Substituent interactions in *trans*-2-substituted methoxycyclohexanes: an explanation to the conformational behaviour in a chemometric and theoretical view

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Abstract

Principal component analysis of theoretical data [B3LYP/6-311 + g(d,p)] may predict the main interactions governing the conformational equilibrium of a series of *trans*-2-substituted methoxycyclohexanes. The classical *syn*-1,3-diaxial repulsion, as well as the '*gauche* effect' for some substituents, explain the preference towards the $eq-eq$ conformation, although dipolar and steric repulsions between the $eq-eq$ substituents is also an important intramolecular interaction present in these systems favouring the $ax-ax$ form. The intramolecular interactions were supported by theoretical variables, such as nuclear repulsion energy, hardness, charges and bond order (obtained from the density matrix of the theoretical calculations), which led to the conformers separation into $ax-ax$ and $eq-eq$ classes. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Conformational analysis; Principal component analysis; Substituent interactions; Theoretical calculations; *trans*-2-Substituted methoxycyclohexanes

1. Introduction

trans-1,2-Disubstituted cyclohexanes are useful models to rationalise the governing factors in conformational equilibria [1–4], but the main intramolecular interactions which lead the conformational preferences of these systems have not been clearly established, since classical effects, as steric and electrostatic, have not fully explained the observable results. In the case of *trans*-2-substituted methoxycyclohexanes, the $eq-eq$

conformation has been preferred in the vapour phase or in non-polar solvents, with difference of energies varying from 0.1 to 0.6 kcal mol^{-1}, when substituents are H, F, Cl, Br and OMe [3,5–7].

Here, we report the principal component analysis (PCA) [8] of data obtained from theoretical calculations (B3LYP/6-311 + g**) on *trans*-1-methoxy-2-X-cyclohexanes (X = H, Me, NMe$_2$, OMe, F, Cl and Br) to elucidate which properties determine their conformational equilibria. Theoretical data which can express intramolecular interactions, from steric effects to the known '*gauche* effect', were criteriously chosen.

PCA has been successfully applied in physical organic chemistry in order to correlate substituent

effects with chemical shifts or coupling constants [9,10], as well as in conformational analysis, when considering symmetry of *N*-membered carbocyclic rings $(N = 4, 5, 6, ...)$ [11].

In the present work, we searched to separate the two classes of conformers of the *trans*-2-substituted methoxycyclohexanes, *ax−ax* and *eq−eq*, and identify which effects were contributing to this separation, through PCA [8].

In the first step for performing the PCA [8] a data matrix is built, where each row (i) corresponds to an object and each column (k) to a variable. Through an adequate algorithm the data x_{ik} of the matrix is expressed by Eq. (1)

$$x_{ik} = \alpha_k + \sum_{a=1}^{A} \theta_{ia}\beta_{ak} \qquad (1)$$

where α_k corresponds to the average of the variable k, for all the objects i. β_{ak} are called loadings, inherent to the variable k, and θ_{ia} are the scores, related to the object i. In the sum, A is the number of principal components.

The new variables are linear combinations of the original ones, they are orthogonal and constructed in decreasing order of the variance which they describe. Thus, the PCA [8] tries to group the old variables, which are highly correlated to each other, into new variables called principal components. In the present work, the objects i are the main conformers of each molecule and the variables k corresponds to

the theoretically calculated data which can represent the intramolecular interactions.

2. Computational details

The energy minima for each molecule were identified in its potential energy surfaces, obtained through the semi-empirical AM1 method. Each minimum was optimised with the DFT B3LYP method and 6-311 + g(d,p) basis set, available in the GAUSSIAN 98 program [12]. This level of theory leads to accurate results [13] and thus the results were introduced in the data matrix for performing the PCA.

