CHIRAL RECOGNITION IN BICYCLIC GUANIDINES

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A theoretical study of chiral recognition in bicyclic guanidines has been carried out by means of B3LYP/6-31+G(d,p) DFT calculations. A series of complexes between protonated 4,8-dimethyl-1,5,7-triazabicyclodecene (DTBD) and 2,5-disubtituted chiral cyclopentanones have been evaluated for chiral recognition, both in the gas phase and in benzene solution as per the polarizable continuum model (PCM) and analyzed by AIM and NBO methodologies. An inversion in the sense of chiral recognition has been observed between gas phase and solvated results for cyclopentanone complexes. Among the different correlations found (i.e. between electron density, hydrogen bond distance, second-order perturbation energy), a linear correlation has been established between the chiral recognition energy and different molecular parameters.

Keywords: Chiral recognition; Guanidines; Cyclopentanones; DFT calculations; Natural bond orbital theory; Atoms in molecules theory.

Biological evolution has long since perfected chiral organocatalysis via biomolecular systems such as proteins with near-perfect enantioselectivity. Whatever the reason, this selection today corresponds to a necessity in the synthesis and study of chirally-pure bioactive compounds. Although molecular chirality has been studied since the experiments of Pasteur more than 150 years ago, the sheer diversity of interactions involved (electrostatic, hydrogen bonding, London forces, solvation), combined with often-minuscule energetic discrimination between enantiomers, means that the present understanding of molecular chiral recognition remains incomplete. Thus, rationalization of chiral recognition constitutes one of the current goals of theoretical chemistry. Simplified theories such as the three-point attachment model have long since been debunked via both theoretical studies[1] and the work of Koshland and Mesecar[2], and yet their application

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remains routine in the absence of a stronger conceptual model. We have contributed to chiral recognition with a significant number of papers[3].

The present article underlines a central difficulty in our perception of chiral recognition: that steric effects, although important, constitute only a portion of molecular reality; and that only a consideration of the complete spectrum of forces can provide a justified theoretical insight into the mechanics of chiral recognition. Hence, we have investigated the homo- and heterochiral interaction of a series of chiral disubstituted cyclopentanones (R = methyl, *tert*-butyl, ethynyl, trifluoromethyl, cyano, fluoro and chloro, see Fig. 1) with the disubstituted chiral bicyclic guanidine (4*R*,8*R*)-4,8-dimethyl-1,5,7-triazabicyclodecene (DTBD) shown in Fig. 1.

DTBD constitutes a synthetically viable[4–6] chiral derivative of the known organocatalyst 1,5,7-triazabicyclodecene, otherwise known as TBD. Several chiral derivatives of TBD have been investigated to develop a viable enantioselective organocatalyst for both the Michael and the Henry reactions and yet the rational design of such an agent remains obscure. Therefore, a theoretical study of such chiral TBD derivatives, as it applies to this design, may provide a key insight into present flaws in our understanding of chiral recognition[7,8] as it applies not only to biological systems but also to organocatalysis.

Chiral bicyclic guanidines have shown promising results as enantioselective organocatalysts as demonstrated by Corey and Grogan[9] in the Strecker synthesis of α-aminonitriles from *N*-benzhydryl imines. More recently, these compounds have been shown to provide exceptional enantioselectivity as basic catalysts in Diels–Alder reactions of anthrones[10,11]. Wynberg et al.[12] first suggested the use of a chiral analogue of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as an enantioselective catalyst for both the

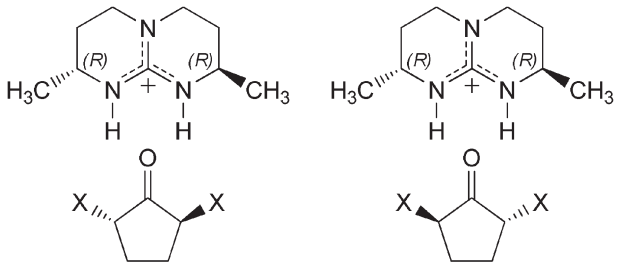

FIG. 1
Homo- and heterochiral complexes of bicyclic guanidine with cyclopentanones (X = CH_3, *t*-Bu, C≡CH, CF_3, CN, F, Cl) studied

Micheal and Henry reactions, but despite the excellent catalytic activity of achiral TBD [13] in such reactions, to our knowledge such a chiral derivative for enantioselective variations has yet to be perfected. Davis and Dempsey[13] reported poor enantiomeric enhancement using the chiral biphenyl analogue to perform nitroaldol reactions; despite strong host–guest complexation of the critical intermediate having been reported[12] and chiral recognition using similar TBD derivatives having been experimentally demonstrated by de Mendoza et al.[14] (albeit for carboxylate anions).

