47	0.40	1.18
3–5	−0.45	−0.03	−0.14	0.02	−0.19	−0.10

[a] STR = stretching terms; BND = bending terms; 1,4 = 1,4 van der Waals terms; vdW = all van der Waals terms except 1,4; TOR = torsional terms. [b] A is the 5α-androstane molecule.

These results are given in Table IV and will be discussed in detail in the following section.

Force Field Calculations

The NMR spin–lattice relaxation measurements thus allows one to obtain energetic values for the rotational barriers (RB) of the methyl groups. In order to gain a better insight into the details of the rotation processes, a force field study of the same compounds was undertaken. This will provide an understanding of the origin of the RB's in term of intramolecular steric interactions.

The force field used was developed by Allinger.[38,39] It has already been used by us with great success in a variety of conformational problems involving reactivity,[40] circular dichroism,[41–43] and NMR studies.[44,45] For each of the compounds **1**–**5**, the RB of the methyl groups was computed and the results are given in Table IV.

As can be seen from Table IV, the agreement between NMR and force field values is reasonable, the standard deviation of the differences between the two sets of numbers being 0.43 kcal/mol. A similar agreement was obtained in a preceding paper.[37]

The force field studies allow a discussion of the RB's in term of stretching, bending, van der Waals (vdW), and torsional energies.[39] Although it is not possible to enumerate the mechanistic details for all the methyl gorups, a presentation of some representative cases is interesting.

The idea of gearing between 1,3-diaxial methyl groups must be dismissed. A two-dimensional conformational energy map, a function of the two dihedral angles referencing the positions of the two methyl groups, shows a single maximum when the angles remain in a 120° range.

An interacting axial methyl group, however, does have a definite effect on the RB of its partner. The isolated 10-methyl group has, in the androstane molecule, an RB of 3.2 kcal/mol. When the same methyl function experiences a single axial interaction as in **1** or **2**, the RB drops to 2.4 and 2.1 kcal/mol, respectively.

When another interacting methyl group is added, the RB may increase by ca. 0.5 kcal/mol (see Me 10 in **2** and **3**) or may remain unchanged (Me 8 in **2** and **4**).

Finally, conformational transmission occurs also. The effect of the stereochemistry of methyl 13 on the RB of methyl 10 in the pairs of compounds **2** and **4** and **3** and **5** is 0.8 and 0.4 kcal/mol, respectively.

Each of these types of interaction will now be discussed.

(*a*) *One Diaxial Interaction* (*Two Interacting Methyl Groups*). The origin of the decrease in RB due to a single interacting methyl group is discussed first. Table V gives the partitioning of the energy of the RB of methyl 10 in 5α-androstane (A) and **2**. As can be seen from Table V, the difference in the two RB values

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(38) Allinger, N. L.; Yuh, Y. *Q.C.P.E.* **1980**, *12*, 395.

(39) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

(40) Aranda, G.; Bernassau, J. M.; Fetizon, M. *J. Org. Chem.* **1977**, *42*, 4256.

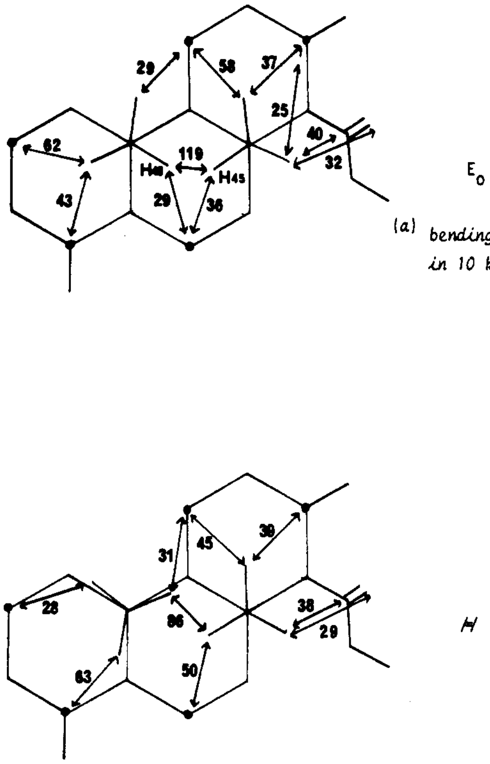
(41) Bernassau, J. M.; Fetizon, M.; Hanna, I. *Tetrahedron* **1979**, *35*, 1649.

