A Theoretical Analysis of Enantiomerization in Aromatic Amides

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The mechanisms for enantiomerization in benzamide (**B**), *N*,*N*-dimethylbenzamide (**DB**), 1-naphthamide (**N**), and *N*,*N*-dimethyl-1-naphthamide (**DN**) were investigated both in the gas phase and in solution at the MP2-FC/6-311+G(d,p)//B3LYP/6-31+G(d,p) theory level. The effect of solvent (DMSO, chloroform) was taken into account by using the polarizable continuum model−united atom Hartree−Fock (PCM−UAHF) model. Two different kinds of mechanisms were found. The first kind proceeds through rotation about the Ar−CO bond and inversion at the nitrogen atom, while the second one consists of concerted Ar−CO and C−N rotations. Solvent effect destabilizes mostly the transition states (TSs) with concerted rotations owing to the loss of amide conjugation in these structures. According to our results using DMSO and chloroform as solvents, for benzamide, the mechanism through inversion is, respectively, 14.1 and 13.2 kcal mol^{-1} more favorable than that through concerted rotations. This difference diminishes when a second ring is introduced (11.3 and 10.7 kcal mol^{-1}, respectively, for **N**) and even more when the hydrogen atoms on N are substituted by methyl groups so that for **DB** the route through inversion is, respectively, 5.5 and 4.8 kcal mol^{-1} more favorable than that through concerted Ar−CO and C−N rotations and for **DN** this difference reduces to 1.1 and 0.6 kcal mol^{-1}, respectively, rendering both mechanisms practically competitive in this case.

Introduction

The axial chirality presented by aromatic amides is relevant to asymmetric synthesis. These amides adopt conformations in which the amide group cannot lie in the plane of the aromatic ring for steric reasons,[1] and the stereochemical course of their reactions can be strongly influenced by the bulk of the groups on nitrogen. When the conformers of aromatic amides interconvert sufficiently slowly,[2,3] they are atropisomers,[4,5] which can be used as synthetic tools acting as chiral auxiliaries in asymmetric induction.[6] Therefore, the study of the mechanisms of interconversion of the different conformational minima of aromatic amides and the analysis of the factors determining the corresponding energy barriers are of interest and have been the goal of a number of investigations.[2,3,7−12]

Variable-temperature NMR studies[7] on 2-substituted benzamides and 2-unsubstituted 1-naphthamides have shown that these systems are conformationally labile about the Ar−CO bond rotation and cannot be atropisomeric at room temperature.[8,9] Their rotational Gibbs energy barriers are typically 14−18 kcal mol^{-1}, so even the slowest racemizations, the reactions are half-complete in a second. On the other hand, 2,6-disubstituted benzamides and 2-substituted 1-naphthamides have the potential for atropisomerism and can be resolved into enantiomers.[2,3] For these systems, Ar−CO rotational barriers are generally greater than 21 kcal mol^{-1}.[10,11]

Two primary factors have been proposed to determine the barriers to rotation about the chiral axis of tertiary aromatic amides: the size of the nitrogen substituent lying trans to oxygen (R^N) and the size of the 2-substituent on the aromatic ring (R^R).[10] Two different mechanisms for the enantiomerization process have been suggested. The first one (when $R^R = H$ and R^N is small) would pass through a planar transition state (TS) in which the C−R^R and N−R^N bonds bend sufficiently to allow R^N to slip past R^R. The other one (when $R^R \neq H$ and R^N is large) would imply an alternative TS for concerted Ar−CO and C−N rotation in which the loss of conjugation of the carbonyl group with the lone pair on nitrogen is compensated to some extent by an increment of conjugation with the aromatic ring.

Trying to get a deeper understanding of these mechanisms for enantiomerization in aromatic amides and the role played in them by different substituents on the nitrogen atom as well as the presence of a second ring in 1-naphthamides, we present in this work a density functional theory (DFT) conformational study of benzamide (**B**), *N*,*N*-dimethylbenzamide (**DB**), 1-naphthamide (**N**), and *N*,*N*-dimethyl-1-naphthamide (**DN**), both in gas phase and in solution.