It should be noted here that the asymmetric Henry reaction has since been achieved using a bifunctional organocatalyst combining both the guanidinium and thiourea functional groups[15]. Other novel applications include a calix-6-arene coupled to a chiral TBD derivative to function as an artificial acetylcholine esterase[16]. Although somewhat structurally far from our studies, such catalysts demonstrate the utility of the guanidium moiety in chiral recognition and strongly indicate future applications throughout organocatalysis.

Despite this, and to the best of our knowledge, only one reference addressing the theoretical study of bicyclic guanidium organocatalysis could be found[17] relating specifically to the mechanism of Corey's aforementioned Strecker reaction (for other catalysts, see e.g. refs[18,19]). Therefore, although not explicitly addressing the mechanics of organocatalysis, results arising from the present study may be used in the further rationalization of the role of chiral TBD derivatives in future organocatalytic chemistry.

COMPUTATIONAL METHODS

A series of complexes between protonated (*R*,*R*)-4,8-dimethyl-1,5,7-triazabicyclodecene (DTBD) and both (*R*,*R*)- and (*S*,*S*)-2,5-disubtituted cyclopentanones (CPOs) were optimized via the B3LYP/6-31+G(d,p)[20] method as implemented in the Gaussian 03 software package[21]. This level of calculation has shown to provide analogous results to the ones obtained at the MP2 level for the chiral discrimination of other hydrogen bonded systems[22–25].

Each monomer was first independently optimised using the ultrafine grid option and subsequently subjected to single-point PCM calculations[26,27] using gas phase geometry with tight SCF convergence criteria to establish the solvation energy using benzene as solvent. Otherwise all parameters were as per Gaussian 03 default.

In the monomers, both the axial and the equatorial substituents were considered. In those cases where the axial/equatorial distinction was in-

dicated as less than 3 kJ mol^{-1} both conformers were investigated in the actual complexes while in the rest of the cases only the most stable conformer were considered. The optimized geometries of the monomers were then employed as a starting point for the optimization of the complexes, which were solvated similarly. In the case that a solvated monomer changed its axial/equatorial conformational preference upon solvation, the new preference was also explored in the solvated complex.

Complexes have been defined as homochiral when both substituents were orientated similarly to the (*R*,*R*)-1,5-difluorocyclopentanone. This is correct for all the substituents considered except for the methyl derivative which has less chemical priority, but we have made an exception in this case for the sake of clarity.

Frequency calculations were used to verify each structure as an energetic minimum. The C_2 point group was used throughout. The interaction energy has been obtained as the difference of the dimer and the sum of the monomers. Chiral discrimination energies were calculated as the difference of the electronic energy for homo- and heterochiral complexes.

QT-AIM [28] and NBO [29] analyses have been employed to further investigate the underlying nature of the interactions within the complexes. All QT-AIM and NBO analyses were carried out using AIMPAC [30] and MORPHY98 [31] software with wavefunctions calculated using the Gaussian 03 software package.

RESULTS AND DISCUSSION

Geometries and Energies

In terms of geometries, gas-phase optimization of the 1,5-disubtituted cyclopentanone monomers (CPOs) demonstrated a preference for the equatorial configuration in all cases except for the 1,5-difluoro and 1,5-dichloro disubstitutions. These CPOs exhibited a difference of less than 3 kJ mol^{-1} between the axial and equatorial cases and, thus, both conformers were investigated. DTBD itself demonstrated a preference for the equatorial conformation in both gas-phase and benzene-PCM calculations.

Regarding the dimers' geometries, all the complexes generally adopt a planar configuration (see example in Fig. 2a). One notable exception is the *tert*-butyl disubstituted species, which adopted a perpendicular configuration, most likely due to steric hindrance between the large *tert*-butyl groups and the DTBD's methyl moieties (Fig. 2b).

