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MOLECULAR ORBITAL THEORY OF THE ELECTRONIC STRUCTURE OF ORGANIC COMPOUNDS—II

TRANSANNULAR INTERACTIONS IN DIOXODIAZACYCLOALKANES

J. Marañón and O. M. Sorarrain[*]
Departamento de Física, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, La Plata, Argentina

and

H. Grinberg, S. Lamdan and C. H. Gaozza
Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina

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Abstract—The CNDO/2 MO and INDO MO methods were used to study the molecular electronic structure of the bicyclic molecules derived by transannular interaction of the amide groups in two isomeric dioxodiazacyclodecanes. A physical model based on the invariance of the MO's with respect to linear transformation of the basis set allowed to determine a functional relation between the bond atomic population M_{C-N} and r_{C-N} (transannular) in a set of closely related lactams (dioxodiazacycloalkanes). Further, the stabilities of a set of cyclopeptides as determined by Shemyakin *et al.* allowed to calculate a minimum value of M_{C-N} and a maximum transannular distance r_{C-N} beyond which is not possible the transannular interaction between the amide groups in this kind of molecules. These approaches were used together to provide quantitative results which enable to account for the different behaviour of 6,10-dioxo-1,5-diazacyclodecane and 4,10-dioxo-1,5-diazacyclodecane towards ring contraction reactions.

In a previous paper[1] some molecular properties of a restricted set of dioxodiazacyclalkanes 1 upon the application of the CNDO/2 and INDO methods were described. The results were encouraging enough for a reasonable description of a set of molecules having the same molecular symmetry and functional groups. Here a theoretical analysis of the molecular electronic structure of some bicyclic molecules derived by transannular interaction of the amide groups will be undertaken. As model systems for the calculations those derived from 6,10 - dioxo - 1,5 - diazacyclodecane 1a and 4,10 - dioxo - 1,5 - diazacyclodecane 4b were chosen, namely the isomeric lactams 3 and 6b and their respective precursors, the cyclols 2 and 5 (Scheme 1). The purpose of this paper is to report the results of MO calculations in the CNDO/2 approximation[2,3] on ring contraction of the isomeric 10-membered rings 1a and 4b. In fact, it was observed that the cyclopeptide 4b rearranges to the lactam 6b via the cyclol 5,[4] but such reaction was not observed for the closely related dilactam 6,10 - dioxo 1,5 - diazacyclodecane 1a.[5,6]

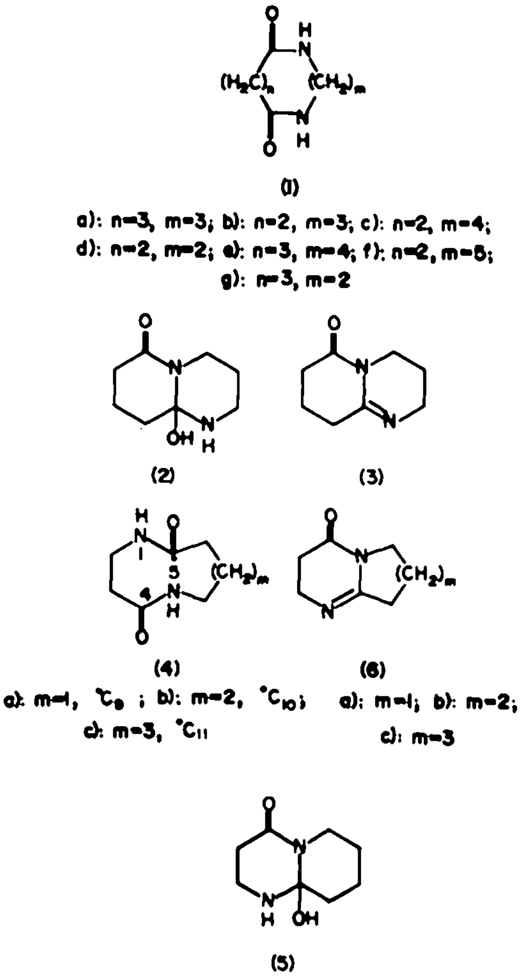
COMPUTATIONAL METHOD

Molecular wave functions for molecules 2, 3, 4b, 5 and 6b were calculated using the CNDO/2 method employing the original parameterization given by Pople *et al.*[2,3] In the present study, standard bond lengths and angles[7] were used to estimate geometries. Calculations for molecules 2, 3, 5 and 6b were performed using standard conformations to provide a consistent basis for comparison since reliable experimental geometries are not available. Although the use of standard bond lengths and angles will result in some deviations from the true conformations, we felt that the use of a well-defined conformational model was preferable to making arbitrary adjustments in several individual conformations and was more practical than optimizing each of them through calculations. Hence, the geometry of each bicyclic molecule was found by minimizing the total energy with respect to the geometrical variables defining its structure.