Methods

Full optimizations by means of the Schlegel algorithm[13] at the B3LYP DFT level[14] with the 6-31+G(d,p) basis set were performed using the Gaussian 98 series of programs.[15] The nature of the stationary points was further checked and zero-point vibrational energies (ZPVEs) were evaluated by analytical computations of harmonic vibrational frequencies at the same theory level. Intrinsic reaction coordinate (IRC) calculations at the HF/6-31G(d,p) level were also carried out to check the connection between all of the critical structures located using the Gonzalez and Schlegel method[16] implemented in Gaussian 98. Single-point calculations on the B3LYP geometries were performed at the MP2-FC/6-311+G(d,p) level. MP2 calculations using a triple-ζ basis set have proved to be an adequate theory level to evaluate rotational barrier in *N*-methylbenzamide.[12]

The ΔH, ΔS, and ΔG values were also calculated to obtain results more readily comparable with experiment within the ideal gas, rigid rotor, and harmonic oscillator approximations.[17] A

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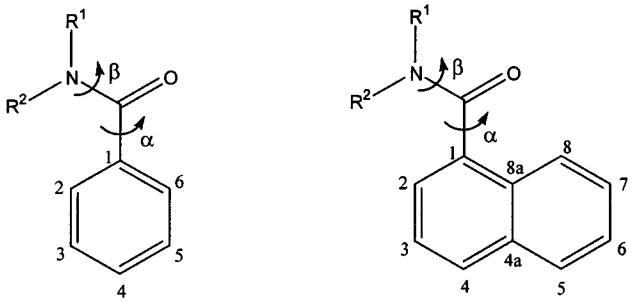
SCHEME 1



pressure of 1 atm and a temperature of 298.15 K were assumed in the calculations.

Quantum chemical computations in solution were carried out on gas-phase optimized geometries using a general self-consistent-reaction field (SCRF) model.[18] In this model, the solvent is represented by a dielectric continuum characterized by its relative static dielectric permittivity, ϵ. The solute is placed in a cavity created in the continuum, the shape of which is chosen to fit as best as possible the solute molecular shape according to the solvent accessible surface. The solute charge distribution polarizes the dielectric, which in turn creates an electric field that modifies both the equilibrium geometry and the electronic charge of the solute. One may take into account this interaction at the self-consistent field (SCF) level by minimizing the energy of the solute plus the electrostatic free energy change corresponding to the solvation process that is given by

$$\Delta G = -^1/_2 E_{\text{int}}$$

where E_{int} is the interaction energy:

$$E_{\text{int}} = \sum_{\alpha} V_{\text{el}}(\mathbf{r}_\alpha) Z_\alpha - \int V_{\text{el}}(\mathbf{r}) \rho(\mathbf{r})\, d\mathbf{r}$$

In this equation, V_{el} is the electrostatic potential created by the polarized continuum in the cavity, $\mathbf{r}_\alpha$ and Z_α are the position vector and the charge of nucleus α, respectively, and $\rho(\mathbf{r})$ is the electronic density at point $\mathbf{r}$. V_{el} may be computed following different approaches. In the model used here the united atom Hartree−Fock (UAHF) parametrization[19] of the polarizable continuum model (PCM)[20] was used, including both electrostatic and nonelectrostatic solute−solvent interactions. A relative permittivity of 46.7 and 4.9 was used to simulate DMSO and chloroform, respectively, as solvents.

Atomic charges were computed carrying out a natural population analysis (NPA) using the corresponding B3LYP/6-31+G(d,p) density matrixes.

Results and Discussion

We present first the results obtained for the two benzamides and then for the two naphthamides studied. Figures 1−4 display the optimized geometries of the critical structures located for **B**, **DB**, **N**, and **DN**. Tables 1−4 collect the corresponding energies for the four systems studied in this work.

