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KINETICALLY AND THERMODYNAMICALLY CONTROLLED SYNTHESIS OF 2,6-DISUBSTITUTED CYCLOHEXANONE SEMICARBAZONES. A MOLECULAR MECHANICS STUDY OF $A^{1,3}$-STRAIN

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Abstract.- Reasonable values for Me-Me, H-Me and Me-H $A^{1,3}$-strain have been evaluated by molecular mechanics calculations on differently substituted methylenecyclohexanes (5.46-6.75, 1.03 and 0.71 kcal/mol[#], respectively). The chair-to-chair inversion barrier of methylenecyclohexanes has also been calculated. Methods are described for the thermodynamic and for the kinetic preparation of acylhydrazones of 2,6-dialkylcyclohexanones. A PMR analysis of the cis and trans-2,6-dimethylcyclohexanone semicarbazones has allowed the determination of the preferred conformers. The results agree with MM results on model hydrocarbons. Finally, a MM study of hydrocarbon models for the antibiotics isocycloheximide, cycloheximide and neocycloheximide points out to a decrease in stability on going from the former to the later, in agreement with the reported experimental results.

INTRODUCTION

Cycloheximide, 1, an antibiotic of the glutarimide family that acts at the ribosome level, is a cis-2,6-disubstituted cyclohexanone derivative[1].

Related with our work on the synthesis of modified biologically active molecules bearing a photoactivable reactive group[2], we are interested in some acylhydrazone derivatives of 1 amenable to be active substrates in aromatic nucleophilic photosubstitution[3,4] and therefore also useful as photoaffinity probes for the identification of active sites in biological receptors[5]. When the synthesis of 2, which fulfils the above conditions, was attempted, we found unexpected difficulties. Johnson and Duquette[6] have reported that the more stable cis-2,6-dialkylcyclohexanones, **3a**, were converted into their less stable trans-isomers, **3b**, by semicarbazone formation followed by decomposition of these derivatives with nitrous acid. In their conditions, 2,6-cis-disubstituted cyclohexanones produce largely the semicarbazone of the trans isomers, and they justified this result by the strong allylic interaction ($A^{1,3}$-strain) that should exist in the cis-semicarbazone isomers. After some preliminary experiments we felt that something similar could happen, among other things, in the case of 1 giving rise to isomerizations.

The influence of allylic strain interactions of $A^{1,3}$ type in the shapes and even in the reactivity of six-membered rings is well documented in the chemical literature[7]. This $A^{1,3}$-strain is considered to be largely due to steric hindrance. However, very recently electrostatic repulsion has been included[8], the scope of such extension being obviously limited to molecules containing polar substituents. As far as we know, no molecular mechanics calculations (MM) have been carried out on this subject. With such powerful computational technique (MM)[9] available as a new tool for stereochemical analysis, it is now feasible to study explicitly the effects of intramolecular

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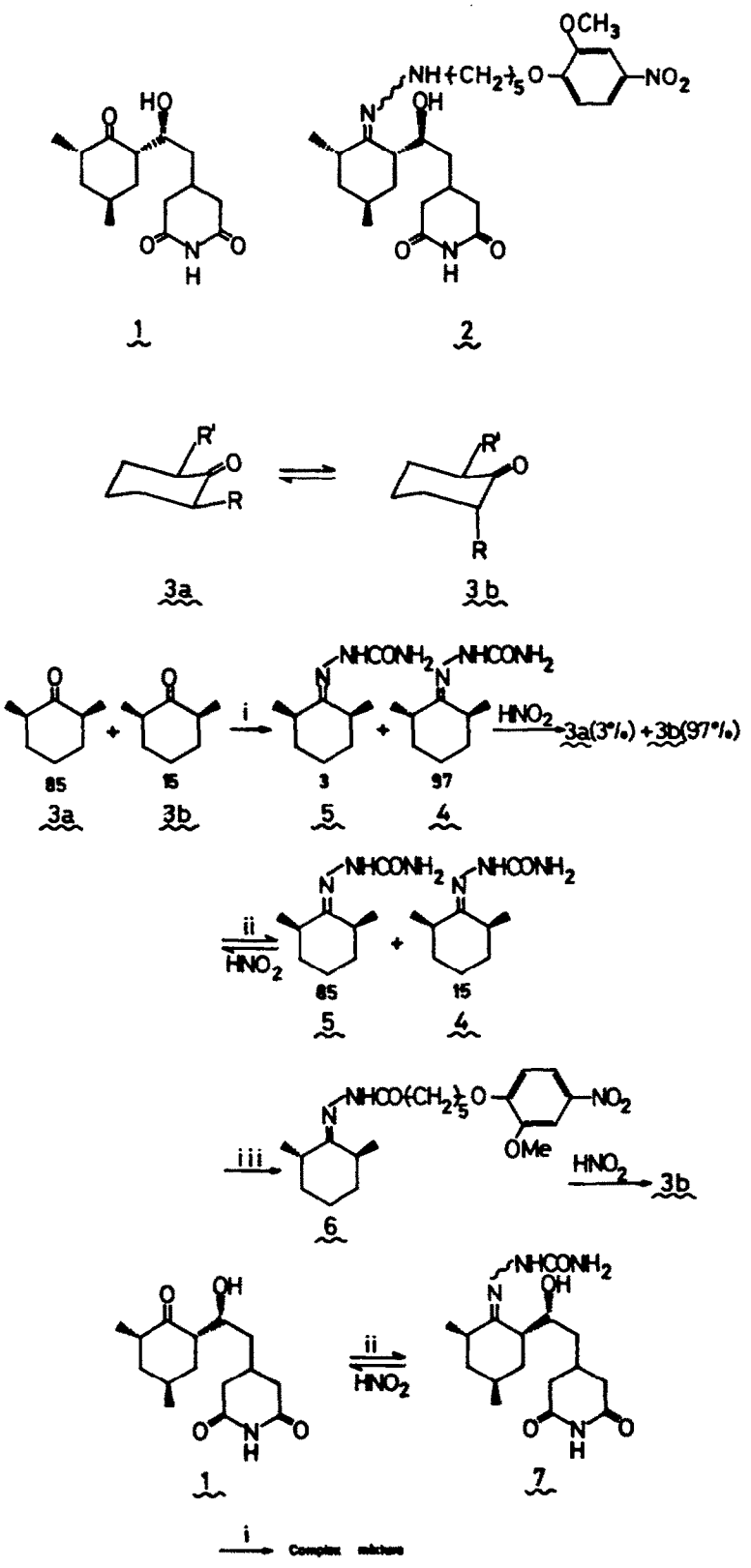
[#]1 kcal = 4.18 kJ.



i: Semicarbazide Hydrochloride, MeOH/KOAc (stoichiometric), reflux 18h.

ii: Semicarbazide hydrochloride, MeOH/H_2O/NaOAc(excess)/pH 5, r.t., 3h.

iii: 11, MeOH/AcOH, reflux 18h.