In our analysis the stability of the cyclopeptide 4b, the geometrical structure of which was derived adopting a C_1 symmetry, and those of the *cis* and *trans* conformations of 2, 3, 5 and 6b have been examined within the constraints placed upon the molecular parameters we have chosen to vary. This was done by interpolation between energies calculated for a number of specific geometries around the minimum (local) energy. With the optimized structural parameters, density and overlap matrices, total and bond energies and dipole moments for 2, 3, 5 and 6b (*cis* and *trans* conformers) and 4b were determined. Calculations were performed on a IBM 360/50 computer with a QCPE program CNDO/2 using STO as basis set.[8] For purposes of comparison the option INDO for the bicyclic molecules 2, 3, 5 and 6b was also allowed for. The program was modified to suit local input–output requirements and to facilitate changing dimension statements.

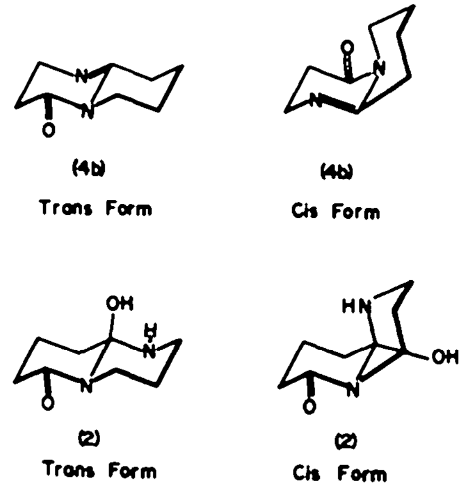
RESULTS AND DISCUSSION

Standard molecular models predict the existence of two rigid conformations for the bicyclic molecules 2, 3, 5 and 6b, being the HO group the only flexible part of the cyclols 2 and 5. On the other hand, the differences in bond lengths and angles as well as the force for bond stretching and bond bending angle between heterocycles and carbocycles hardly influence the Van der Waals forces, at least those existing between H atoms.[9] There-



Scheme 1.

fore, for a theoretical analysis of the bicyclic molecules the three dimensional structures were determined taking as possible stable conformational states the *cis* and *trans* forms of the analogous carbocyclic saturated compounds[10] (Scheme 2).



Scheme 2. Conformations of the computed bicyclic molecules.

From Table 1 it can be observed the *cis* conformer to be more stable than the *trans* isomer. The lower symmetry of the lactam **6b** compared with **3** is reflected in a higher dipole moment for the former in both conformers. The higher dipole moments of the cyclols **2** and **5** follow from the presence of a HO group with some degree of hindered rotation although both molecular models and calculations within this level of approximation fail to show it. These are lower in both *trans* conformers than in the more stable *cis* conformers. It can be appreciated that the CNDO/2 and INDO methods give the same difference for the total and bond energies between both conformers. For the cyclopeptide **4b** (symmetry C_1) these are very close to those corresponding to the isomeric dilactam **1a** (symmetry C_{2v}).[1] On the other hand, the change of symmetry ($C_{2v} \rightarrow C_1$) which is observed on going from **1a** to **4b** is reflected in a higher dipole moment for the latter.[1]

The transformation of the cyclols **2** and **5** into the lactams **3** and **6b** respectively depends not only on the spatial orientation of the leaving groups but also upon the electronic densities in both the broken and formed bonds in the elimination process. As stated, practical problems remain in obtaining good quantum mechanical wave functions for the cyclols **2** and **5**. Thus, it may turn

Table 1. Energies (eV) and electric dipole moments (D) for the computed molecules

Molecule	Conformation	Method	Total energy	Bond energy	Dipole moment
2	*cis*	CNDO/2	−3475.778	−303.636	3.507
2	*trans*	CNDO/2	−3466.826	−294.484	3.477
2	*cis*	INDO	−3348.462	−291.337	3.532
2	*trans*	INDO	−3339.537	−282.412	3.532
3	*cis*	CNDO/2	−2923.927	−288.670	1.611
3	*trans*	CNDO/2	−2933.401	−288.017	1.314
3	*cis*	INDO	−2828.833	−276.897	1.692
3	*trans*	INDO	−2828.152	−276.317	1.490
5	*cis*	CNDO/2	−3475.560	−303.418	3.765
5	*trans*	CNDO/2	−3464.622	−292.480	3.621
5	*cis*	INDO	−3348.136	−291.038	3.539
5	*trans*	INDO	−3337.252	−280.154	3.482
6b	*cis*	CNDO/2	−2935.142	−289.706	2.797
6b	*trans*	CNDO/2	−2933.292	−287.936	1.961
6b	*cis*	INDO	−2829.812	−277.977	2.694
6b	*trans*	INDO	−2827.826	−275.991	2.450
4b	—	CNDO/2	−3470.050	−297.911	3.424

