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Conformational Relaxation as Limitation of Chemical Models. Empirical Force Field Calculations and ^{13}C NMR Shielding Effects for Some Cyclohexanes, Bicyclo[2.2.1]heptanes, Bicyclo[3.3.1]nonane, and 11β-Substituted Estrenes[1]

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Abstract: Molecular mechanics calculations on the title compounds demonstrate the redistribution of steric effects of conceptual single origin over the whole molecule. Sterically induced substituent effects on ^{13}C NMR shifts are obtained as the sum of up to ten single forces; use of nonrelaxed structures leads to gross overestimations of the interactions. A potential surface comparison between bicyclo[3.3.1]nonane and cyclohexane reveals that introduction of the bridge into cyclohexane rather extends than limits the number of conformations with similar energy in the chair inversion transition state. Considerable differences are found between published X-ray and force field derived structures of estrene derivatives, although the reflex angle between diaxial methyl groups is similar and comparable to that in isolated cyclohexanes. A potential surface calculation shows that both the C-ring distortion and the skeleton curvature brought about by axial substituents on the steroidal β side induce little strain energy variation in comparison to the binding energy to steroid hormone receptors.

In many studies of structure/energy relations and particularly of steric substituent effects, geometry variation is allowed for only in the molecule part under focus, while other parts are treated as rigid. The advent of highly efficient energy minimizing force fields[2] enables one to calculate molecular energies for any steric distortion with relaxation of *all* structural parameters. In a study of acetylcholine and derivatives, Gelin and Karplus,[3] e.g., have shown that the structural flexibility thus accessible can lead to significant variations in calculated minimum geometries and transition energies. Pursuing sterically induced substituent effects on ^{13}C NMR shifts, which are a most sensitive tool for recognition of remote steric distortions, we realized the importance of overall conformational relaxation for the observed shielding.[4] ^{13}C NMR shielding variations can be obtained by calculation of intramolecular steric forces F exerted on C–H bonds,[5] but it is necessary to localize the F contributions and to account for the redistribution of steric substituent effects with the aid of a suitable force field.[4] Because of their restricted mobility, cyclohexanes, bridged analogues, and steroids lend themselves as seemingly simple mode models for the evaluation of shielding mechanisms. The present paper is addressed to the impact of full conformational relaxation in these molecules, which contain some classical problems of conformational analysis. The structures were investigated with the Allinger MM1 force field,[2a] which provides rapid access to a large range of compounds, including hetero-substituted ones. Some recognized shortcomings of the MM1 version[6] will not alter the conclusions of the present investigation, which aims more at relative energy distributions than at accurate minima. In view of the particular sensitivity of nonbonded interactions to parametrization ambiguities we have also used an equation for the evaluation of nonbonded steric forces[4] which is based on the Lifson-Warshel force[7] field.

Substituted Cyclohexanes and Bicyclo[2.2.1]heptanes. Strain energy redistribution by relaxation is well known for axial substituted cyclohexanes, where repulsion between the substituent and 1,3-diaxial hydrogens is not solely the destabilizing factor.[5] Although numerical values dissecting the different strain contributions depend on the potential functions and parametrizations used in the force fields,[2,6] it is not disputable that the gauche hydrogen effect between the equatorial hydrogen at Cα (H8 in **1**) and the equatorial hydrogen at Cβ (H9 in **1**) can be a significant factor destabilizing the conformer

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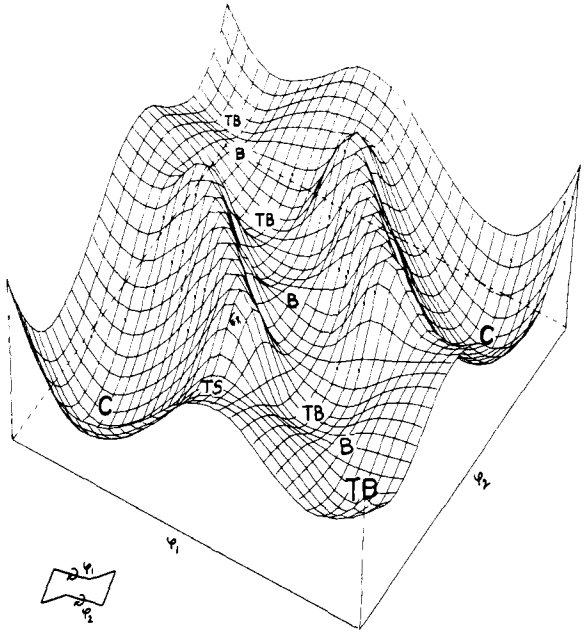
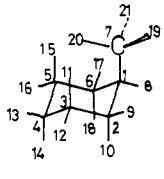