The zero value for the rotation angles about the aryl−CO bond (α) and about the C−N bond (β) are indicated in Scheme 1 where atom numbering is also displayed. Counterclockwise rotations are taken as positive when looked at from the amidic C and from the N atom. Unless otherwise stated, we will give in the text the relative MP2-FC/6-311+G**//B3LYP/6-31+G** electronic energies including the ZPVE correction.

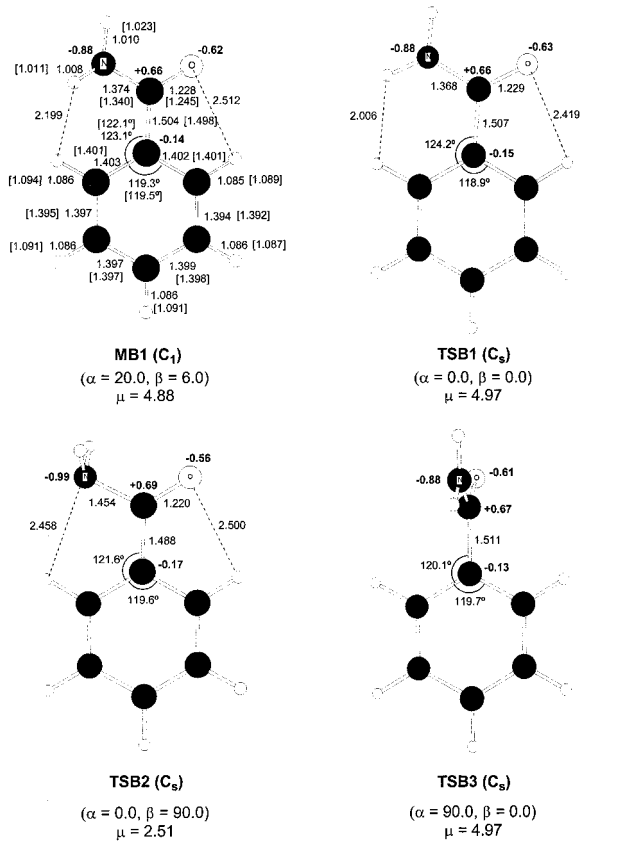


Figure 1. B3LYP/6-31+G(d,p) optimized geometries for benzamide. Distances and angles are given in Å and deg, respectively. In square brackets, experimental values from ref 21 are given. NPA charges (in e) are given in boldface. Dipolar moments in DMSO, μ, are given in D.

Benzamides. The most stable conformation located for benzamide corresponds to **MB1**, which presents two equivalent structures ($\alpha = 20.0°$, $\beta = 6.0°$ and $\alpha = -160.0°$, $\beta = 6.0°$) and their enantiomers **MB1'** ($\alpha = -20.0°$, $\beta = -6.0°$ and $\alpha = 160.0°$, $\beta = -6.0°$). These structures present a H-bond interaction between the oxygen atom and one of the ortho hydrogen atoms located at a distance of 2.512 Å and a small repulsive interaction between one of the amide hydrogen atoms and the other ortho hydrogen atom located at a distance of 2.199 Å. Because of these interactions, the angle C(amide)−C1−C2 is forced to be 123.1°. The nitrogen atom is slightly pyramidalized (the sum of the H−N−H and the two C−N−H bond angles, ω, is 354.9°) with the hydrogen atoms oriented outward. **MB1** is connected with its enantiomer **MB1'** accross the ring through two different routes. The first one takes place through inversion at the N atom and corresponds to a rotation of $\Delta\alpha = 20.0°$ and $\Delta\beta = 6.0°$ with a diminution of the pyramidalization to reach a planar TS, **TSB1**, of C_s symmetry that is 1.0 kcal mol^{-1} less stable than **MB1**. **TSB1** presents a H-bonding interaction between the oxygen atom and the hydrogen atom bonded to C6 2.419 Å away from it and a repulsive interaction between one of the amidic hydrogen atoms and the hydrogen atom bonded to C2 located at a distance of 2.006 Å, causing the C(amide)−C1−C2 angle to become 124.2°. The second route corresponds to a mechanism without inversion at the N atom going through a TS, **TSB2** ($\alpha = 0.0°$; $\beta = 90.0°$), of C_s symmetry, for the concerted rotations α and β with an energy barrier of 12.1 kcal mol^{-1}. **TSB2** is stabilized by a H-bonding interaction between the oxygen atom and the hydrogen atom bonded to C6 at a distance of 2.500 Å. The nitrogen atom is strongly pyramidalized ($\omega = 318.9°$) with the amidic hydrogen