(42) Bernassau, J. M.; Fetizon, M.; Hanna, I. *Tetrahedron* **1979**, *35*, 1653.

(43) Bernassau, J. M.; Fetizon, M.; Hanna, I.; Rens, J.; Viger, C. *Tetrahedron* **1979**, *35*, 1657.

(44) Bernassau, J. M.; Drakenberg, T.; Liljefors, T. *Acta Chem. Scand., Ser. B* **1977**, *31*, 836.

(45) Aranda, G.; Bernassau, J. M.; Fetizon, M.; Hanna, I. *J. Org. Chem.*, accepted for publication.



(a) bending energy is given in 10 kcal/mole

Figure 3. Relevant steric interactions in **2**. The bending energy is given in 10 kcal/mol.

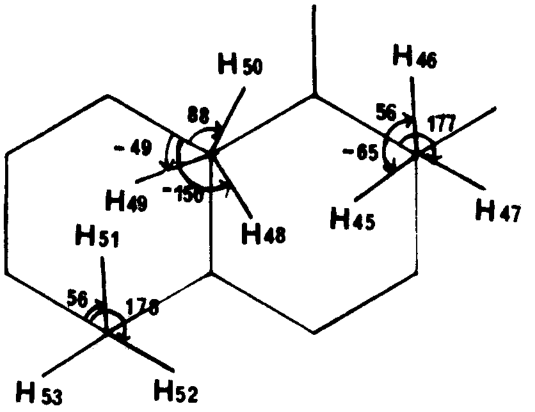


Figure 4. Position of the three methyl groups of **3** in the MNEC. The didhedral angles are given in degrees.

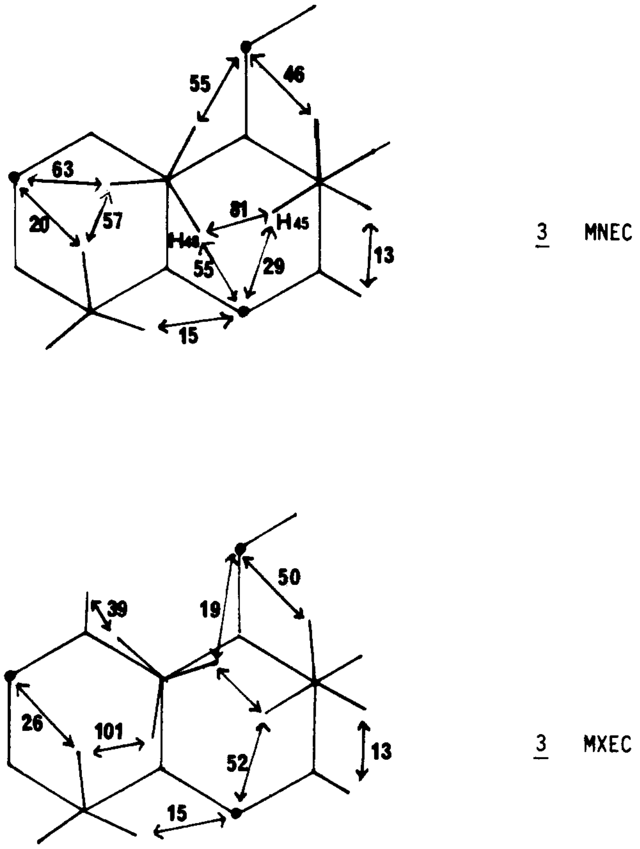


Figure 5. Principal van der Waals repulsions in the MNEC and MXEC of **3**.

TABLE VI: Partitioning of the Energy of the Rotational Barrier of Methyl-8 in Some Representative Compounds[a]

	total	STR	BND	1,4	vdW	TOR
2	2.48	0.04	-0.30	0.55	-0.20	2.39
4	2.42	0.09	0.54	0.59	-0.06	1.24
2-4	0.06	-0.05	-0.84	-0.04	-0.14	1.15
5	2.24	0.08	0.29	0.58	-0.17	1.45
4-5	0.18	0.01	0.24	0.01	0.11	-0.21

[a] See Table V, footnote a.

arise mainly because of the torsional, vdW, and bending terms.