Figure 1. Potential surface of cyclohexane as a function of φ_1 and φ_2 (C, chair; TB, twist boat; B; boat form).

with an axial substituent X. This gauche hydrogen repulsion, however, is sizable only for compounds with bulky substituents; thus the outward bending of CH_3 in **1** will push H8 substantially toward H10/18, thus transmitting a classical reflex effect as found recently with 2,2-dimethylcyclohexanes.[8] Conformational relaxation also is manifested in the quantification of the steric forces F[4] on ^{13}C NMR shielding, where, e.g., for the axial methyl group in cyclohexane only 75% of $\sum F$ on Cγ-H are calculated to be due to the interaction between H20 and H11/15 in **1**. If the "ideal" nonrelaxed structure[5] for **1** is used,



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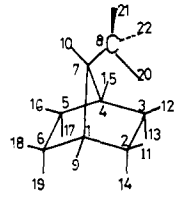

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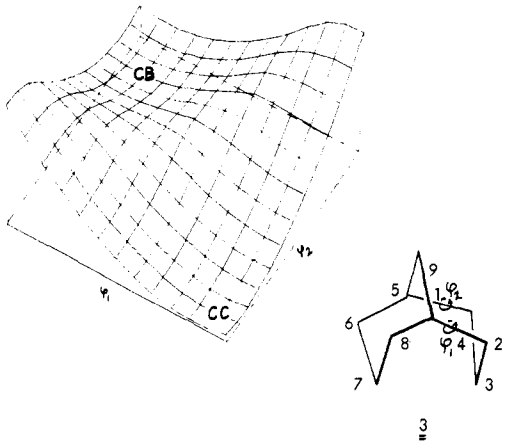
the steric forces obtained on Cγ-H(3/15) are exaggerated by 500% (F = 1.5 mdyn instead of 0.30 mdyn). In the more strained 7-methylnorbornane **2** the analysis of steric forces F on C2/3-H[4] yields an even more delicate balance of single forces after full relaxation of the structure: only 71% stem from "direct" H20···H11/12 interaction, another 40% from C7···H11/12, 12% from C8···H11/12, and −23% from C6···H14 forces. The latter quantity is negative since the relevant angle θ[4] is <90° (55°); for similar reasons ($\theta \simeq 90°$) the interactions H19···H14 are below 2%. Further numerical examples can be found in supplementary tables.[4,9]

Comparison of Cyclohexane and Bicyclo[3.3.1]nonane. The potential surface of cyclohexane itself has been studied with particularly suited force fields[10,11] and no attempt is made to improve the numerical results. Figure 1 aims at visualizing the chair-chair interconversion; transition state TS is obtained by MM1 as slightly twisted half-chair (twist angle φ_{TS} = 10 ± 2.5°, $E_{rel.TS}$ = 10.7 ± 0.1 kcal/mol), the intermediate as twist boat TB with $E_{rel.TB}$ = 5.33 kcal/mol. These values come close to the results of the improved MM2 force field[6a] as well as to Ermer's[11] calculation based on the Lifson-Warshel force field[7] (φ_{TS} 13,[6a] 13°;[11] $E_{rel.TS}$ = 10.5[6a] or 11.07[11] kcal/mol; $E_{rel.TB}$ = 5.5 kcal/mol[6a]).



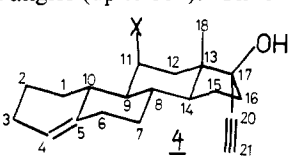
3

Figure 2. Potential surface of bicyclo[3.3.1]nonane as a function of φ_1 and φ_2 (CC, chair-chair; CB, chair-boat forms).