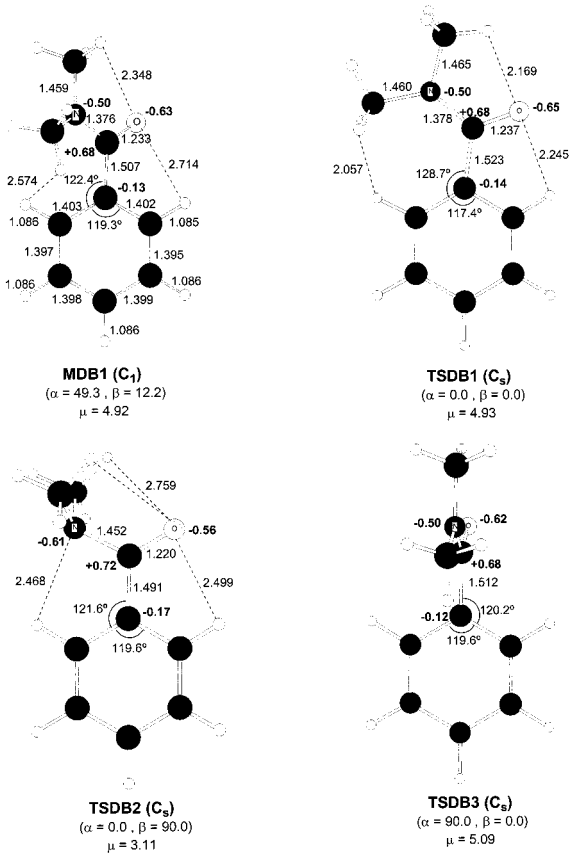


Figure 2. B3LYP/6-31+G(d,p) optimized geometries for *N*,*N*-dimethylbenzamide. Distances and angles are given in Å and deg, respectively. NPA charges (in e) are given in boldface. Dipolar moments in DMSO, μ, are given in D.

atoms oriented outward. **MB1** is also connected with its enantiomer **MB1'** on the same side of the ring through a TS, **TSB3** ($\alpha = 90.0°$; $\beta = 0.0°$), of C_s symmetry with an energy barrier of 2.2 kcal mol^{-1}.

For *N*,*N*-dimethylbenzamide, calculations render an energy profile qualitatively similar to that found for benzamide. The most stable conformer, **MDB1**, appears at $\alpha = 49.3°$ and $\beta = 12.2°$. The oxygen atom is now 2.714 Å away from the hydrogen atom bonded to C6, and the distance between the hydrogen atom bonded to C2 and the nearest hydrogen atom of one of the methyl groups is 2.574 Å (see Figure 2). The nitrogen atom presents a slight pyramidalization ($\omega = 357.7°$). The TS for α rotation and inversion at the N atom, **TSDB1** ($\alpha = 0.0°$; $\beta = 0.0°$) of C_s symmetry, presents an energy barrier of 8.3 kcal mol^{-1} and displays a strong repulsive interaction between the hydrogen atom bonded to C2 and two of the hydrogen atoms of the methyl group oriented toward the ring (both H···H distances 2.057 Å) as well as two hydrogen-bonding contacts between the oxygen atom and the hydrogen atom bonded to C6 and one of the hydrogen atoms of the second methyl group (CH···O distances of 2.245 and 2.169 Å, respectively). The TS for the α and β concerted rotations without inversion, **TSDB2** ($\alpha = 0.0°$, $\beta = 90.0°$) of C_s symmetry, is 11.1 kcal mol^{-1} above **MDB1** and is stabilized by a hydrogen-bonding interaction between the oxygen atom and the hydrogen atom bonded to C6 (CO···H distance of 2.499 Å). In **TSDB2**, the nitrogen atom is strongly pyramidalized ($\omega = 332.5°$). **TSDB1** and **TSDB2** connect **MDB1** with its enantiomer across the ring, **MDB1'**. **MDB1** is connected with its enantiomer on the same side of the ring, **MDB1'** ($\alpha = 130.7°$; $\beta = -12.2°$) through a TS, **TSDB3** ($\alpha = 90.0°$; $\beta = 0.0°$), of C_s symmetry with an energy barrier of 0.5 kcal mol^{-1}.