Usually the bending and torsional terms can be considered as a consequence of some strong vdW interactions: the molecule distorts itself so as to avoid severe steric interactions between pairs of nonbonded atoms. As can be seen in Figure 3, in the minimum energy conformation (MNEC) of **2**, the repulsion between H_{48} and H_{45} (1.19 kcal/mol) forces the molecule to distort its A and B rings. In the maximum energy conformation (MXEC, transition state), this interaction diminishes and allows a relaxing of the constraints inside the two rings.

A similar effect occurs in **1** and is responsible, in the end, for the lowering of the RB on going from androstane to **1** or **2**.

(*b*) *Two Diaxial Interactions* (*Three Interacting Methyl Groups*). When the 10-methyl group suffers two diaxial interactions, from Me-4 and Me-8 as in **3**, the RB increases. Thus, although a single methyl interaction decreases the barrier (vide supra), the second methyl interaction raises it by ca. 0.5 kcal/mol.

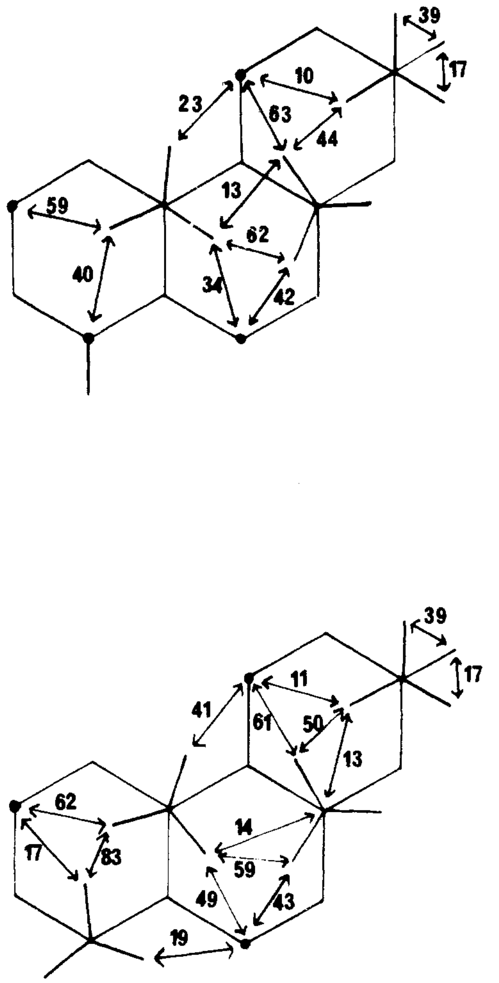
Here again, this behavior can be rationalized by studying the partitioning of the energy in term of the force field parameters. Table V compares **2** and **3**. As can be seen, and in contrast with the results obtained when comparing A and **2**, the -0.52 kcal/mol difference between the RB's of **2** and **3** are the sum of terms of different signs, there being a large positive contribution from the torsional terms and negative contributions of vdW and bending terms.

The lower contribution of the torsional term can easily be rationalized by considering the positions of the various methyl groups in the MNEC of **3** (see Figure 4). As can be seen, Me-10 is severely displaced from a pure staggered form and, therefore, the torsional contribution during the rotation process is small. The sum of all torsional terms along the C(10)-Me(10) bond is 0.70 kcal/mol in **3**, whereas it is 2.16 kcal/mol in **2**.

On the other hand, inspection of Table V reveals large negative contributions of the van der Waals and bending terms in the **2**-**3** comparison. The MXEC of **3** must therefore be more constrained than the MXEC of **2**. This is easily recognized in Figure 5 in which the vdW interactions of the MNEC and the MXEC of **3** are depicted. The behavior of the vdW terms (and therefore, indirectly, of the bending term) is now completely dissimilar to that observed in comparing the androstane molecule and **2**: the transition state is more constrained than the MNEC.

Quite surprisingly, the 8-methyl group displays another type of behavior, its RB being the same when it experiences one or two diaxial interactions (as in **2** and **4**). Table VI details the contributions of the force field terms to the energetic barrier.

As can be seen by comparing Tables V and VI, the origin of the RB of the 8-methyl group in **2** is similar in nature to that of Me-10. The torsional contribution, however, is lower in the latter case (1.93 instead of 2.39 kcal/mol) and this accounts for the difference in RB.