In all cases, the distances found between the O atom of the CPO unit and the H atoms of the guanidinium cation were within the accepted range for a hydrogen bond[32] (HB) as shown in Table I. These HB distances were shorter in the heterochiral than in the homochiral complexes indicating, as we have previously shown[33], stronger interactions in the heterochiral complexes. Exceptions to this trend were found in those dimers formed with the axial fluoro and chloro derivatives where the O···H distances were slightly shorter for the homochiral complexes.

With regard to gas-phase chiral discrimination energies (Table II), in general, the heterochiral complexes are more stable than the homochiral and the greatest difference was found for the C≡CH disubstituted species (–3.26 kJ mol^{-1} in favor of the heterochiral complex, see Table II). Exceptions are the *tert*-butyl- and Cl(ax)-CPO complexes whose homochiral complexes are more stable. In the case of the CN- and F(eq)-CPO complexes a real discrimination cannot be considered since the energy values obtained are very small (±0.08 kJ mol^{-1}). The inversion in stability of the *tert*-butyl-CPO:DTBD complex, could be explained by its perpendicular con-

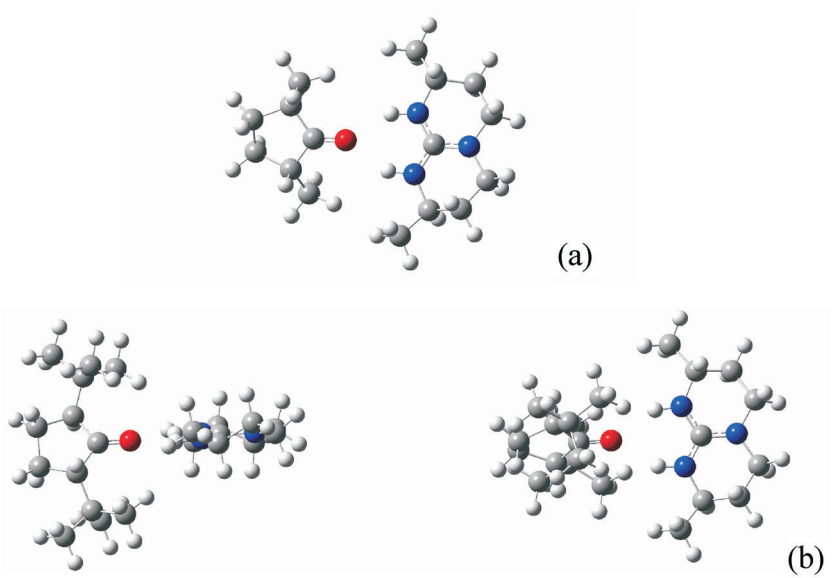

FIG. 2
Planar CH_3-CPO:DTDB complex (a), 90°-rotated views of the perpendicular *t*-Bu-CPO:DTDB complex (b)

figuration since in this configuration the homochiral interaction locates the substituents of each monomer far from each other (Fig. 3).

To further analyse the nature of the gas-phase chiral discrimination energies, correlations with different molecular parameters were investigated to the optimized complexes in order to elucidate which of their features were

TABLE I
Distances between the CPO's O atom and both guanidine H atoms (d(O···H) in Å) in homo- and heterochiral complexes calculated at B3LYP/6-31+G(d,p) level

Complexes	Homo	Hetero	Δ[d(O···H)]
CH_3-CPO:DTBD	2.023	2.005	0.018
t-Bu-CPO:DTBD	2.045	2.036	0.009
CCH-CPO:DTBD	2.060	2.031	0.030
CF_3-CPO:DTBD	2.140	2.118	0.022
CN-CPO:DTBD	2.155	2.152	0.003
F(axial)-CPO:DTBD	2.086	2.089	–0.003
F(equatorial)-CPO:DTBD	2.058	2.057	0.001
Cl(axial)-CPO:DTBD	2.070	2.076	–0.007
Cl(equatorial)-CPO:DTBD	2.090	2.068	0.022

TABLE II
Gas-phase chiral discrimination energies, Δ*E*, of CPO:DTBD complexes, negative energies indicate a heterochiral preference, positive energies indicate homochiral