SCHEME - 1

long-range non-bonded interactions on molecular properties.

Therefore it appeared of interest to carry out a series of MM calculations for methylenecyclohexanes differently substituted with methyl groups, in order to obtain a reliable estimation of the Me-Me $A^{1,3}$-strain magnitude in these systems. The influence of Me-Me $A^{1,3}$-strain in the chair-to-chair interconversion barriers for six-membered carbocyclic rings was studied as well. Calculations were also extended to some models of the antibiotic cycloheximide, **1**.

With all its shortcomings, due to the change of nitrogen atoms by carbons (MM2 is not parameterized for carbon-nitrogen double bond), we believe that our calculation results show a clear trend in complete agreement with the experimental results about cis-trans isomerizations observed in the preparation reactions of acylhydrazones of 2,6-dimethylcyclohexanone and cycloheximide. Our model calculations are even consistent with some spectral PMR features of these molecules.

EXPERIMENTAL RESULTS

The semicarbazone of trans-2,6-dimethylcyclohexanone, **4**, was obtained from a comercial mixture of cis- and trans-2,6-dimethylcyclohexanones (85:15 by g.l.c.) following Johnson's procedure[6] (thermodynamic conditions). However, the use of buffered media and room temperature (see experimental part) gave rise to a 85:15 mixture of cis and trans-2,6-dimethylcyclohexanone semicarbazones (**5** and **4** respectively) (kinetic control), showing that no isomerization had taken place (Scheme 1). From this mixture, pure **5** was obtained by recrystallization. The two semicarbazones were completely characterized and the respective percentage of formation in both reactions confirmed by decomposition with nitrous acid[6] and comparison (g.l.c.) of the resulting cyclohexanones with authentical samples. The PMR chemical shifts in different solvents for the C2 and C6 methyl groups of these semicarbazones are reported in Table 1. The PMR spectra of **4** and **5** did not show any sign of coalescence when the temperature was raised up to 135°C, using a mixture of α-chloronaphthalene/DMSO-d_6 or pure DMSO-d_6 (for **4** and **5**, respectively).

Using buffered media and room temperature we could also prepare the semicarbazone **7**[10]. Although this product was already reported, the literature does not give any spectral data, and considering the results just described for the 2,6-dimethylcyclohexanones we felt it necessary to demonstrate that the resulting product was trully the semicarbazone of **1** (**7**) and not that of any of its isomers isocycloheximide **8** or neocycloheximide **9** (see Scheme 6). Specially the semicarbazone of **9** would exhibit very similar spectral properties. The PMR spectrum of our product showed two doublets centered at δ 0.84 and 0.92 corresponding to two methyl groups. Decomposition of this product with nitrous acid[6] rendered a ketone which was identified as **1** by double irradiation experiments and by comparison with an authentical sample.

Table 1.- PMR spectral data of prepared acylhydrazones.

Product nº	Solvent	Chemical Shifts (δ) 2-CH_3	6-CH_3	4-CH_3
4	$CDCl_3$	1.11	1.07	---
	DMSO-d_6	1.03[a]		---
	α-chloronaphthalene/DMSO-d_6 [b]	1.07[c]	1.04[c]	---
5	$CDCl_3$	1.17		---
	DMSO-d_6	1.12[c]	1.04[c]	---
6	$CDCl_3$	1.10	1.04	---
	DMSO-d_6	1.03[a]		---
7	DMSO-d_6	---	0.84	0.92

[a] Some splitting of the bands could be observed indicating the presence of two doublets.
[b] One to one ratio.
[c] No coalescence was observed rising the temperature up to 135°C.

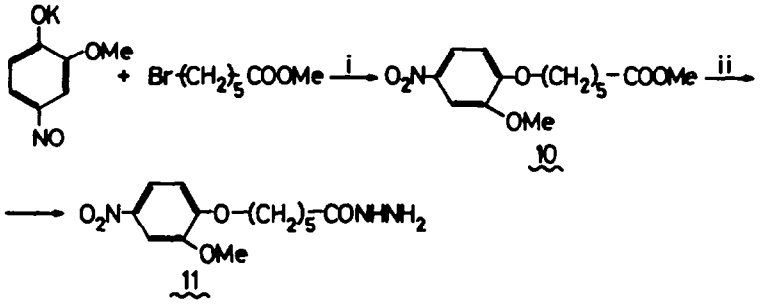
The 6-(2-methoxy-4-nitrophenoxy)hexanoic acid hydrazide, 11, needed to prepare the photoactivable derivative 2, was prepared following standard procedures as shown in Scheme 2.

Reaction of 11 with 2,6-dimethylcyclohexanone (cis/trans 85:15) following Johnson's conditions[6] (thermodynamic control) gave rise to trans-2,6-dimethylcyclohexanone acylhydrazone 6 (Scheme 1). Treatment of 6 with nitrous acid rendered trans-2,6-dimethylcyclohexanone, 3b. However, we were unable to find in this case kinetic conditions that lead to the cis acylhydrazone due to solubility problems. All the attempted reactions gave 6 as the major product. Also attempts to prepare compound 2 were unsuccessful.