4

5

Figure 6. Principal van der Waals interactions in the MNEC of **4** and **5**.

The difference of RB between **2** and **4** is, as in the case of **2** and **3**, the sum of terms of opposite signs. But, in the **2**–**4** case, the torsional term is slightly higher than in the **2**–**3** case, and the van der Waals term smaller (in absolute value). The positive and negative contributions now equilibrate yielding the same RB for the Me-8 in **2** and **4**.

The subtle difference in each of the terms can be explained, as in the Me-10, in terms of interatomic interactions. But the net effect is the result of two counterbalancing types of interactions: a decreased torsional term (because of a semieclipsed type of methyl conformation) and increased van der Waals and bending terms (because of a more congested MXEC).

(*c*) *Three Diaxial Interactions* (*Four Interacting Methyl Groups*). Compound **5** provides an example of conformational transmission in which the 13-methyl group affects the RB of Me-10 through the participation of Me-8. Comparison of **3** and **5** is therefore informative. As can be seen in Table V, the increase of the Me-10 RB observed in going from **3** to **5** arises because of a slightly more strained MXEC (0.19 vdW and 0.14 bending interactions).

The main difference between **3** and **5** is the position of Me-8. Due to the cooperative effects of Me-10 and Me-13, the 8-methyl group assumes in the MNEC of **5** a conformation midway between the staggered and eclipsed forms with H–C–C–C angles equal to 30° (Figure 6), whereas in **3** (Figure 4) the same angles possess values close to 55°. This semieclipsed form, in fact, decreases the strain of Me-10 in the MNEC (H_{45}–H_{48} interaction being now 0.59 kcal/mol, it having been 0.81 kcal/mol in **3**) (see Figure 5 and 6). Thus, in the end, the decrease of Me-10 strain in MNEC increases the barrier of Me-10 in **5** with respect to **3**.

A similar effect can be observed for the methyl 10 in the pair of compounds **2** and **4**, for Me-8 in the **2**–**3** pair, and for Me-4 in the **1**–**3** pair.

TABLE VII: Partitioning of the Energy of the Rotational Barriers of Methyl-4 (Equatorial) and Methyl-13 of 2

	total	STR	BND	1,4	vdW	TOR
Me-4	4.23	0.22	0.67	0.37	0.93	1.97
Me-13	3.17	0.08	0.19	0.54	0.18	2.14
Δ4–13	1.06	0.14	0.48	−0.17	0.75	−0.17

In going from **4** to **5**, however, the appearance of an axial 4-methyl group decreases the RB of Me-8. As can be seen in Table VI, this is a consequence of the MNEC being more constrained in **5** than in **4** (vdW and bending terms, 0.11 and 0.24 less, respectively). As can be seen in Figure 6, the increased eclipsed conformation of Me-10 enhances its interactions with axial hydrogens in positions 6 and 11.

Finally, the case of compounds **1** and **5** shows that more remote effects (Me-13 and Me-4) are not important in cyclohexane type systems.

(*d*) *Equatorial Methyl Groups*. Although the main discussion focused on axial methyl groups, the equatorial groups deserve some general remarks.

Firstly, there is a striking difference in RB between the equatorial 13- and 4-methyl groups. Table VII depicts the contributions of the various force field terms to the RB of the two equatorial methyl groups of **2**. As can be seen in Table VII, the main difference between the two RB's arises from the vdW and bending contributions. The former is due mostly to interaction between one of the 4-methyl hydrogens and the equatorial hydrogen in position 6. This interaction rises to more than 1 kcal/mol in the MXEC.

Secondly, inspection of Table IV reveals that the axial 4-methyl group does not induce any conformational effects on it equatorial homologue. This can be ascribed to the fact that the geminal dimethyl groups have very little interaction. Moreover, the effect imparted by Me-10 on the axial 4-methyl group is not as important as that previously described for Me-8 or Me-10.

Conclusion

The force field calculations allowed a very fine analysis of the delicate phenomena involved during the rotational process of axial methyl groups on the perhydrophenanthrene skeleton. Although a single methyl interaction decreases the RB, adding further interactions may increase or leave the RB unchanged. This is a consequence of the RB being the result of a delicate equilibrium between torsion and vdW terms in multiaxial interactions.