While cyclohexane shows an energy surface with distinct minima and maxima, the picture for bicyclo[3.3.1]nonane is altered in an at first sight unexpected way (Figure 2).[9] Originally we expected for this bicyclic compound an increase of the chair-boat inversion barrier (**3**, CC ⇌ CB)[12] owing to the additional bridge in this cyclohexane which eventually should render twist forms more difficult. The unusual flat surface obtained by the force-field calculation is a direct consequence of conformational relaxation with the aid of the additional bridge which can accommodate considerable twisting under actual relief of torsional strain and nonbonded interactions. Thus the rather low-lying transition state (5 kcal/mol) will be populated with symmetric C_s as well as with strongly twisted C_{2v} forms. Ill-defined energy surfaces must be expected for molecules where conformational relaxation extends over larger parts and in which ground states of higher energy come relatively close to transition states. Some discrepancies between force-field results[13] are in fact due to the occurrence of these flat surfaces.

11β-Substituted Estrenes. Geometries and ^{13}C NMR shifts in these pharmacologically important compounds **4** can be compared to those of axial-substituted cyclohexanes which should provide insight into the conformational transmission of reflex effects between X and axial H or CH_3. ^{13}C shifts of Cα to Cδ (C11, C9, C12, C13, C8, C10, C18) in **4**[9] are similar to those in corresponding cyclohexanes.[8] Exceptions such as stronger deshielding of C11 for X = Me are understandable on the basis of MM1-calculated[9] bond-angle increases (e.g., for Me-C11-C9 by 6°); the same reasoning can be applied to the difference of β effects on C9 and C12.[9] The sterically induced shielding on C8 and C10 provides another test for the correlation with $\sum F$[4] (Figure 3) for which up to ten single F contributions[9] have to be considered.

11β-Substituted lynestrenoles have also been chosen for the present investigation because a series of excellent X-ray analyses for these compounds was available.[14] Comparison of the corresponding internal coordinates in the crystal and the MM1 minimized geometries revealed substantial differences in C-C bond lengths (up to 0.04 Å), CCC bond angles (up to 3°), and torsional angles (up to 10°).[9] The reflex effect of the



4

11β substituents with other axial atoms produces distortions of the C ring chair, characterized by torsional angles of 52° for φ_1 (C9-11-12-13) and of 55° for φ_2 (C8-9-11-12) in the crystal of **4**, X = Me.[9] Since the MM1 calculated geometry

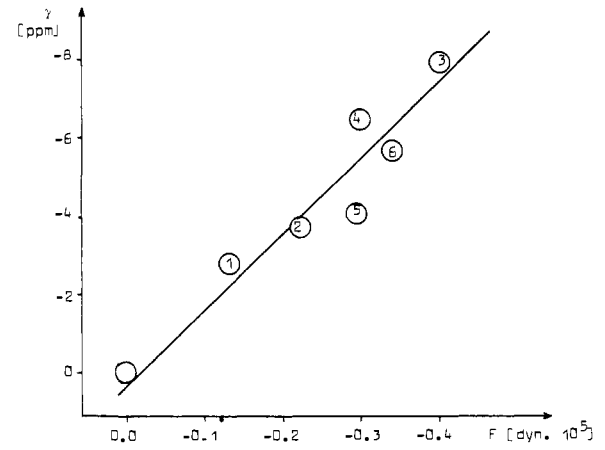


Figure 3. Correlation of methyl group substituent effects on syn-γ-carbon shielding with corresponding steric forces $\sum F$. Points 1, 2, and 3 denote 7-, 2-*exo*-, and 2-*endo*-methylnorbornanes; 4, a methylcyclohexane; 5, C10; 6, C8 in 11β-methyllynestrenole.