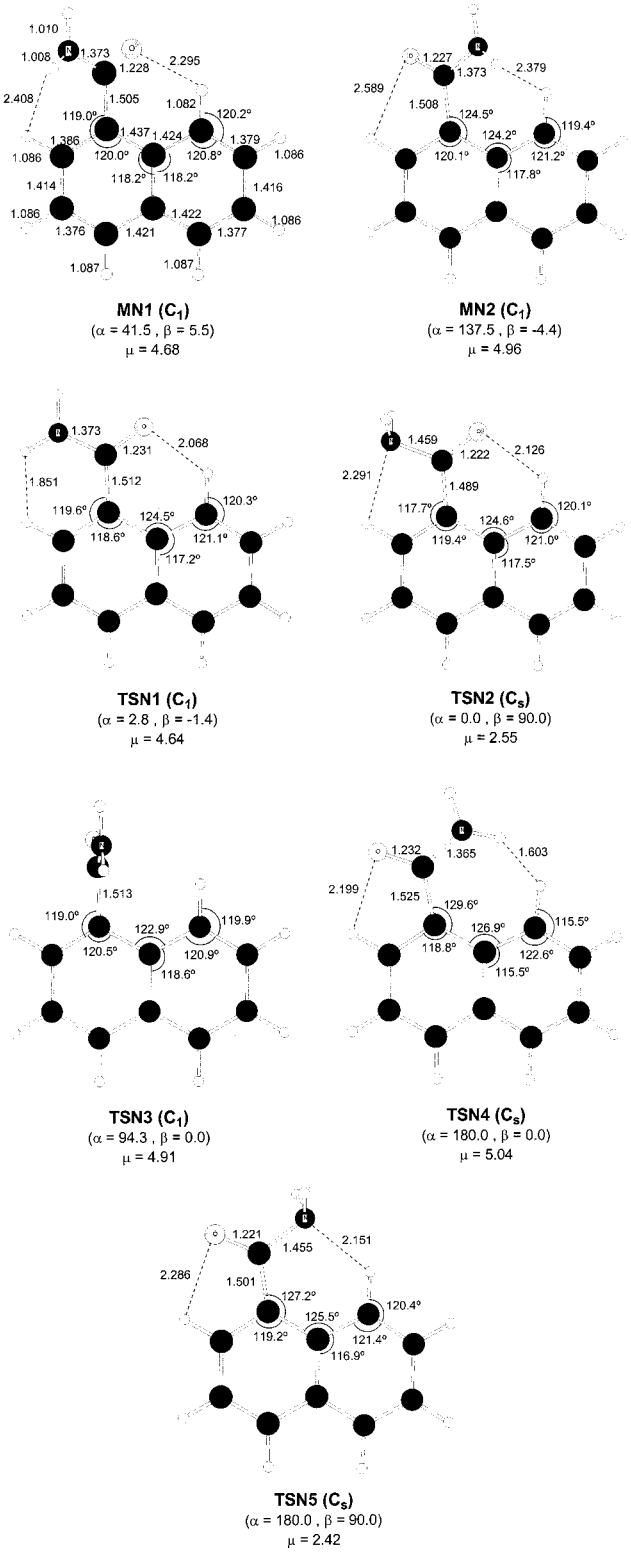


Figure 3. B3LYP/6-31+G(d,p) optimized geometries for 1-naphthamide. Distances and angles are given in Å and deg, respectively. Dipolar moments in DMSO, μ, are given in D.