COMPUTATIONAL RESULTS

Technique.-

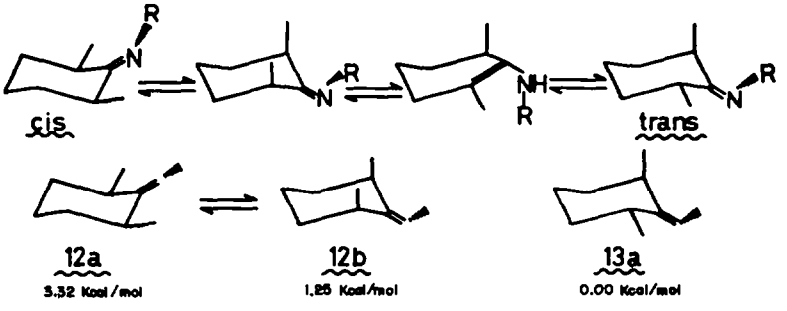
A modification (MM2')[11] of Allinger's latest force field MM2[12] was used through this work. Although this force field has not been parameterized neither for the C=N nor for the N-N functions, and consequently can not handle semicarbazones, we took the corresponding hydrocarbons cis and trans-2,6-dimethylethylidenecyclohexane, 12 and 13, respectively, as models for the kinetically and thermodynamically obtained semicarbazones of 3 (R=R'=Me) with the aim of evaluating the $A^{1,3}$-strain existing in 2-substituted cyclohexanone derivatives (see Scheme 3).



i: DMF, 72h, r.t., 89% yield.

ii: 80% Hydrazine, r.t. 82h, 98%

SCHEME-2



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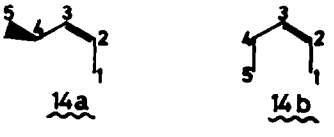


Parameters corresponding to sp^2 carbon atom and to C=O were transferred untouched from MM2. Torsional energy surfaces were covered by driving bonds at a constant interval of 10° using our highly automated version of MM2 program[13]. Finally, the original data points were fit into a smoothed surface using a program based on spline functions[13].

Molecular Mechanics Calculations.-

Evaluation of the Me-Me $A^{1,3}$-strain: In his review[7], Johnson defined the $A^{1,3}$-strain as the interaction existing in molecules having "groups syn to one another on the C-1 and C-3 positions of an allylic (A) system" (like in **12a**) (see Scheme 3) and also states that when these groups "are moderate in size they will interfere each other drastically, in fact more so than if they were 1,3-diaxially related in a cyclohexane ring".

No good estimate for the Me-Me $A^{1,3}$-strain has been yet published, mainly because of the lack of good computational methods until now. Two estimations[7] were placed at 4.5 and 1 kcal/mol although qualitative experimental results seemed to agree with a somewhat intermediate value[7].

The simplest compound possesing a Me-Me $A^{1,3}$-strain interaction is cis-2-pentene, **14**, but the evaluation of such interaction in **14** must be done in a quite unrealistic situation: a semi-circular and planar conformation, **14b**, which should be a saddle point in its conformational energy surface, the global minimum being the conformation **14a**. By constrain of 2-3-4-5 torsional angle in a zero degrees conformation and allowing to minimize all other variables, we can calculate the steric energy for **14b**. Comparison of calculated steric energies for **14b** and **14a** (4.59 and 1.10 kcal/mol, respectively) gives out a value of 3.49 kcal/mol for Me-Me $A^{1,3}$-strain. The presence of this strain in **14b** is obvious and, as a consequence, the MM calculated structure for **14b** presents a rather distorted geometry (skeletal C-C-C bond angles are: 1-2-3=130.7°, 2-3-4=132.5° and 3-4-5=120.5°). However, 3.49 kcal/mol is a smaller value than the experimentally obtained pure Me-Me 1,3-diaxial interaction in cyclohexane rings (3.7 kcal/mol)[14], thus, producing an impossibility to shift the **12a** ⇄ **12b** equilibrium to the right hand side.