3. Results and discussion

Geometries for all possible conformers of *trans*-2-substituted methoxycyclohexanes were optimised through molecular orbitals calculations at B3LYP/6-311 + g(d,p) level and are presented in Fig. 1. For performing PCA, only the most stable conformations were taken into account, i.e. *Xa*1, *Xa*2, *Xe*1 and *Xe*2 conformations, since the *anti* ones (*Xa*3 and *Xe*3) presented very high-energy values. For Br and Me derivatives, *Xe*1 conformation is not a minimum, and in the case of NMe$_2$ and OMe derivatives a number of rotations is also possible for the substituents. Among them, just the more stable forms *Xa*1′, *Xa*2′, *Xe*1′ and

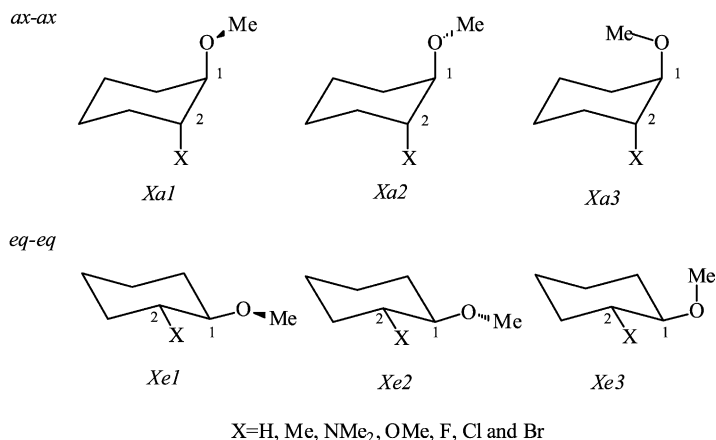X=H, Me, NMe$_2$, OMe, F, Cl and Br

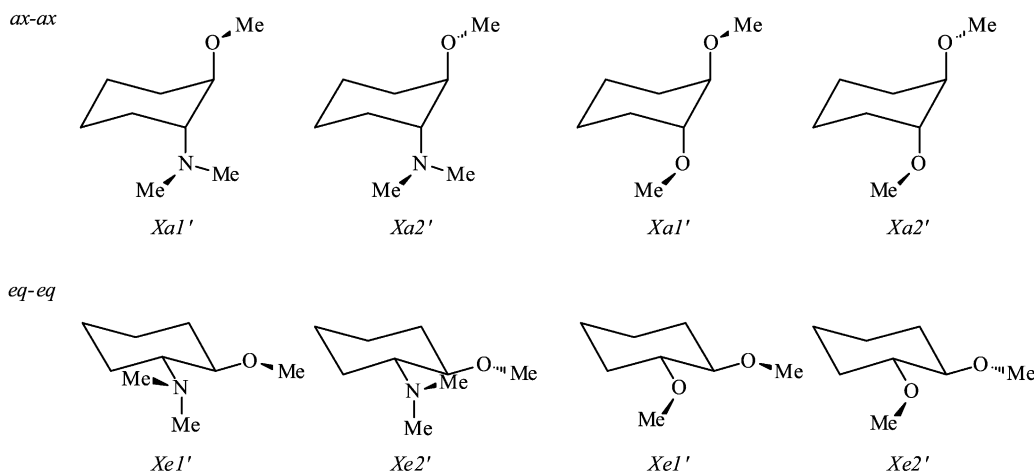Fig. 1. Possible conformations for *trans*-2-substituted methoxycyclohexanes.

Fig. 2. More stable conformers of *trans*-2-*N*,*N*-dimethylaminemethoxycyclohexane and *trans*-1,2-dimethoxycyclohexane.

Xe2′ (Fig. 2) were taken into account in the PCA. Table 1 shows the relative energies of each conformer inserted as objects in the PCA data matrix.

For all the molecules, the *eq–eq* conformation is the most stable one. Theoretical variables were selected to represent possible intramolecular interactions, which would be governing the conformational preferences of the systems here studied, and are described as follows.

NRE. NRE corresponds to the relative nuclear repulsion energy between one conformer (of lowest NRE) and another, both concerning to the same substituent. This variable describes steric effects, such as the classical *syn*-1,3-diaxial and γ-*gauche* repulsions.