Naphthamides. The most stable conformation located for naphthamide corresponds to **MN1** with $\alpha = 41.5°$ and $\beta = 5.5°$. This structure presents a H-bond interaction between the oxygen atom and the hydrogen atom bonded to C8 located at a distance of 2.295 Å and a repulsive interaction between one of the amide hydrogen atoms and the hydrogen atom bonded to C2 located

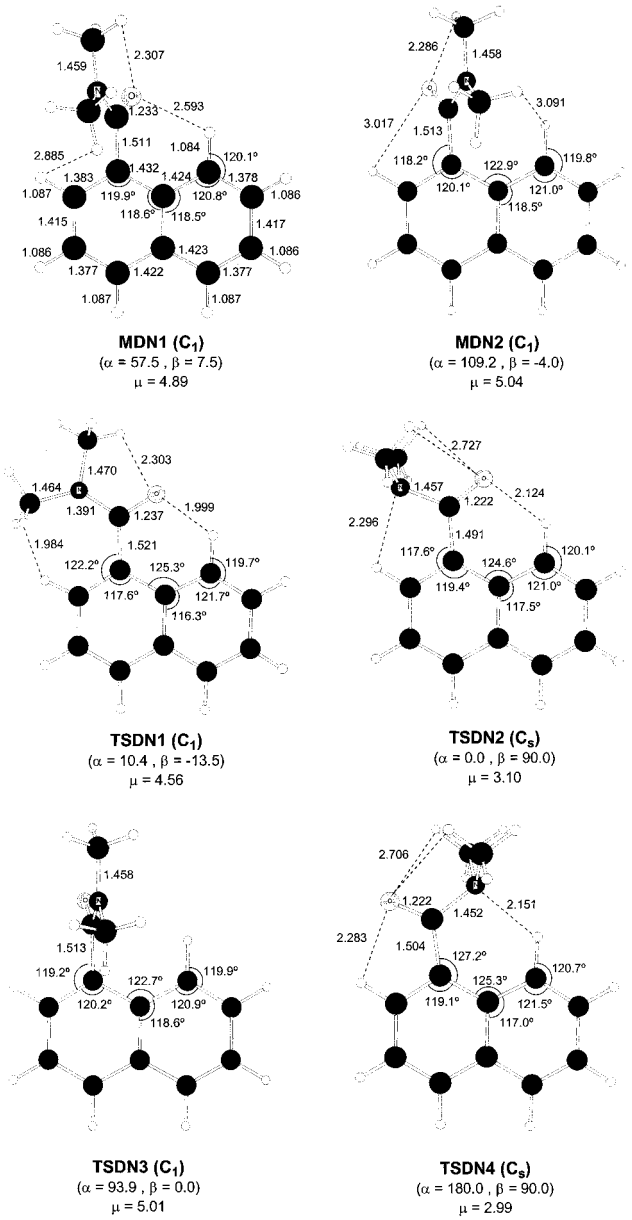


Figure 4. B3LYP/6-31+G(d,p) optimized geometries for *N*,*N*-dimethyl-1-naphthamide. Distances and angles are given in Å and deg, respectively. Dipolar moments in DMSO, μ, are given in D.

TABLE 1: MP2-FC/6-311+G(d,p)//B3LYP/6-31+G(d,p) Relative Electronic Energies, ZPVE Corrections, Entropic Contributions, and ΔG Values in Gas Phase and in DMSO and Chloroform (kcal mol^{-1}) for Benzamide[a]

benzamide structures	ΔE	ΔE + Δ(ZPVE)	$-T\Delta S$	ΔG_{gas}	DMSO ($\epsilon = 46.7$) $\Delta G_{solution}$	chloroform ($\epsilon = 4.9$) $\Delta G_{solution}$
MB1	0.0	0.0	0.0	0.0	0.0	0.0
TSB1	1.4	1.0	0.6	1.3	1.0	1.1
TSB2	12.6	12.1	0.7	12.4	15.1	14.3
TSB3	2.6	2.2	0.9	2.8	2.7	2.7