Moreover, relaxation times NMR studies allowed corroboration of the theoretical results. Detailed T_1 analysis yields overall diffusion parameters and the rate of internal motion for each of the methyl groups. The latter values have been shown to correlate with the force field computed RB, thus linking the molecular computations to macroscopic observations.

Experimental Section

The force field computations were performed on a NAS 9080 computer. The program used is based on Allinger's MM2[24,30] version interfaced with input and output subroutines allowing modification and visualization of the structures. Typical running time for one conformation calculation is 5 min.

The ^{13}C NMR spectra were run on a VARIAN XL-100 spectrometer. For each compound several T_1 measurements were performed, in order to optimize the set of τ values of the inversion recovery sequence.[33,34] Since only a limited amount (25 mg) of **2** was available, its spectra were recorded on a Brucker WM 500 spectrometer. To ascertain the dipolar nature of the relaxation ^1H–^{13}C, NOE spectra were recorded on both spectrometers, and enhancements close to the maximum value of 2.98 were found for all protonated carbons.

4,4-Dimethylpodocarp-13-one. Liquid NH_3 (150 mL) was distilled over Na and condensed in a three-neck flask. Li (150 mg) was allowed to react with the solvent and upon reaction completion, 360 mg of podocarp-8,14-ene-13-one dissolved in 20 mL of anhydrous ether was added dropwise, followed by 0.17 mL of anhydrous *t*-BuOH. After 1 h the reaction was complete and

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anhydrous EtOH was added until the solution was colorless. After evaporation of NH$_3$, water was added and the mixture of ketone and alcohol was extracted with ether. This crude reaction product was oxidized with PCC[46] (810 mg) in 4 mL of CH$_2$Cl$_2$. After 2 h, ether was added and the solution was filtered on Florisil. The 400 mg of mixture thus obtained was chromatographed on silica gel (2:1 pentane/ether) to yield 282 mg of saturated ketone: mp, 101–103 °C; ^{1}H NMR (CDCl$_3$) δ 0.83 and 0.85; ^{13}C NMR (see Table I).

4,4-Dimethylpodocarpane (**1**). **1** (280 mg) was dissolved in 3 mL of anhydrous EtOH. *p*-Toluenesulfonylhydrazine (280 mg) was added and the mixture refluxed for 1 h. After extraction the crude compound was treated with 350 mg of NaBH$_3$CN and 50 mg of *p*-toluenesulfonic acid in 5 mL of a mixture of DMF–sulfolane (1:1) and 5 mL of cyclohexane. The solution was heated at 110 °C under argon for 3 h. After extraction the product (250 mg) was chromatographed on silica gel to yield 155 mg of podocarpane: ^{1}H NMR (CDCl$_3$) δ 0.83, 0.84, and 0.86.

Catalytic Hydrogenation of Methyl Isoanticopalate. Methyl isoanticopalate (970 mg) was hydrogenated in acetic acid with PtO$_2$. The mixture was chromatographed to yield 610 mg of **5** and 260 mg of **3**.

3: ^{1}H NMR (CCl$_4$) δ 3.55, 1.71, 1.00, and 0.85.

5: ^{1}H NMR (CCl$_4$) δ 3.57, 2.15, 1.19, 1.01, and 0.84.

Catalytic Hydrogenation of Methyl nor-19-Isoanticopalate.[48] Methyl nor-19-isoanticopalate (255 mg) was hydrogenated in acetic acid with PtO$_2$. The mixture was chromatographed to yield 190 mg of **4** and 25 mg of **2**.

2: ^{1}H NMR (CDCl$_3$) δ 3.56, 1.69, 0.98, 0.74–0.72, and 0.70.

4: ^{1}H NMR (CDCl$_3$) δ 3.58 2.2, 1.20, 1.03, 0.77, and 0.74.

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(46) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647.

(47) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.

(48) Bastard, J.; Do Khac Manh, D.; Fetizon, M. *Bull. Soc. Chim. II* **1984**, 444.

Axial Hydrogen Interactions and Methyl Group Rotation in Steroids

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The rotation barrier of the two methyl groups of several unsaturated steroids is studied by NMR and force-field calculation. Results can be explained on the basis of interactions between the axial hydrogens beared by the rings and the methyl hydrogens.