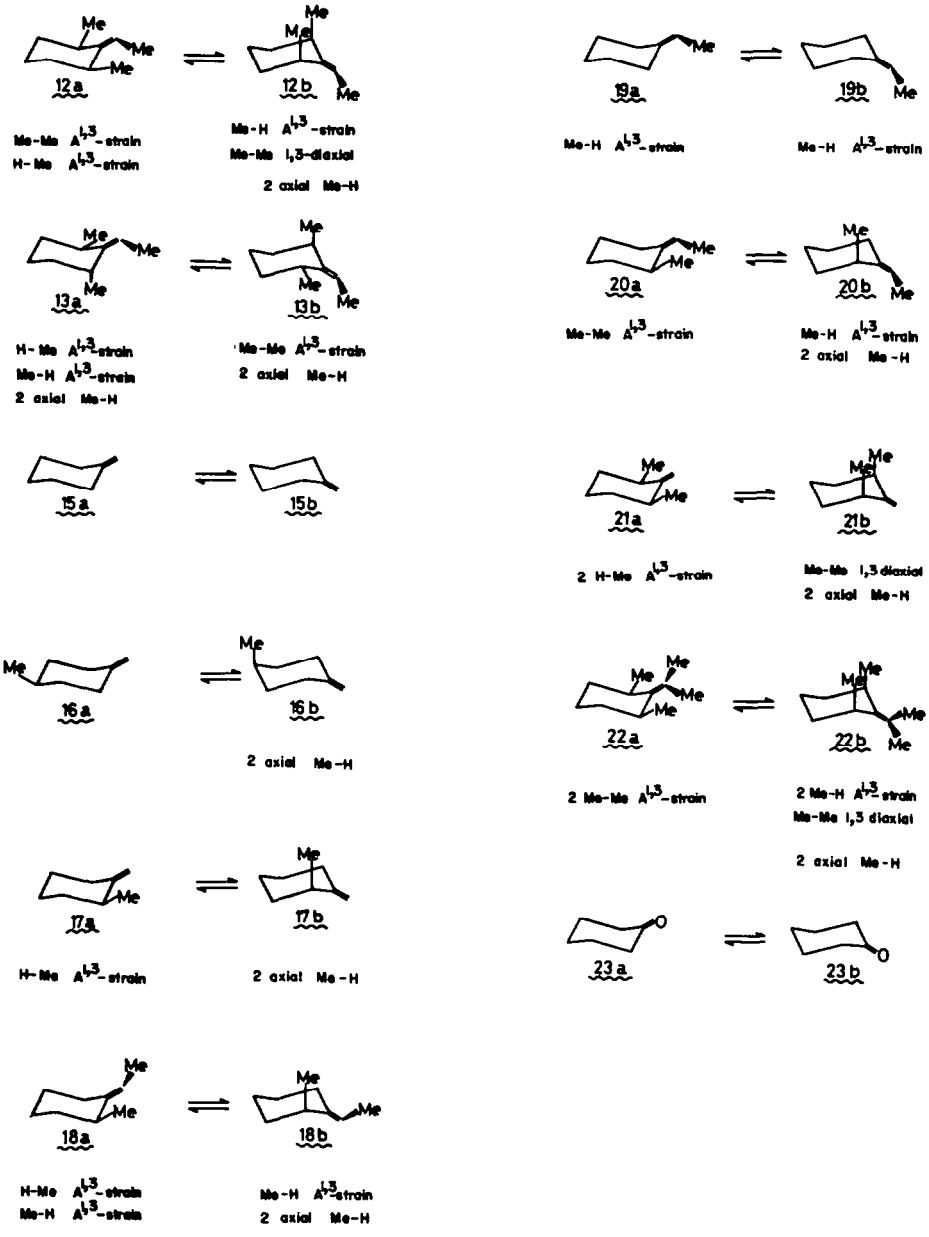
Since according to Johnson[7] Me-Me $A^{1,3}$-strain may force a chair cyclohexane ring to interconvert into its another chair conformer with axial substituents (see **12b**), it is important to evaluate the methyl conformational energy in methylenecyclohexane systems (Scheme 4). MM2' perfectly reproduces the methyl conformational energy in methylcyclohexane obtained by dynamic NMR (experimental[15]: 1.74 0.06 kcal/mol, calculated[11]: 1.74 kcal/mol), thus, we may assume a good performance in **16** as well. Our MM2' calculated energy difference between equatorial- and axial-4-methylmethylenecyclohexane, **16**, due to two Me-H axial interactions, is 1.70 kcal/mol (Scheme 4). This slightly smaller calculated value compared to methylcyclohexane is produced by the flattening[16] of the ring in **16b**, opening the axial substituent and thus making the position energetically less disfavoured than in cyclohexane.

However, equatorial-2-methylmethylenecyclohexane, **17a**, is more stable than its axial isomer **17b** by only 0.67 kcal/mol. Since the major steric interactions existing in **17** are one H-Me $A^{1,3}$-strain in **17a** and two axial Me-H in **17b**, it can be deduced that H-Me $A^{1,3}$-strain is 1.03 kcal/mol (1.70 minus 0.67 kcal/mol).

This H-Me $A^{1,3}$-strain seems to be slightly larger when E-2-methylethylidenecyclohexane, **18**, is considered (1.70-0.40=1.30 kcal/mol) as a consequence of the presence of one Me-H $A^{1,3}$-strain in each conformer, which makes it difficult to dissipate strain by distorsion of the exocyclic double bond. The Me-H $A^{1,3}$-strain can be estimated by comparing steric energies between **17a** and ethylidenecyclohexane, **19**; Me-H $A^{1,3}$-strain is 0.32 kcal/mol lower in energy than H-Me $A^{1,3}$-strain. Since heretofore H-Me $A^{1,3}$-strain is considered to be 1.03 kcal/mol, Me-H $A^{1,3}$-strain is given a value of 0.71 kcal/mol.

The estimation of Me-Me $A^{1,3}$-strain can be easily deduced from Z-2-methylethylidenecyclohexane, **20**. Since **20a** is 3.05 kcal/mol less stable than **20b**, Me-Me $A^{1,3}$-strain is, then, equal to 5.46 kcal/mol (3.05+1.70+0.71 kcal/mol). When the same procedure is applied to compound **13** a value of 6.32 for Me-Me $A^{1,3}$-strain is obtained (4.58+1.03+0.71 kcal/mol).

The pure Me-Me 1,3-diaxial interaction in methylenecyclohexane can be considered to be equal to 2.65 kcal/mol, value calculated from cis-2,6-dimethylmethylenecyclohexane, **21** (2.29+(2x1.03)-1.70



Compound	Conformer a	(%)	Conformer b	(%)
12	2.07	(2.94)	0.00	(97.06)
13	0.00	(99.94)	4.58	(0.04)
16	0.00	(94.65)	1.70	(5.35)
17	0.00	(75.64)	0.67	(24.36)
18	0.00	(66.28)	0.40	(33.72)
20	3.05	(0.57)	0.00	(99.43)
21	0.00	(97.96)	2.29	(2.04)
22	7.74	(0.00)	0.00	(100.00)

Scheme 4.- Main interactions[a] and relative steric energy for the a and b conformers of compounds 12, 13, 16, 17, 18, 20, 21 and 22 as calculated by MM2'. Entropy contributions have been neglected in the calculation of percentages.

[a]Regarding $A^{1,3}$-strain the first symbol refers to the double bond substituent while the second to the ring substituent, i.e., H-Me means a H in the exocyclic double bond and a Me group in the ring.

kcal/mol). Thus, Me-Me $A^{1,3}$-strain in cis-2,6-dimethylisopropylidenecyclohexane, 22, achieves a value of 6.75 kcal/mol ((7.74+2.65+1.70+(2x0.71))/2 kcal/mol).

The Me-Me $A^{1,3}$-strain is larger than 1,3-diaxial Me-Me interaction in methylenecyclohexanes as can be deduced from the mentioned data. However, we must add two H-Me axial interactions (1.70 kcal/mol) to the pure Me-Me diaxial one (2.65 kcal/mol), giving rise to a global steric energy difference of 4.35 kcal/mol. Consequently, one may expect the **b** conformer to be more stable than **a** in 12, compound which may be taken as the hydrocarbon model of one of the studied semicarbazones, 5. In fact, **12b** is calculated to be 2.07 kcal/mol lower in energy than **12a** (Scheme 4). Therefore, Me-Me $A^{1,3}$-strain will be 6.10 kcal/mol in this system (2.07+2.65+1.70+0.71-1.03 kcal/mol).