Complexes	Gas phase, kJ mol^{-1}	Benzene PCM, kJ mol^{-1}
CH_3-CPO:DTBD	–1.76	4.09
t-Bu-CPO:DTBD	0.87	0.66
CCH-CPO:DTBD	–3.26	0.63
CF_3-CPO:DTBD	–0.13	1.42
CN-CPO:DTBD	0.08	–0.21
F(axial)-CPO:DTBD	–0.03	–0.33
F(equatorial)-CPO:DTBD	–0.08	0.09
Cl(axial)-CPO:DTBD	0.20	–0.60
Cl(equatorial)-CPO:DTBD	–0.70	2.77

most involved in chiral discrimination. The four parameters chosen are as follows:

– The dipole moment of the uncomplexed CPO ligand in the gas phase (μ).

– The difference in the homo- and heterochiral distances between the DTBD methyl hydrogen and the nearest atom on the CPO (ΔD, Fig. 4).

– The electronegativity of the most near CPO substituent atom (EN).

– The van der Waals radius of the same atom (vdW).

A multiple linear regression fitting of those four parameters to the chiral discrimination energy yields the following equation:

$$\text{chiral discrimination (gas phase)} = 0.4\mu - 7.14\ \Delta D + 0.29\ EN + 0.69\ vdW - 3.898$$

$$R^2 = 0.969,\ n = 9.$$

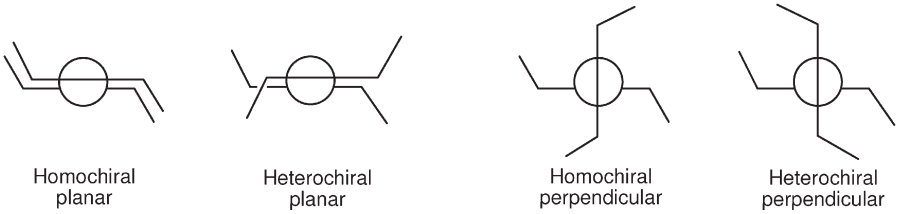

FIG. 3

Possible interactions between the subtitutents of CPO and DBDT depending on the planar or perpendicular arrangements

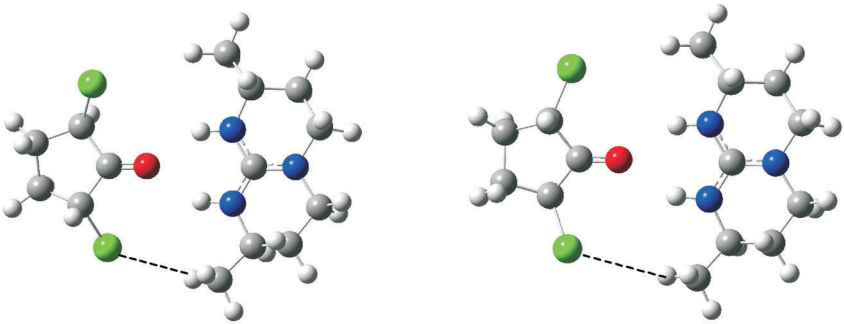

FIG. 4

Definition of the molecular parameter ΔD: difference of [Cl···HCH_2] distance between the hetero- (left) and homochiral (right) complexes

Although the predictive value of this correlation may not be very high, it is clear from that the proximity of the substituent to the guanidine's methyl group (ΔD) is very important in the chiral discrimination of these CPO complexes. This follows from their geometries, since the planar arrangement of the homochiral CPO complexes the substituent is placed very near to the guanidine's methyl group. The sign of every coefficient may also be explained by the planarity of these complexes; taking these parameters as an indication of the interaction between the CPO's substituents with the methyl groups of DTBD, it is evident that the planar arrangement of the CPO series generally places these moieties in closer proximity in the homochiral system (Figs 3 and 4).

Thus, regardless of whether the nature of this interaction is attractive or repulsive (and, hence, independent of the chiral discrimination sign), in the gas phase, planar complexes will exhibit stronger interactions in heterochiral systems while for perpendicular complexes the homochiral case interacts stronger. This follows from the difference in distances between both series of complexes as evidenced in Fig. 3.