Introduction

Numerous natural or synthetic compounds possess cyclohexane structures bearing axial methyl groups. These methyl groups are generally undergoing rather fast internal rotation around their C_{3v} symmetry axis, and several NMR relaxation studies presented numerical values for the diffusion constant and for the energetic barrier associated with the rotational process.[1-3] The values thus obtained were invariably rationalized on the grounds of interactions between axial hydrogens on the cyclohexane rings and the hydrogens of the methyl group.

This paper is aimed at identifying precisely the nature of the interactions responsible for the energy barrier of the rotational process of methyl groups on cyclohexane structures. In particular, the axial hydrogen–methyl group interaction hypothesis is tested by the introduction of double bonds at various places in the molecular framework. Force-field calculations are used to gain a quantitative insight into the delicate intramolecular interactions arising in these systems, and ^{13}C NMR relaxation studies provide an experimental determination of the net energy barrier of the rotational process.

The compounds choosen for the present study all possess the androstane skeleton. Androstane and 4 unsaturated derivatives at positions 2, 4, 5, and 7 were prepared from 3β-hydroxyandrost-5-ene by standard methods.[4-8]

Relaxation Studies

Five compounds were studied: 5α-androstane (**1**), androst-2-ene (**2**), androst-4-ene (**3**), androst-5-ene (**4**), and androst-7-ene (**5**). The ^{13}C spectra of these compounds were taken from the literature.[8,9] Relaxation times were measured by inversion–recovery[10,11] and the results are presented in Table I.

In order to ascertain the dipolar nature of the relaxation process a ^{1}H–^{13}C NOE measurement was performed.[12] Finding the enhancements to within 5% of their maximum theoretical value[13] allows one to dismiss other relaxation pathways and retain only the dipole–dipole mechanism.

From the T_1s of Table I, reorientational parameters can be extracted via a least-squares fit.[14-16] In general, the diffusive motion of a molecule can be characterized by six parameters: three diffusion constants and three angles.[16] However, the experimental data did not allow the determination of all these parameters, and in most cases, three diffusion constants and one angle were determined. Table II presents the results obtained and Figure 1 gives a definition of the axis system.

The results of Table II support those obtained by Levy[3] on similar compounds. Motion is faster around the elongated axis of the molecule and the consistency of this result for the five

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(1) Apsimon, J. W.; Beierbeck, H.; Saunders, J. K. *Can. J. Chem.* **1975**, *53*, 338.

(2) Beierbeck, H.; Easton, J. W.; Saunders, J. K.; Bell, R. A. *Can. J. Chem.* **1982**, *60*, 1173.

(3) Levy, G. C.; Kumar, A.; Wang, D. *J. Am. Chem. Soc.* **1983**, *105*, 7536.

(4) Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547.

(5) Dauben, W. G.; Fullerton, D. S. *J. Org. Chem.* **1971**, *36*, 3277.

(6) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

(7) Ohloff, G.; Maurer, B.; Winter, B.; Giersch, W. *Helv. Chim. Acta* **1983**, *66*, 192.

(8) Jackson, W. R.; Lovel, C. G. *Aust. J. Chem.* **1982**, *35*, 2111.

(9) Eggert, H.; Djerassi, C. *J. Org. Chem.* **1981**, *46*, 5399.

(10) Canet, D.; Levy, G. C.; Peat, I. R. *J. Magn. Reson.* **1975**, *18*, 199.

(11) Bernassau, J. M.; Hyafil, F. *J. Magn. Reson.* **1980**, *40*, 245.

(12) Freeman, R.; Hill, H. D. W.; Kaptein, R. *J. Magn. Reson.* **1972**, *7*, 327.

(13) Kuhlmann, K. F.; Grant, D. M.; Harris, R. K. *J. Chem. Phys.* **1970**, *52*, 3439.

(14) Berger, S.; Kreissl, F. R.; Grant, D. M.; Roberts, J. D. *J. Am. Chem. Soc.* **1975**, *97*, 1805.

(15) Bernassau, J. M.; Fetizon, M.; Pinheiro, J. A. *J. Phys. Chem.* **1986**, *90*, 1051.

(16) Huntress, W. T. *Adv. Magn. Reson.* **1970**, *4*, 1.

0022-3654/86/2090-3941$01.50/0