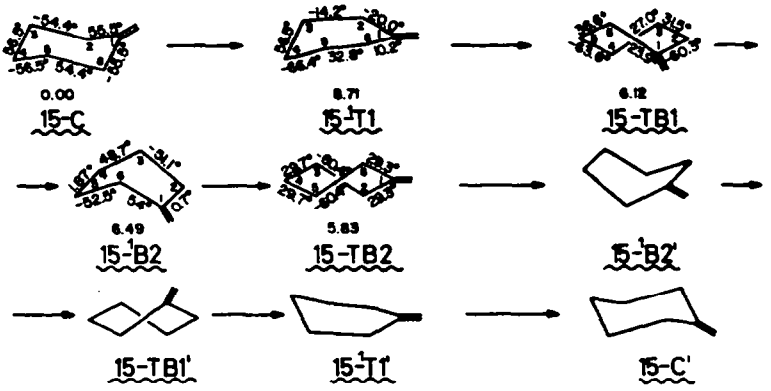
Probably, a range of values such as 5.46-6.75 kcal/mol is the best estimate for the Me-Me $A^{1,3}$-strain interaction in methylenecyclohexanes,in view of the recognized large uncertainties in the additivity of intramolecular steric interaction energies[9].

Torsional energy surface calculation: With the aim of testing the possibility of experimental studies on the conformational behaviour of our acylhydrazones using dynamic NMR methods, we undertook torsional energy surface calculations in order to evaluate the **a** ⇕ **b** interconversion barriers of our methylenecyclohexane models.

The accuracy of MM calculations has been fully demonstrated in the reproducibility of rotational barriers about $C(sp^3)$-$C(sp^3)$ bonds, mainly in acyclic molecules[11,17]. MM2' fairly reproduces the inversion barrier in cyclohexane itself[11] as well as in some other six-membered rings[11,18].

However, not so much has been done in the case of methylenecyclohexane, 15, which exists in a chair conformation having a measured $\Delta H^{\neq}$ for the ring inversion[19] of 8.6 kcal/mol. Anet and coworkers[20] studied the ring inversion process in 15 by means of MM calculations following Boyd's procedure[21]. Its calculated $\Delta H^{\neq}$=8.1 kcal/mol is slightly lower than the experimental (8.6 kcal/mol) while our MM2' calculations give 8.71 kcal/mol.

The torsional energy surface for the interconversion process of 15 was covered following Ōsawa's procedure[22], i. e., an initial coverage by using the two-bond drive technique[13] completed with a total analysis of all stationary points by using BIGSTRN-3 program[23]. Driving two opposite bonds (ω_{23}=1-2-3-4 and ω_{56}=1-6-5-4) proved satisfactory for the present purpose[24]. Ring inversion in six-membered rings usually proceeds via twist-boat conformers[25a] and by producing an asymmetric deformation of the chair conformer. However, in 15, results of the second step suggest the most favoured path under MM2' force field is likely to be that in which both driven bonds, ω_{23} and ω_{56}, move almost simultaneously (Scheme 5), passing through a transition state, 15-^{1}T1 (ω_{23}= 14°,



Scheme 5.- Endocyclic dihedral angles (degrees) and relative steric energy (kcal/mol) for the different stationary conformers in the chair-to-chair interconversion pathway for methylenecyclohexane, 15, as calculated by the tandem MM2'-BIGSTRN3. Upper indexes indicate the number of negative vibrational frequencies (eigenvalues) of each conformer (no number means zero).

ω_{56}= 32°, where C-C(=C)-C-C dihedral angles deviates from zero and leading to a twist-boat conformer, 15-TB1, which in turn will undergo pseudorotation to achieve its equivalent 15-TB1' conformer and from there through 15-^{1}T1' to 15-C'. This fact does not correlate with the ring inversion process of cyclohexanone 23 which has been said to proceed via a symmetric path[25], where C-C(=O)-C-C dihedral angles are nearly zero.

We have also extensively studied the conformational behaviour of 13 by calculating a few torsional energy surfaces[26] only under the first step. The calculated barrier for the chair-to-chair interconversion process was ca. 8.6 kcal/mol, too low as to be able to freeze the equilibrium in our available experimental conditions. A very similar value was obtained for 12 (8.0 kcal/mol).

Calculations on cycloheximide type models.-

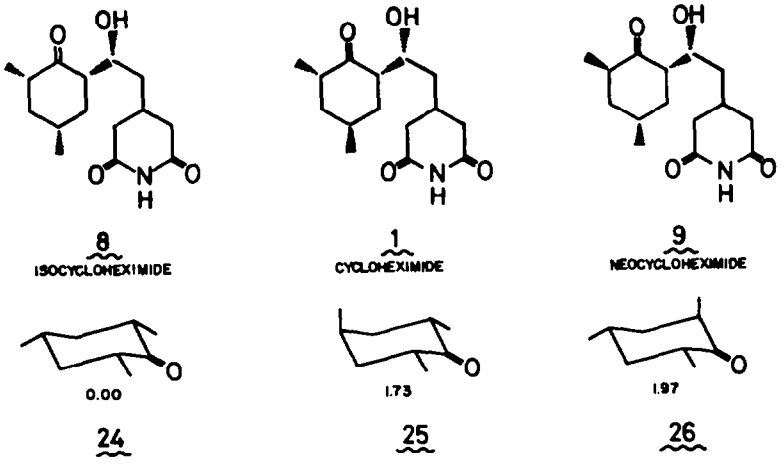
Compound 1 may be seen as a trisubstituted cyclohexanone. MM calculations on three different 2,4,6-trimethylcyclohexanones, 24, 25 and 26 (Scheme 6), used as models of 8, 1 and 9 corroborate experimental results which indicate that on isomerization conditions both 1 and 9 yield 8[1]. The Scheme 6 includes relative steric energies for these three models.