The effect that an organic solvent such as benzene can exert on these complexes was studied by single point PCM calculations. Among the benzene-solvated complexes, the discrimination was generally larger and differed substantially from results in the gas phase. Here, the CH_3 disubstituted CPO complex showed the greatest discrimination (4.09 kJ mol^{-1} in favor of the homochiral complex). Although H_2O solvated dimers were also computed; the calculations revealed all CPO complexes to be non-physical, i.e. exhibiting positive dimerization energies, thus any discussion of chiral discrimination energies in these cases is rendered moot.

With regard to the benzene-solvated energies of chiral discrimination, the most important result is the inversion of sign observed among the CPO complexes with respect to gas phase results (except the axial difluoro complex, which has already been shown to be a transition state). This inversion could be explained based on our previous results dimerization of α-amino-alcohols. In this case, the heterochiral complexes formed with C_i, symmetry, showing a null dipole moment, were the most stable in the gas phase. However, those dimers with C_2 symmetry (homochiral ones), and therefore showing a certain dipole moment, were more stable in solvated systems. Thus, in the present case, we could assume that the heterochiral complexes will benefit from greater stability in the gas phase, while the heterochiral complexes will be stabilized in a benzene solution. As heterochiral and homochiral complexes thus encounter opposite effects upon solvation, the

net result is thus an inversion of sign between the solvated and gas-phase energies of chiral discrimination.

Analysis of the Intermolecular Interactions

In all complexes studied the interactions established between the two monomers upon chiral recognition occurs between two N–H groups from the guanidine derivative and the O atom of the cyclopentanone system. The nature and strength of these interactions was analysed by means of two complementary methodologies: the atoms in molecules theory (AIM) which analyses the electron density around the atoms involved in the interaction, and the natural bond orbital theory (NBO) which indicates the MO involved in such an interaction.

According to the AIM results obtained, all the NH···O interactions (two per complex) correspond to strong HBs since each of them presents a bond critical point (BCP) with an electron density (ρ(BCP), a.u.) in the 10^{-2} order of magnitude and the Laplacian of these electron densities ($\nabla^2\rho$(BCP), a.u.) is positive. Results are presented in Table III and an example of all the BCPs detected in a CPO:DTBD complex is shown in Fig. 5.

In general, in each complex the HBs formed seem to be slightly stronger for the heterochiral system than for the homochiral one, in agreement with the HB distances and the chiral discrimination values calculated in the gas phase.

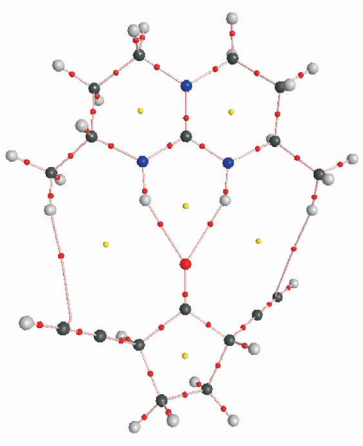

FIG. 5
BCPs (red dots between atoms) found in the interactions established in the CCH-CPO:DTBD heterochiral complex

TABLE III
AIM and NBO analyses for the HB formed between the N–H groups and the O atom and additional interactions in all CPO:DTBD complexes calculated at B3LYP/6-31+G(d,p) level