Bond order. The values for this variable are found in the density matrix of the theoretical calculations in

Table 1
Relative energies (B3LYP/6-311 + g**, kcal mol^{-1}) for each conformer of *trans*-2-substituted methoxycyclohexanes utilised in the PCA data matrix

Conformer	Substituent						
	H	Me	NMe$_2$	OMe	F	Cl	Br
Xa1	0.55	2.64	2.35	0.95	1.10	0.28	0.50
Xa2	0.55	2.64	2.13	0.75	0.81	0.30	0.59
Xe1	0	–	0.69	0	0	0.01	–
Xe2	0	0	0	0.62	0.78	0	0

the intersection of the oxygen and the substituent atoms bonded to C-2 (H, C, N, O, F, Cl and Br). It represents the interaction (attractive or repulsive) or bond order (BO) between these atoms, and it can evaluate the occurrence of the *gauche* effect in the compounds here studied. The *gauche* effect has been postulated to explain the tendency of the ethane fragment in adopting the conformation which has a maximum number of *gauche* interactions between adjacent electrons or polar bonds. This effect has been frequently observed in the case of highly electronegative substituents [14]. Thus, it is expected that NMe$_2$, OMe, F and Cl derivatives exhibit this effect, but not bulky or non-polar groups, such as Br, H and Me. Epiotis [15] attributed this *gauche* effect to an attractive interaction between the lone pairs n_O and n_X via σ^*_{CC} orbital (Fig. 3), when the molecules are arranged in the *eq–eq* conformation, which decreases in the order F > Cl > Br > I. The Epiotis [15] interpretation to the *gauche* effect was adopted here. More recent interpretations to the *gauche* effect may be found in literature [16–21], where a hyperconjugative interaction or an *anti* destabilisation, due to poorer overlap between the C–C σ-bond forming orbitals caused by bond bending at the carbon nuclei, are invoked.

CX, *CO*, *CC1* and *CC2*. They correspond to atomic charges over X (H, C, N, O, F, Cl and Br), oxygen, carbon-1 and carbon-2, respectively. These variables can aid in predicting interactions, such as dipolar
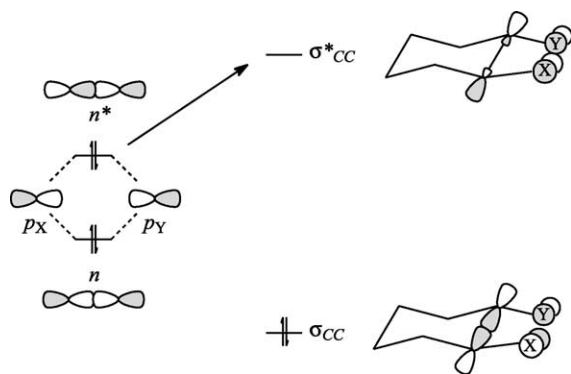
Fig. 3. Interaction between the lone pairs n_X and n_Y with σ_{CC} and σ^*_{CC} orbitals in the *eq–eq* conformation. The arrow indicates the interaction which favours the charge transfer.

repulsions or hyperconjugative effects, e.g. $n\sigma^*_{CO\ or\ CX}$ and $\sigma_{CO\ or\ CX}\sigma^*_{CX\ or\ CO}$ [22].

HOMO and LUMO. They mean the energies of highest occupied and lowest unoccupied molecular orbitals, respectively, and can be interpreted in terms of larger or smaller facility in the occurrence of intramolecular interactions in the conformers studied here. AM1 calculations have shown that the HOMO is mainly over the lone pairs, while LUMO is on the C–O and/or C–X bonds. The role played by these variables are better understood after the introduction of the *Hardness*.

Hardness. It is the molecule hardness. A hard molecule is defined as having a large energy gap between HOMO and LUMO [Hardness = (LUMO − HOMO)/2]. A hard molecule resists to changes in its electron charge cloud, both the total amount of charge and also the charge distribution in space, while a soft molecule has an easily changed electron distribution [23]. Thus, the Hardness parameter determines how easily electrons are polarised or resist to deformation. These can be correlated with interactions occurring in the *eq–eq* or *ax–ax* conformers of *trans*-2-substituted methoxycyclohexanes.