Obviously, the 1.73 kcal/mol difference between 25 and 24, arises from methyl conformational energy. However, it is not so clear what the reason is for the 0.24 kcal/mol separating 26 from 25. A detailed analysis of the geometries and structures of 25 and 26 as calculated by MM2' allows us to affirm that the difference comes from the torsional term since an axial methyl on C-2 of 26 causes the ring to become more flattened than if it were on C-4 (Table 2). Moreover, the stabilization gained by the existence of a dihedral angle Me-C2-C1=O to near zero (4.69°) in 25, is replaced in 26 by the destabilization caused by the axial methyl (Me-C2-C1=O dihedral angle is -104.12°)[27].

Table 2.- Structural features (dihedral angles) for compounds 25 and 26 as calculated by MM2'.

Compound	Endocyclic angles[a] (°)	Me-C2-C1=O (°)
25	-52.77, 53.05, -55.07, 55.07, -53.05, 52.77	4.69
26	-50.72, 51.81, -56.24, 56.90, -53.61, 51.88	-104.12

[a]Endocyclic dihedral angles are given in the following sequence: 1-2-3-4, 2-3-4-5, 3-4-5-6, 4-5-6-1, 5-6-1-2 and 6-1-2-3.

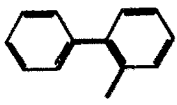


Scheme 6.- Relative steric energy (kcal/mol) for isocycloheximide, cycloheximide and neocycloheximide models 24, 25 and 26, as calculated by MM2'.

Comments on the calculation results.-

The usefulness of MM calculations on dealing with problems produced by long range non-bonded g(+)-g(-) interactions of the 1,5-type has been largely recognized[28]. The $A^{1,3}$-strain interaction is just a special case of the wide group of non-bonded interactions. The 1,4-type covers H-Me and Me-H $A^{1,3}$-strain, while the Me-Me $A^{1,3}$-strain is included into the 1,5-type. The latter case is specially stronger than the usual 1,5-type since the presence of the double bond helps to keep the geometry of the system nearly planar. This is very similar to the situation found in 2-methylbiphenyl 27 (Scheme 7) where the interaction is so strong that forces the rings to scape from planarity. In our system 20 the non planarity is achieved by cyclohexane ring inversion.

MM calculations carried out for differently substituted methylenecyclohexanes show that Me-Me $A^{1,3}$-strain existing in these molecules is very important, its magnitude being at least 2.81 kcal/mol larger than pure 1,3-diaxial Me-Me interaction (5.46-6.75 for Me-Me $A^{1,3}$-strain and 2.65 for 1,3-diaxial Me-Me interactions in methylenecyclohexanes). As a result of this interaction compound 22 is predicted to non exist in a chair conformation with 1,3-diequatorial methyl groups; possibly the most stable conformation would be neither 22a nor 22b but a twist boat, which would relieve the repulsive Me-Me interaction in both forms shown.



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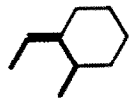

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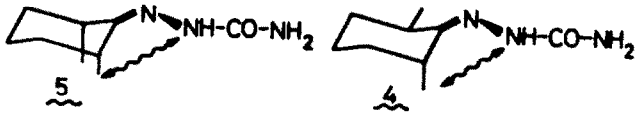
Scheme 7.- Two analogue examples of long-range non-bonded interactions of the 1,5-type: 2-methylbiphenyl, 27, and 2-methylethylidenecyclohexane, 20.

CONFORMATIONAL ANALYSIS OF cis- AND trans-2,6-DIMETHYLCYCLOHEXANONE SEMICARBAZONES, 5 AND 4.

The comparison between the computation results for 12 and 13 and the observed cis-trans isomerization between 5 and 4 when their preparation is carried out under thermodynamic conditions[29] confirm our assumption that at least qualitatively we can take 12 and 13 as hydrocarbon models for 5 and 4, respectively.

The PMR spectral behaviour of the semicarbazones 4 and 5 (see Table 1) shows a great dependence of the chemical shifts on the solvent polarity. This is extreme in the cis isomer 5 since only a doublet (for both methyls) is observed when the spectrum is recorded at 80 MHz using $CDCl_3$ as solvent, while two differenciated doublets appear in DMSO-d_6. MM model calculations for cis-2,6-dimethylethylydenecyclohexane, 12, indicate that the diaxial conformer will be more stable than the diequatorial one by 2.07 kcal/mol. If, as expected, these situation holds for the corrsponding semicarbazone 5, the PMR spectral behaviour can now be explained since the two methyl groups will be far away from the nitrogen substituent (cause of the asymmetry) in the diaxial case. Different chemical shift will be only observed in a strongly solvating solvent that increases the two methyls diastereotopic character by asymmetric solvation of the molecule (Scheme 8).

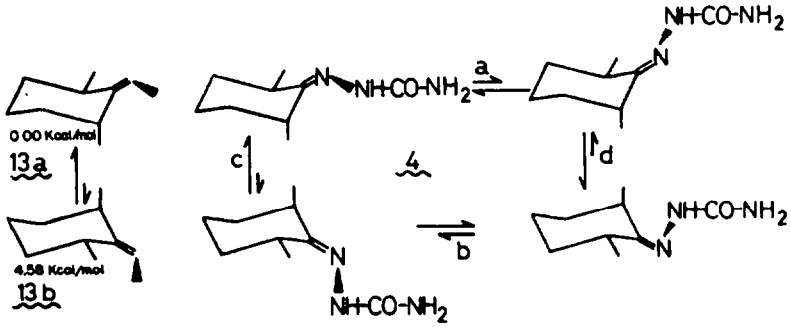


5 4

SCHEME - 8

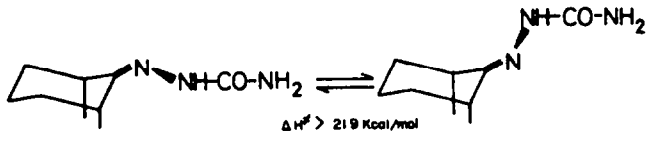
The result is opposite in the trans case **4** (see Table 1) where the two methyls became almost magnetically equivalent (in PMR in DMSO-$\underline{d}_6$). MM calculations for trans-2,6-dimethylethylidenecyclohexane **13** show the conformer **a** to be more stable than **b** by 4.58 kcal/mol. This value is large enough to expect a paralel situation in **4**. The possible conformational equilibria for the semicarbazone **4**, are shown in Scheme 9.