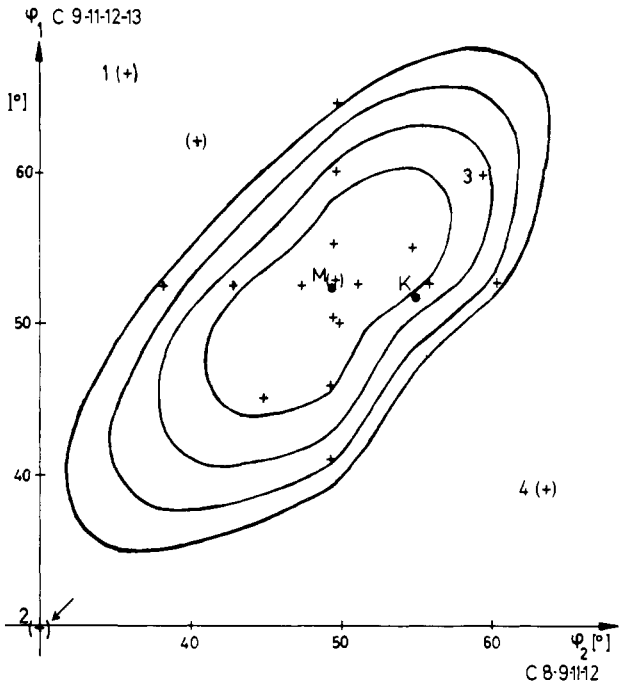


Figure 4. Potential surface of 11β-methyllynestrenole as a function of φ_1, φ_2. K, crystal structure; other explanation, see text. Contour distances 0.5 kcal/mol.

(M in Figure 4) showed 52 (φ_1) and 50° (φ_2) the potential surface was constructed and established a large range of possible conformations with no or small energy differences (Figure 4). The asymmetry of the surface reflects the repulsion between 11β-Me and 13-Me (C18). Reflex effects[15] in cyclohexanes and in steroids[16] can be characterized by the angle ρ[8] between the corresponding axial bonds and are found to be fairly similar (Table I).[9] There is, however, a difference between the cyclohexane and the steroid moiety in that in the more rigid skeleton the angle ρ can be reached by more bond angle and less torsional angle variations.[9] Model calculations on 1,1,3a-trimethylcyclohexane in fact indicate that distortions which require, e.g., 0.94 or 8.61 kcal/mol in the steroid (points 3 or 1 in Figure 4) will require only 0.85 or 5.10 kcal/mol, respectively, in the corresponding 1,1,3a-trimethylcyclohexane model.[9]

The generation of a convex shape on the steroidal β side by the reflex effect of 11β substituents has been found in systematical X-ray analyses[14] and could be related to an increased

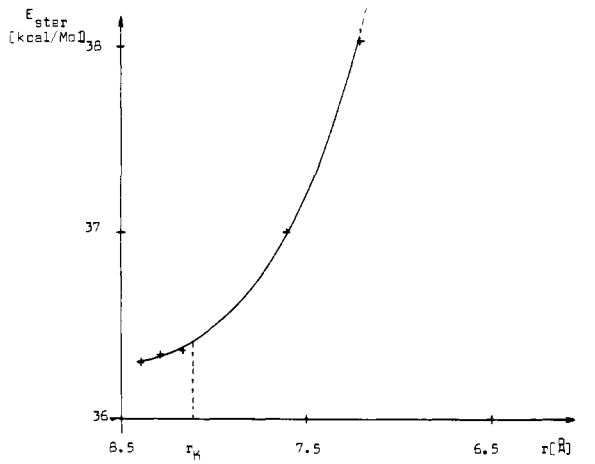


Figure 5. Strain energy in 11β-methyllynestrenole as a function of skeleton bending, characterized by the distance r between 3α-H and C20.

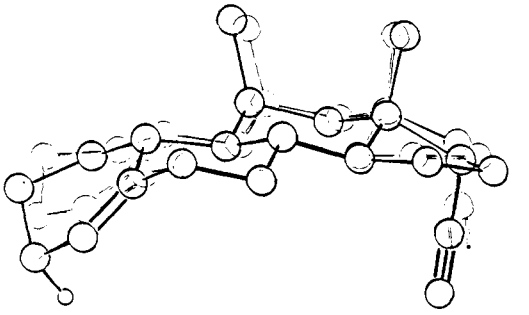


Figure 6. Two forms of 11β-methyllynestrenole differing by only 1.7 kcal/mol.