Complexes	(NH···O)HB			Secondary interactions			
	ρ(BCP) a.u.	$\nabla^2\rho$(BCP) a.u.	$E(2)$ kJ mol^{-1}	Atoms	Dist. Å	ρ(BCP) a.u.	$\nabla^2\rho$(BCP) a.u.
CH_3-CPO:DTBD homo	0.020	0.065	26.78	H···H	2.625	0.003	0.010
CH_3-CPO:DTBD hetero	0.022	0.068	28.24	H···H	2.716	0.002	0.007
t-Bu-CPO:DTBD homo	0.019	0.063	23.97	H···C	–[a]	–	–
t-Bu-CPO:DTBD hetero	0.020	0.064	24.98	H···C	3.727	0.001	0.004
CCH-CPO:DTBD homo	0.019	0.061	23.26	H···C	2.978	0.004	0.012
CCH-CPO:DTBD hetero	0.020	0.065	25.48	H···C	3.248	0.003	0.007
CF_3-CPO:DTBD homo	0.015	0.051	17.95	H···F	2.669	0.005	0.022
CF_3-CPO:DTBD hetero	0.016	0.054	19.25	H···F	2.609	0.005	0.023
CN-CPO:DTBD homo	0.015	0.050	16.86	H···N	2.774	0.005	0.017
CN-CPO:DTBD hetero	0.015	0.050	17.07	H···N	2.789	0.005	0.016
F(ax)-CPO:DTBD homo	0.018	0.057	21.55	H···F	–[a]	–	–
F(ax)-CPO:DTBD hetero	0.017	0.057	21.30	H···F	3.835	0.0004	0.002
F(eq)-CPO:DTBD homo	0.019	0.061	23.35	H···F	3.319	0.001	0.005
F(eq)-CPO:DTBD hetero	0.019	0.061	23.47	H···F	3.350	0.001	0.005
Cl(ax)-CPO:DTBD homo	0.018	0.059	22.34	H···Cl	3.743	0.001	0.004
Cl(ax)-CPO:DTBD hetero	0.018	0.059	21.88	H···Cl	3.672	0.002	0.004
Cl(eq)-CPO:DTBD homo	0.018	0.057	21.05	H···Cl	3.292	0.003	0.009
Cl(eq)-CPO:DTBD hetero	0.018	0.059	22.43	H···Cl	3.163	0.004	0.012

[a] No secondary interaction has been found for those complexes.

Exceptions are the CN-, F(eq)- and Cl(eq,ax)-CPO:DTBD complexes, where the ρ(BCP) values found are similar for both homo- and heterochiral approaches, and the F(ax)-CPO:DTBD complex where the homochiral system seems to form slightly stronger interactions. These AIM results for the CN- and F(eq)-CPO:DTBD cases is in agreement with the small chiral recognition values found (see Table II), indicating that both the strength of the interactions and the stability are very similar for homo- and heterochiral approaches. In the case of the *t*-Bu-CPO:DTBD complex, and according to the AIM analysis, the HBs established in the heterochiral complex seem to be stronger than in the homochiral one, contrary to the energy results which predict the homochiral complex to be more stable. This can be explained because the perpendicular nature of these complexes as mentioned before.

Moreover, using the AIM approach, secondary interactions (BCPs) have been detected between the substituents of the CPO derivatives and the CH_3 groups of the cycloguanidine cations (for an example, see Fig. 5). These interactions are weak, with ρ(BCP) values in the 10^{-3} order of magnitude, and correspond to close-shell interactions. In most of the cases these secondary interactions are very weak to assist significantly in the chiral recognition. However, in some cases where the ρ(BCP) values of the primary HBs are similar for homo- and heterochiral systems, secondary interactions around 5×10^{-3} can collaborate to determine the stability of one approach over the other. This is the case of the CF_3-, CN- or even the Cl(eq)-CPO:DTBD complexes.

Regarding the NBO analysis of the intermolecular interactions, the most important MO interactions are established between the lone pair of the O atom of the CPO systems and the empty σ* N-H orbital of the DTBD molecule. The second-order perturbation energy ($E(2)$, kJ mol^{-1}) values obtained for these MO interactions are shown in Table III. In most of the cases, the larger the $E(2)$ values the more stable the complex is, in good agreement with the chiral recognition computed in gas the phase. Exceptions to this are the CN-, F(ax)- and *t*-Bu-CPO:DTBD complexes. As before, the similar values obtained for the CN-CPO:DTBD complexes are in agreement with the similar stability of both chiral approaches. Regarding the *t*-Bu-CPO:DTBD case, again it could be explained because the lack of planarity of the complex, that is, even though the interactions are stronger in the heterochiral complex, steric effects energetically favor the homochiral one. The exception of the F(ax)-CPO complex also could be explain because this was not an energy minimum and differences have been found all along this study.