Considering the conformational equilibria shown in scheme 9, the chemical shifts variations on going from $CDCl_3$ to DMSO-$\underline{d}_6$ as solvents in the spectrum can as well be rationalized by asymmetric solvation in the semicarbazone molecule. In this case the $NHCONH_2$ group causing the asymmetry in the molecule is closer to the axial methyl group (downfield in PMR) than to the equatorial one (upfield in the PMR). Therefore, the effect caused by solvation in a very polar solvent like DMSO will be stronger upon the axial than upon the equatorial methyl group. In general, the observed effect of DMSO-$\underline{d}_6$ with respect to $CDCl_3$ is an upfield displacement of chemical shifts[1] (Table 1) larger (0.08 ppm) for the axial methyl group than for the equatorial one (0.04 ppm) in our particular case. Similar results were obtained for the trans-acylhydrazone **6** (Table 1).



SCHEME - 9

Finally, the 2,6-dimethylcyclohexanone semicarbazones were interesting substrates to measure the nitrogen inversion barrier in this type of products. The PMR spectra of semicarbazone **5**, in DMSO-$\underline{d}_6$ did not show any sign of coalescence by increasing the temperature up to 135°C (the maximum we could reach with our NMR spectrometer). Therefore, the nitrogen inversion barrier must be higher than 21.9 kcal/mol[30] in good agreement with the reported values for related products[31] (Scheme 10).



SCHEME - 10

The nitrogen inversion barrier for **4** should be similar if not higher than the one for semicarbazone **5**. No coalescence was neither observed up to 135°C in this case (DMSO-d_6/α-chloronaphthalene as solvent); the barrier being higher than[30] 22.7 kcal/mol. This points out that the c and d equilibria in Scheme 9 can be considered isolated.

EXPERIMENTAL

All the melting points are uncorrected. PMR spectra were recorded at 80 MHz and CMR spectra at 20 MHz both on a Bruker WP80SY spectrometer using TMS as internal standard. Mass spectra were recorded on a Hewlett-Packard 5985B mass spectrometer. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The g.l.c. analyses were performed on a Hewlett-Packard 5830A gas chromatograph with a SE-30 column. Distilled commercial 2,6-dimethylcyclohexanones (as a mixture of 85:15 cis to trans ratio by g.l.c.) were used in our reactions. Calculations were performed in a VAX-11/780 computer in the computing center of this University.

Trans-2,6-dimethylcyclohexanone semicarbazone **4**.

Compound **4** was prepared from 2,6-dimethylcyclohexanone (85:15 cis to trans ratio) following Johnson's[6] procedure. M.p. 191.5-192.5°C (from methanol) (Lit.[6] m.p. 192-194°C). IR (KBr): 3440, 3230, 3180, 3120, 1680, 1565 cm^{-1}. PMR ($CDCl_3$): 1.07 (d, J=6 Hz, 3H), 1.11 (d, J=7.5 Hz, 3H), 1.3-2.1 (m, 6H), 2.4 (m, 1H), 2.90 (m, 1H), 5.45 (broad singlet, 2H), 7.83 (s, 1H). PMR (DMSO-d_6): 1.03 (d, J=7.5 Hz, 6H), 1.2-2.0 (m, 6H), 2.14-2.66 (m, 2H), 6.12 (s, 2H), 8.1 (s, 1H). CMR (DMSO-d_6): 16.2, 17.0, 19.9, 28.1, 31.9, 33.6, 35.9, 157.6, 157.9. This product was contaminated with a 3% of the isomer **5**.

cis-2,6-Dimethylcyclohexanone semicarbazone **5**.

3.370 g (0.027 mole) of 2,6-dimethylcyclohexanone (85:15 cis to trans ratio) in 38 ml of methanol were added to a mixture of 7.52 g (0.067 mole) of semicarbazide hydrochloride and 9.78 g (0.012 mole) of anhydrous sodium acetate in 38 ml of water. The mixture was kept at room temperature for 3 h. Upon addition of water, a precipitate appeared which was filtered and washed with cool methanol and ether, to give 4.036 g (83% yield) of a mixture of semicarbazones **4** and **5**. 2.2 ml of acetic acid and 2.2 ml of a solution of 4.4 g of sodium nitrite in 20 ml of water were added to 0.402 g (2.19 mmole) of this mixture of **4** and **5**. The mixture was kept at 0°C with stirring for 15 min. The solution was then extracted with methylene chloride and the organic layer washed with a saturated sodium bicarbonate solution and water successively, dryed over sodium sulfate and evaporated to give 0.249 g (90% yield) of a mixture of isomers of 2,6-dimethylcyclohexanone. G.l.c. analysis of this mixture and comparison with the g.l.c. analysis of the starting 2,6-dimethylcyclohexanone mixture showed both to be practically identical (85:15 cis to trans ratio).

Pure **5**, m.p. 184-186°C resulted from two recrystallizations in methanol. IR (KBr): 3410, 3300, 3160, 3070, 1670, 1645, 1550 cm^{-1}. PMR ($CDCl_3$): 1.17 (d, J=7.5 Hz, 6H), 1.3-2.1 (m, 6H), 2.17-3.1 (m, 2H), 5.6 (broad singlet, 2H), 8.0 (s, 1H). PMR DMSO-d_6: 1.04 (d, J=6.5 Hz, 3H), 1.12 (d, J=7.5 Hz, 3H), 1.55 (m, 6H), 3.0 (m, 2H), 6.17 (s, 2H), 9.03 (s, 1H). CMR (DMSO-d_6): 15.3, 17.2, 20.4, 27.7, 29.9, 30.7, 35.7, 156.7, 157.2 (Found: C, 58.97; H, 9.22; N, 22.83; Calc. for $C_9H_{17}N_3O$: C, 58.99; H, 9.35; N, 22.83%).

Cycloheximide semicarbazone **7**.