out that the properties of the physical model to be outlined below can be related to the orientation of the HO group in both cyclols during the dehydration process, but at this time, there is insufficient knowledge and computational data to attempt a connection with such ideas. Consequently, a Mulliken Population Analysis[11] of the C–O and N–H bonds in the cyclols 2 and 5, that of the C=N bond in the lactams 3 and 6b, and that of the C_{10}–N_5 bond in the cyclopeptide 4b seemed promising in order to derive some quantitative results. The bond atomic population M_{A-B} for the involved A–B bond is given by

$$M_{A-B} = \sum_{\mu} \sum_{\nu} P_{\mu\nu} S_{\mu\nu} \qquad (1)$$

where $P_{\mu\nu}$ and $S_{\mu\nu}$ are the elements of the density and overlapping submatrices respectively and the sums extend over the atomic orbitals located on both atoms. The results are given in Table 2. It can be observed that M_{A-B} is independent of the conformational changes due to both conformers have the same molecular symmetry (C_1). Moreover, the cyclols 2 and 5 have almost the same value of M_{C-O} and M_{N-H} in both *cis* and *trans* conformers.

Table 2. Bond atomic population data (CNDO/2)

Molecule	Conformation	M_{N-H}	M_{C-N}	M_{C-O}
2	*cis*	0.671	—	0.493
2	*trans*	0.689	—	0.419
5	*cis*	0.690	—	0.490
5	*trans*	0.689	—	0.360
3	*cis*	—	0.954	—
3	*trans*	—	0.943	—
6b	*cis*	—	0.974	—
6b	*trans*	—	0.936	—

The cyclopeptide 4b has no symmetry plane like that of molecule 1a. Consequently, there are two possible transannular interactions: those between C_{10}–N_5 and C_4–N_1; nevertheless, only the former was observed.[4] The transannular interaction between C and N atoms in 1a might give the cyclolic structure 2, leading 2 to the lactam 3 by dehydration. This lactam is a dihexagonal system with the same symmetry and functional groups as the cyclopeptide 4b. Then it should be interesting to compare the bond atomic population for the molecules 1a and 4b between the bonds involved in the transannular interactions (C–N for 1a and C_{10}–N_5 for 4b) leading to the corresponding bicyclic systems. From Table 2, the value $q = 2.14 \times 10^{-4}$ is obtained for the ratio $M_{C-N}/M_{C_{15}-N_5}$.

Therefore, if 1a would have the same behaviour as 4b, the strength of the interaction (extended to the whole set of basis orbitals, namely: $2s_C$, $2p_{xC}$, $2p_{yC}$, $2p_{zC}$, $2s_N$, $2p_{xN}$, $2p_{yN}$ and $2p_{zN}$) between the atoms involved in the transannular interaction should be 10^4 times lower than the corresponding one for the atoms C_{10} and N_5 in 4b. This result could in principle, account for the experimental difficulties to isolate 3 from 1a.[6] However, although both molecules 1a and 6b have very close values for their total energies, different molecular symmetries were adopted for them. Then, it should be doubtful to consider the parameter q as very significant for this type of ring contraction.

Calculations were not carried out for 1a like those made for 4b adopting a C_1 symmetry,[1] due to difficulties on attaining a local minimum energy on varying the geometry. However, as a hypothesis that finally will have to be corroborated, it is possible to reason on the basis of the relative stabilities of a series of closely related cyclopeptides. In fact, Shemyakin *et al.*[4] have observed that the yield of the 4→6 transformation decreases on increasing the ring size. Assuming that the yield obtained for the 4b→6b reaction is the same achieved under thermodynamic control conditions of the reversible transformation 4b ⇄ 6b, it can be postulated the interatomic distance C_{10}—N_5 in 4b to be the maximum one for which is possible the transannular interaction between them, since for the cyclopeptide 4c, where supposedly the corresponding distance C_{11}—N_5 has to be slightly higher, the yield of the transformation 4c→6c is zero.[4]

The orbital atomic populations $M_{\mu\nu}$ (μ, ν atomic orbitals centred on different atoms) are dependent on the overlapping integral $S_{\mu\nu}$ while the values of $M_{\mu\nu}$ decrease as the interatomic distance increases. Therefore, there must be a minimum value of M_{C-N} for this type of rings (in particular, in 10-membered rings with these same functional groups, for instance 1a) below which the transannular interaction between C and N is negligible. This minimum should be determined by the interatomic distance C_{10}—N_5 in 4b. From this, it seemed promising to adopt a relationship between M_{C-N} and r_{C-N}, being r_{C-N} the transannular interatomic distance between C and N. Therefore, by comparing a set of molecules with the same molecular symmetry and functional groups, the interatomic distance C—N (transannular) for 1a should be given by interpolation.