Several correlations have been found between all the parameters calculated. Thus, as usual[34–36], there is a very good logarithmic correlation between the HB distance and the ρ(BCP) (Eq. (*1*)):

$$d(HB) = -0.419 \ln [\rho(BCP)] + 0.392 \qquad R^2 = 0.995,\ n = 36. \qquad (1)$$

As well, and as found before[37–39], a good linear correlation has been established between the second order perturbation energy from the NBO analysis and the electron density at the BCP from the AIM theory, indicating the good agreement between both complementary theories in the results here obtained (Eq. (*2*)):

$$E(2) = 409.14\ \rho(BCP) - 2.09 \qquad R^2 = 0.995,\ n = 36. \qquad (2)$$

CONCLUSIONS

A theoretical study of chiral recognition in complexes of the bicyclic guanidine 4,8-dimethyl-1,5,7-triazabicyclodecene with a series of 2,5-disubstituted cyclopentanones has been carried out by means of DFT calculations in both the gas phase and in benzene solution using the polarizable continuum model.

The geometry of the cyclopentanone complexes has been found to be generally planar, except for the complexes formed by the *t*-Bu-CPO, which adopt perpendicular arrangements. In general, the heterochiral complexes have been found to be more stable for the planar complexes and the homochiral one for the perpendicular *t*-Bu-CPO:DTBD complexes. In the case of the CN- and F(eq)-CPO:DTBD complexes the energy difference is so small that no real discrimination can be claimed. Regression analysis has been employed to probe the nature of the interactions underlying the observed gas-phase energies of chiral discrimination.

An inversion of sign between gas phase and benzene solvated results for cyclopentanone complexes has been observed and shown to be a result of the differing effects of the molecular dipole moment in solvation versus its effect in the gas phase.

Parameters obtained from the AIM and NBO analysis, in general confirm the results obtained in terms of chiral recognition energies, and thus, those cases were the HB interactions are stronger, based on the ρ(BCP) and *E*(2) values, correspond to the chiral complex that is more stable. An exception again is the *t*-Bu-CPO case, which is perpendicular and here steric effects

seem to play a more important role that the strength of the intermolecular HBs formed.

Finally, very good correlations between HB distance, ρ(BCP) and $E(2)$ have been found, as a good indication of the robustness of the results obtained in this study utilizing different methodologies.

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REFERENCES

1. Inai Y., Ousaka N., Miwa Y.: *Polym. J.* **2006**, *38*, 432.
2. Mesecar A. D., Koshland D. E.: *Nature* **2000**, *408*, 668.
3. a) Picazo O., Alkorta I., Elguero J., Sundberg M. R., Valo J.: *Eur. J. Inorg. Chem.* **2007**, 324; b) Alkorta I., Elguero J., Zborowski K.: *J. Phys. Chem. A* **2007**, *111*, 1096; c) Zborowski K., Alkorta I., Elguero J.: *Pol. J. Chem.*, **2007**, *81*, 621; and references therein.
4. Echavarren A., Galán A., de Mendoza J., Salmerón A., Lehn J.-M.: *Helv. Chim. Acta* **1988**, *71*, 685.
5. Martín-Portugués M., Alcázar V., Prados P., de Mendoza J.: *Tetrahedron* **2002**, *58*, 2951.
6. Blondeau P., Segura M., Pérez-Fernández R., de Menoza J.: *Chem. Soc. Rev.* **2007**, *36*, 198.
7. Bentley D.: *Arch. Biochem. Biophys.* **2003**, *414*, 1.
8. Alkorta I., Elguero J.: *Ann. Eur. Acad. Sci.* **2009** in press.
9. Corey E. J., Grogan M. J.: *Org. Lett.* **1999**, *1*, 157.
10. Shen J., Nguyen T. T, Goh Y.-P., Ye W., Fu X., Xu J., Tan C.-H.: *J. Am. Chem. Soc.* **2006**, *128*, 13692.
11. Leow D., Lin S., Chittimalla S. K., Fu X., Tan C.-H.: *Angew. Chem. Int. Ed.* **2008**, *47*, 5641; and references therein.
12. van Aken E., Wynberg H., van Bolhuis F.: *J. Chem. Soc., Chem. Commun.* **1992**, 629.
13. Davis A. P., Dempsey K. J.: *Tetrahedron: Asymmetry* **1995**, *11*, 2829.
14. Echavarren A., Galan A., Lehn J.-M., de Mendoza J.: *J. Am. Chem. Soc.* **1989**, *111*, 4994.
15. Sohtome Y., Takemura N., Takada K., Takagi R., Iguchi T., Nagasawa K.: *Chem. Asian J.* **2007**, *2*, 1150.
16. Cuevas F., Di Stefano S., Magrans J. O., Prados P., Mandolini L., de Mendoza J.: *Chem. Eur. J.* **2000**, *6*, 3228.
17. Li J., Jiang W.-Y., Han K.-L., He G.-Z., Li C.: *J. Org. Chem.* **2003**, *68*, 8786.
18. Gordillo R., Houk K. N.: *J. Am. Chem. Soc.* **2006**, *128*, 3543.
19. Ibrahem I., Rios R., Vesely J., Hammar P., Eriksson L., Himo F., Córdova A.: *Angew. Chem. Int. Ed.* **2007**, *46*, 4507.
20. Becke A. D.: *J. Chem. Phys.* **1993**, *98*, 1372.
21. Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Montgomery J. A., Vreven T., Kudin K. N., Burant J. C., Millam J. M., Iyengar S. S., Tomasi J., Barone V., Mennucci B., Cossi M., Scalmani G., Rega N., Petersson G. A., Nakatsuji H., Hada M., Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M.,