PCA. In the 26 (conformers: *Ha*1, *Mea*1, etc.) × 9 (variables: CX, CO, CC1, CC2, NRE, BO, HOMO, LUMO and Hardness) data matrix, the elements are the relative values instead of absolute ones, since in a same column different substituents can present values with different orders of magnitude. However, if for each row the relative values are taken among the conformers for a same substituent, the figures for all

conformers are similar for a given variable. For example, the calculated values of the NRE variable for F substituent are 508.5445, 508.9276, 502.1209 and 500.3373 hartree, for the conformers *Fa*1, *Fa*2, *Fe*1 and *Fe*2, respectively, while in the case of the N substituent, the corresponding values are 710.8626, 710.3284, 703.7988 and 704.7390 hartree. As can be observed, the absolute values are very different between F and N, but the relative values are not, i.e. 8.2072, 8.5903, 1.7836 and 0, for the conformers of the F substituent, and 7.0638, 6.5296, 0 and 0.9403 for the ones of the N substituent. Moreover, the data were autoscaled by subtracting column averages and dividing by column standard deviations. In this way, for each one of the variables are given identical weights in the principal component analyses. Data analysis was performed using the Pirouette software package [24].

The importance of the *gauche* effect in conformational analysis of *trans*-1,2-disubstituted cyclohexanes has been discussed extensively [1–4,18], and for its evaluation it was firstly necessary to obtain a scores plot (Fig. 4) through PCA, where are included the variables referring to all the conformers proposed in this work, whose substituent atoms attached to C-2 are H, C, N, O, F, Cl and Br. In this plot, represented as PC1 versus PC2, one can observe two clusters (solid and open labels) due to the separation of the *eq–eq* and *ax–ax* conformer classes. However, none of these two PCs are able to separate, exclusively, these two classes. But it can be noted that the elements which
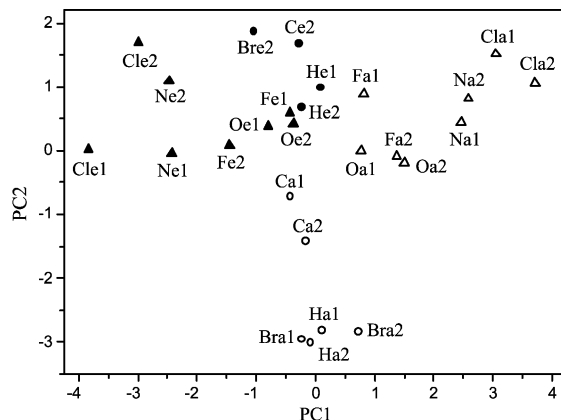

Fig. 4. Graphical representation of scores in PCA when including all substituents.

are expected to not present a *gauche* effect (H, C and Br-solid and open circle labels of Fig. 4) do not allow the classes separation in PC1. On the other hand, PC2 is able to distinguish the *ax–ax* and *eq–eq* conformers bearing these substituents (*He*, *Ce* and *Bre* from the *Ha*, *Ca* and *Bra*). The loadings in PC2 of Fig. 4 are described according to the coefficients in Eq. (2)

$$PC2 = 0.30\ LUMO + 0.30\ CC2 + 0.28\ CX$$
$$+\ 0.21\ HOMO + 0.16\ CO + 0.15$$
$$Hardness - 0.58\ CC1 - 0.44\ BO - 0.35$$
$$NRE. \tag{2}$$

Clearly, the more important variables in separating *He*, *Ce* and *Bre* from *Ha*, *Ca* and *Bra* are CC1 and BO, which can be interpreted as follows.

BO. This variable is very unfavourable to *He*, *Ce* and *Bre*, indicating the repulsion between the substituents is stronger than the attractive interaction, which confirms the premise that the elements H, C and Br do not present a *gauche* effect.

CC1. The compression of the oxygen electron cloud by the substituents in C-2 leads to a more negative charge (or less positive) in C-1, indicating that the repulsion between O and X (X = H, C and Br) is really important in the *eq–eq* conformation, in opposite to the *gauche* effect.