Table I. Calculated Reflex Angles ρ

	between bonds	parent structure	ρ, deg
lynestrenole, 11βX = H	C13-C18/C11-H	4	11.6
lynestrenole, 11βX = CH_3	C13-C18/C11-CH_3	4	24.4[a]
cyclohexane, 1,1-dimethyl-	C1-CH_3/C3-H11	1	13.4
cyclohexane, 1,1,3a-trimethyl-	C1-CH_3/C3-CH_3[b]	1	29.4

[a] A value of 24.3° is obtained from the crystal structure. [b] CH_3 instead of H11.

binding to the corresponding receptor.[14,17] In order to investigate the energy needed for such an overall bending a computer experiment was designed, in which the strain energy was calculated as a function of the distance r between 3αH and C20 (Figure 5).[9] In the force field minimized structures the distance difference for X = H and X = Me is Δr = 0.095 Å; in the crystal structures, however, Δr = 0.377 Å. Yet the additional strain energy (for Δr = 0.377 Å) would require only 0.1 kcal/mol, and even a strong bending (Δr = 1.2 Å) as depicted in Figure 6 not more than 1.7 kcal/mol. This is much less than the binding energies to steroid hormone receptors (~12 kcal/mol[17]), which consequently could impose substantial bending on the seemingly rigid steroid by an induced fit mechanism.[18]

Conclusions

Conformational relaxation considerably extends the scope of geometries, energies, and interactions to be evaluated in structure/property investigations. This is particularly true for strongly coupled systems such as bicyclic or steroidal compounds and for steric substituent effects which necessarily generate distortions that tend to equilibrate over larger molecular areas. Energy differences between selected geometries

are often very small, even in comparison to vibrational amplitudes, which can lead to serious difficulties in the localization of minimum geometries. The results emphasize the need of explicit crystal lattice energy considerations[19] in the use of X-ray analyses for evaluating conformations or reactivities[20] of "free" molecules. In relating effectors to biological receptors several conformations have to be considered also for seemingly rigid molecules; the then urgent question on the origin of selectivity in biological recognition must be seen against the background of the small energies needed for conformational changes in small molecules under full relaxation.

Experimental and Computational Details

All calculations have been performed in Fortran on the Telefunken TR 440 of the Rechenzentrum der Universität des Saarlandes. The parametrization of the force field is given in the literature.[2a,7] Potential energy surfaces were constructed by interpolation between energy minimized points (denoted "+" in Figure 4) obtained in 10–20° steps of torsional angles (see Figures 1 and 2); some transition states and ground-state minima were traced in 5° steps. The usual limit of 2–5 cal/mol for the minimization was increased to 20 cal/mol in the exploration of higher energy states (Figure 4). Interpolations were performed either manually (Figure 4) or by a program INTERPOL which fits stepwise three energy-minimized points to paraboloid curves.

For the simulation of the steroid bending an artificial attraction function was imposed on **4**, X = Me, between 3α-H and C-20, which had no influence on the strain energy in the minimized structures.

^{13}C NMR spectra were measured in the PFT mode at 22.62 MHz on Bruker instruments HX 90 or WH 90 in $CDCl_3$ as solvent (~20%) and with Me_4Si as internal standard, if not noted otherwise; digital resolution was usually ±0.025 ppm.

Acknowledgments. We are particularly indebted to Professor N. L. Allinger, who helped us with his program and valuable comments. The Deutsche Forschungsgemeinschaft is thanked for financial support, Organon B.V., Oss, Holland, and Dr. F. J. Zeelen for a gift of lynestrenoles. We thank the referees for useful suggestions.

Supplementary Material Available: Tables of steric energy contributions, internal coordinates, steric force contributions, and ^{13}C NMR shifts and figures of a potential surface, reaction profile, and internal coordinates for bicyclo[3.3.1]nonane and of lynestrenols (17 pages). Ordering information is given on any current masthead page.

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