Nakajima T., Honda Y., Kitao O., Nakai H., Klene M., Li X., Knox J. E., Hratchian H. P., Cross J. B., Bakken V., Adamo C., Jaramillo J., Gomperts R., Stratmann R. E., Yazyev O., Austin A. J., Cammi R., Pomelli C., Ochterski J. W., Ayala P. Y., Morokuma K., Voth G. A., Salvador P., Dannenberg J. J., Zakrzewski V. G., Dapprich S., Daniels A. D., Strain M. C., Farkas O., Malick D. K., Rabuck A. D., Raghavachari K., Foresman J. B., Ortiz J. V., Cui Q., Baboul A. G., Clifford S., Cioslowski J., Stefanov B. B., Liu G., Liashenko A., Piskorz P., Komaromi I., Martin R. L., Fox D. J., Keith T., Al-Laham M. A., Peng C. Y., Nanayakkara A., Challacombe M., Gill P. M. W., Johnson B., Chen W., Wong M. W., Gonzalez C., Pople J. A.: *Gaussian 03*. Gaussian, Inc., Wallingford, CT 2003.

22. Alkorta I., Elguero J.: *J. Chem. Phys.* **2002**, *117*, 6463.
23. Picazo O., Alkorta I., Elguero J.: *J. Org. Chem.* **2003**, *68*, 7485.
24. Picazo O., Alkorta I., Elguero J.: *J. Phys. Chem. A* **2005**, *109*, 3262.
25. Alkorta I., Elguero J.: *J. Phys. Chem. A* **2006**, *110*, 2259.
26. Tomasi J., Coitino E. L., Cammi R.: *J. Comput. Chem.* **1995**, *16*, 20.
27. Tomasi J., Cammi R.: *J. Comput. Chem.* **1995**, *16*, 1449.
28. Bader R.: *Atoms in Molecules: A Quantum Theory*. Oxford University Press, Oxford 1994.
29. Reed A. E., Curtiss L. A., Weinhold F.: *Chem. Rev.* **1988**, *88*, 899.
30. Biegler-König F. W., Bader R. F. W., Tang T. H.: *J. Comput. Chem.* **1982**, *3*, 317.
31. Popelier P. L. A., with a contribution from Bone R. G. A. (UMIST, England, EU): *MORPHY98*, A Topological Analysis Program. 1999.
32. Alkorta I., Rozas I., Elguero J.: *Chem. Soc. Rev.* **1998**, *27*, 163.
33. Grabowski S. J.: *J. Phys. Chem. A* **2001**, *105*, 10739.
34. Alkorta I., Rozas I., Elguero J.: *J. Struct. Chem.* **1998**, *9*, 243.
35. Alkorta I., Barrios L., Rozas I., Elguero J.: *J. Mol. Struct. (THEOCHEM)* **2000**, *496*, 131.
36. Espinosa E., Alkorta I., Elguero J., Molins E.: *J. Chem. Phys.* **2002**, *117*, 5529.
37. Rozas I., Alkorta I., Elguero J.: *J. Phys. Chem. B* **2004**, *108*, 3335.
38. Rozas I., Alkorta I., Elguero J.: *Org. Biomol. Chem.* **2005**, *3*, 366.
39. Rozas I.: *Phys. Chem. Chem. Phys.* **2007**, *9*, 2782.