When the substituents H, Me and Br are excluded from the data matrix, the *ax–ax* and *eq–eq* conformers separation in PC1 becomes perfect (Fig. 5). PC1 describes 49% of total variance in the data (nine PCs describe 100% of them). The loading results allow us to describe PC1 as Eq. (3):

$$PC1 = 0.41\ NRE + 0.41\ Hardness + 0.33\ CC2$$
$$+\ 0.31\ LUMO - 0.37\ HOMO - 0.34\ CX$$
$$-\ 0.32\ BO - 0.31\ CO + 0.03\ CC1. \tag{3}$$

The variables employed for separation of the *ax–ax* and *eq–eq* conformers in PC1 have weights according to the coefficients of Eq. (3). Positive coefficients indicate that the variable values are larger for the *ax–ax* conformation, while negative values indicate that the variable values are larger to the *eq–eq*
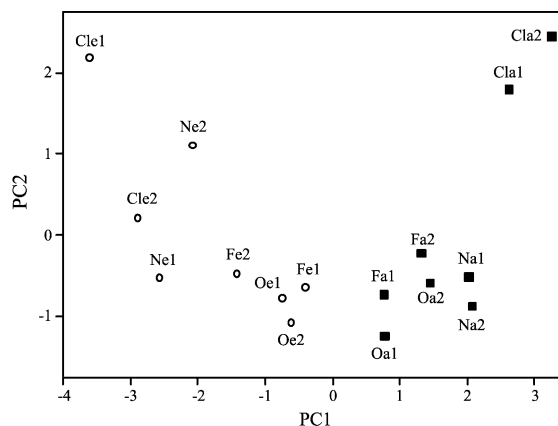

Fig. 5. Graphical representation of scores in PCA when including only the electronegative substituents.

conformation. With exception of CC1, all the variables were important in the classes separation, mainly NRE, Hardness and HOMO.

According to Eq. (3) and Fig. 5, where the compounds bearing N, O, F and Cl atoms attached to C-2 are only included, the NRE and Hardness parameters are the important variables in the separation of the *eq–eq* and *ax–ax* conformers of the *trans*-2-substituted methoxycyclohexanes. The former, which is larger for the *ax–ax* ones, explains the classical *syn*-1,3-diaxial steric effects, while the latter, also larger for the *ax–ax* conformers, suggests that the charge distribution in the *eq–eq* conformation has been perturbed by intramolecular interactions, as dipolar or *gauche* repulsions between the substituents. Dipolar repulsion can also be deduced by the charge variables behaviour, since CX and CO are less negative in the *eq–eq* than in the *ax–ax* conformers, and CC2 is less positive for the *eq–eq* ones, suggesting that the charge separation in *eq–eq* is smaller than in *ax–ax* to alleviate a strong dipolar repulsion.

The *gauche* effect, whose importance has been very often discussed, shows to be an important effect in describing the *trans*-2-substituted methoxycyclo-hexanes conformational preferences, when substituent atoms are F, Cl, O and N. When H, Me and Br are included (Fig. 4), the classes separation in PC1 does not occur, and this is attributed to the occurrence of intramolecular interactions which are important for

the *ax−ax* or *eq−eq* conformers bearing electronegative substituents, but not for the conformers with H, Me and Br as substituents, namely the *gauche* effect.

Finally, the *eq−eq* preference in the vapour phase for *trans*-2-substituted methoxycyclohexanes is governed by *syn*-1,3-diaxial repulsion present in the *ax−ax* conformation and also by the *gauche* attractive interaction between the substituents, although dipolar and/or van der Waals repulsion between substituents is also significant in the *eq−eq* conformation, and it favours the *ax−ax* form.

4. Conclusions

PCA from theoretically calculated data was successfully applied to predict the interactions governing the conformational equilibria of some *trans*-2-substituted methoxycyclohexanes. The main intramolecular interactions occurring in these systems are steric effects (*syn*-1,3-diaxial repulsion), and dipolar (for electronegative substituents) and van der Waals repulsions between the *eq−eq* substituents. The *gauche* effect, an attractive interaction between electronegative atoms in *gauche* position [13] and whose importance in describing the conformational preferences of *trans*-1,2-disubtituted cyclohexanes has been questioned in the literature, plays an important role in the stabilisation of the *eq−eq* conformers bearing electronegative substituents, namely F, Cl, OMe and NMe_2.

Acknowledgments

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