The basis of this reasoning is as follows. In the CNDO method, the resonance integrals $\beta_{\mu\nu}$ are handled in a semiempirical manner, but so as to satisfy the required invariance conditions. This is done by assuming that $\beta_{\mu\nu}$ is proportional to the overlap integral $S_{\mu\nu}$[2,12] since the bonding capacity of the overlap will increase as the overlap increases. Such approximations have frequently been used in independent electron calculations, following the original suggestion by Mulliken.[13] For the calculations to be invariant under transformations of the atomic basis sets, it is required the proportionality factor between $\beta_{\mu\nu}$ and $S_{\mu\nu}$ to be the same for all atomic orbitals. This is necessary since $S_{\mu\nu}$ itself transforms correctly.

The relation between $\beta_{\mu\nu}$ and r will is assumed to be an exponential one; this is justified since $\beta_{\mu\nu}$ must vanish for infinite r, and its decrease as r increases, must be roughly proportional to the overlap integral (hence to $\exp(-r/a)$) of the atomic orbitals. Introduction of the invariance conditions and eqn (1) leads after a little algebra to

$$M_{A-B} = b|\beta^{\circ}_{A-B}|^{-1} \exp(-r/a) \qquad (2)$$

where β_{A-B} is a bonding parameter and b and a are constants. From the above discussion, a knowledge of M_{C-N} and the distance r_{C-N} (transannular) for the dioxodiazacycloalkanes 1 would furnish the value of r_{C-N} in 1a for which the bond atomic population is the one found for the cyclopeptide 4b, being this the supposed minimum value to permit transannular interaction in this type of rings.

The $-\lg M_{C-N}$ with the corresponding transannular

C—N distances r_{C-N} for a set of similar dioxodiazacycloalkanes **1** are given in Table 3. From the magnitude of $M_{C_{10}-N}$, extracted from **4b**, it follows the transannular distance C—N in **1a** to be

$$r_{C-N} = 2.93\ \text{Å}.$$

Significantly, this value is higher than the maximal distance $r_{C_{10}-N}$, (Table 3) corresponding to the cyclopeptide **4b**. Therefore, the transannular interaction C—N should be negligible for the dioxodiazacycloalkane **1a**. The behaviour of both isomeric molecules **4b** and **1a** should be quite different and the hypothesis given above is also supported by these theoretical considerations.

Table 3. Transannular interatomic distances r_{C-N} and bond atomic population M_{C-N} (transannular) for the dioxodiazacycloalkanes **1**[a]

Molecule	r_{C-N} (Å)[b]	$-\lg M_{C-N}$[c]
1a	4.54	5.604
1b	4.09	4.412
1c	4.37	4.648
1d	3.86	4.192
1e	4.91	6.032
1f	4.55	4.753
1g	4.07	4.267

[a] The values reported in this Table were fitted by means of the least squares method to give the equation $-\lg M_{C-N} = 2.06\, r_{C-N} - 4.10$.

[b] Interatomic distances computed with a program of coordinates; interatomic distance $r_{C_{10}-N}$, in **4b**: 2.21 Å.

[c] CNDO/2 method; $M_{C_{10}-N}$, in **4b**: 1.16×10^{-2}.

CONCLUSIONS

Using the invariance of the MO's with respect to linear transformations of the atomic basis set, a functional relation between M_{C-N} (bond atomic population) and r_{C-N} (trnasannular) for a set of molecules with the same molecular symmetry was established. In addition, a minimum value of M_{C-N} and a maximum magnitude of r_{C-N} (transannular) were attributed to the 4,10-dioxo-1,5 diazacyclodecane **4b** on the basis of the stability of a set of cyclopeptides. The magnitudes of M_{C-N} resulting of this model are able to explain important differences in the previously observed experimental behaviour of the isomeric molecules **1a** and **4b**. The transannular interaction is feasible only if the magnitude of M_{C-N} is over $M_{C_{10}-N}$, obtained for **4b**. The formula (2) or a similar one would be useful to determine the possibility of transannular interaction for a given set of related molecules with the same molecular symmetry. This model organizes results computed from CNDO/2 (INDO) wave functions and allows the determination of the interatomic distance C—N (transannular) in a dioxodiazacycloalkane if the true ground state wave function of a closely related one is available.

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[10] To this point, we obviously have neglected the destabilizing energies associated with H—H nonbonded repulsions. In these molecules these energies are very small. For instance, the difference of H—H nonbonded repulsion energies between the *cis* and *trans* conformations of the dilactam 3 is only 0.24 kcal/mol (unpublished results).

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