A solution of 1.0 g (8.97 mmole) of semicarbazide hydrochloride and 1.3 g of anhydrous sodium acetate in 5 ml of water was added dropwise to 1.0 g (3.55 mmole) of cycloheximide **1** in 5 ml of methanol. The mixture was left 1 h under stirring at room temperature. The white precipitate was filtered and washed with cold methanol and ether rendering 1.09 g (91% yield) of cycloheximide semicarbazone **7**, m.p. 179-180°C (Lit.[10] 182-183°C). IR (KBr): 3550, 3460, 3280, 3220, 3050, 1690, 1575 cm^{-1}. PMR ($CDCl_3$): 0.84 (d, J=5.3 Hz, 3H), 0.92 (d, J=5.7 Hz, 3H), 1.05-3.25 (m, 14H), 3.65 (broad singlet, 1H), 4.74 (m, 1H), 6.15 (s, 2H), 9.07 (s, 1H), 10.59 (s, 1H). CMR (DMSO-d_6): 16.8, 21.2, 22.0, 26.6, 27.8, 34.8, 36.6, 38.4, 39.5, 40.1, 50.2, 66.8, 153.6, 157.4, 173.1, 173.2.

Cycloheximide semicarbazone **7** was decomposed with nitrous acid following the procedure described previously (see decomposition of **5**) affording pure cycloheximide (65%).

Methyl 6-(2-methoxy-4-nitrophenoxy)hexanoate **10**.

20.33 g (0.097 mole) of methyl 6-bromonexanoate were added to a solution of 22.65 g (0.093 mole) of potassium 2-methoxy-4-nitrophenoxide dihydrate[32] in 140 ml of DMF. The mixture was stirred at 100°C for 3 days. Then the orange solution was poured on 1400 ml of ice-water with stirring. The precipitate was filtered and dryed rendering after recrystallization from methanol 24.61 g (89% yield) of product **10**, m.p. 61-62°C (from methanol). IR (KBr): 1730, 1585, 1510, 1335 cm^{-1}. PMR ($CDCl_3$): 1.34-2.17 (m, 6H), 2.38 (t, J=6.5 Hz, 2H), 3.69 (s, 3H), 3.94 (s, 3H), 4.11 (t, J=6 Hz, 2H), 6.88 (d, J=8.2 Hz, 1H), 7.70 (d, J=2.3 Hz, 1H), 7.85 (dd, J=8.2 and 2.3 Hz, 2H). CMR ($CDCl_3$): 24.3, 25.2, 28.3, 33.5, 51.0, 56.0, 69.0, 106.7, 110.9, 117.4, 141.1, 149.0, 154.0, 173.4 (Found: C 56.70; H, 6.56; N, 4.66; Calc. for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71%).

6-(2-Methoxy-4-nitrophenoxy)hexanoylhydrazine **11**.

A mixture of 13.61 g (45.8 mmole) of **10** and 101.03 g of 80% aqueous hydrazine was stirred at room temperature for 3 days. The formed precipitate was filtered, washed several times with water and dryed to afford 13.31 g (98% yield) of product **11**, m.p. 128-132°C (from $CHCl_3$/CCl_4. IR (KBr): 3310, 3200, 3100, 1640, 1585, 1510, 1340 cm^{-1}. PMR ($CDCl_3$): 1.18-2.39 (m, 8H), 3.75 (broad singlet, 2H), 3.95 (s, 3H), 4.10 (t, J=6 Hz, 2H), 6.88 (d, J=2.3 Hz, 1H), 7.88 (dd, J=8.2 and 2.3 Hz, 1H). CMR (DMSO-d_6): 24.8, 25.0, 28.1, 33.3, 55.9, 68.8, 106.4, 111.4, 117.4, 140.5, 148.6, 154.0, 171.5 (Found: C, 52.54; H, 6.55; N, 14.06; Calc. for $C_{13}H_{19}N_3O_5$: C, 52.52; H, 6.44; N, 14.13%)

trans-2,6-Dimethylcyclohexanone 6-(2-methoxy-4-nitrophenoxy)hexanoylhydrazone **6**.

A mixture of 0.621 g (2.09 mmole) of **11**, 0.264 g (2.09 mmole) of 2,6-dimethylcyclohexanone (85:15 cis to trans ratio), 10 ml of methanol and 0.24 ml of acetic acid was heated under reflux for 18 h. The solution was concentrated to half its volume, diluted with water and extracted with methylene chloride. The organic layer was dryed with sodium sulfate and evaporated to give 0.847 g of crude product that was purified by silica gel column chromatography (hexane/ethyl acetate 40:60)

giving 0.237 g (28% yield) of **6**, m.p. 140-142°C. IR (KBr): 3180, 3150, 1650, 1510, 1340, cm^{-1}. PMR ($CDCl_3$): 1.04 (d, J=6 Hz, 3H), 1.10 (d, J=7.2 Hz, 3H), 1.37-3.0 (m, 16H), 3.92 (s, 3H), 4.12 (t, J=6.2 Hz, 2H), 6.86 (d, J=9 Hz,1H), 7.68 (d, J=2.4 Hz, 1H), 7.88 (dd, J=9 and 2.4 Hz, 1H), 8.91 (s, 1H). MS (70 ev): m/e (%), 405(M^+, 60), 348(100), 237(26), 235(31), 179(74), 169(23), 167(24), 139(26), 124(36), 109(21), 108(21), 97(21), 95(22), 79(23), 69(43), 55(79). (Found: C, 62.13; H, 7.71; N, 10.20; Calc. for $C_{21}H_{31}N_3O_5$: C, 62.20; H, 7.71; N, 10.36%).

Compound **6** was decomposed with nitrous acid following the procedure described previously (see decomposition of **5**) to give, after distillation, trans-2,6-dimethylcyclohexanone **3b** contaminated with a 3% of the isomer **3a** (g.l.c. comparison with an authentical sample).

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27. A dihedral angle Me-C2-C1=O of 4.69° produces an energy of -0.636 kcal/mol while a value of -104.12° gives out 0.722 kcal/mol. Consequently, the 25 and 26 torsional contributions present a difference of 1.35 kcal/mol arising exclusively from the Me-C2-C1=O dihedral angle.
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