[a] ZPVE and thermal corrections were evaluated at 1 atm and 298.15 K from B3LYP/6-31+G(d,p) frequency calculations. $\Delta G_{solution} = \Delta G_{gas} + \Delta G_{solvation}$, where $\Delta G_{solvation}$ was calculated at the B3LYP/6-31+G(d,p) level.

at a distance of 2.408 Å. The nitrogen atom is slightly pyramidalized ($\omega = 356.3°$) with the hydrogen atoms oriented outward. From **MN1**, the system may reach its enantiomer **MN1'** following three different routes. Two of them proceed through α rotation and inversion at the nitrogen atom and the other one through concerted aryl−CO and C−N rotations. The first route through inversion proceeds through **TSN1** ($\alpha = 2.8°$; $\beta = -1.4°$) of C_1 symmetry, in which inversion at the nitrogen atom has already taken place, with an energy barrier of 4.3 kcal mol^{-1}. The second path through inversion goes through the enantiomer of **TSN1**, **TSN1'** ($\alpha = -2.8°$; $\beta = 1.4°$). **TSN1** and **TSN1'** are connected through a planar second-order saddle point of C_s symmetry with $\alpha = 0.0°$ and $\beta = 0.0°$. The third route from **MN1** to **MN1'** consists of concerted α and β rotations through the TS **TSN2** ($\alpha = 0.0°$; $\beta = 90.0°$) of C_s symmetry with an energy barrier of 13.9 kcal mol^{-1}. In **TSN2**, the N atom is strongly pyramidalized ($\omega = 317.9°$) with the hydrogen atoms bonded to it oriented outward. The C(amide)−C1−C2 and H−C8−C8a angles have a value of 117.7° and 118.9°, respectively, making possible the interaction between the oxygen atom and the hydrogen atom on C8 (O···H distance

TABLE 2: MP2-FC/6-311+G(d,p)//B3LYP/6-31+G(d,p) Relative Electronic Energies, ZPVE Corrections, Entropic Contributions, and ΔG Values in Gas Phase and in DMSO and Chloroform (kcal mol^{-1}) for *N*,*N*-Dimethylbenzamide[a]

N,*N*-dimethyl-benzamide structures	ΔE	ΔE + Δ(ZPVE)	$-T\Delta S$	ΔG_{gas}	DMSO ($\epsilon = 46.7$) $\Delta G_{solution}$	chloroform ($\epsilon = 4.9$) $\Delta G_{solution}$
MDB1	0.0	0.0	0.0	0.0	0.0	0.0
TSDB1	8.1	8.3	1.4	9.1	9.3	9.3
TSDB2	11.5	11.1	1.7	12.2	14.8	14.1
TSDB3	0.8	0.5	1.0	1.1	1.3	1.3

[a] ZPVE and thermal corrections were evaluated at 1 atm and 298.15 K from B3LYP/6-31+G(d,p) frequency calculations. $\Delta G_{solution} = \Delta G_{gas} + \Delta G_{solvation}$, where $\Delta G_{solvation}$ was calculated at the B3LYP/6-31+G(d,p) level.

TABLE 3: MP2-FC/6-311+G(d,p)//B3LYP/6-31+G(d,p) Relative Electronic Energies, ZPVE Corrections, Entropic Contributions, and ΔG Values in Gas Phase and in DMSO and Chloroform (kcal mol^{-1}) for 1-Naphthamide[a]

naphthamide structures	ΔE	ΔE + Δ(ZPVE)	$-T\Delta S$	ΔG_{gas}	DMSO ($\epsilon = 46.7$) $\Delta G_{solution}$	chloroform ($\epsilon = 4.9$) $\Delta G_{solution}$
MN1	0.0	0.0	0.0	0.0	0.0	0.0
MN2	0.6	0.7	0.0	0.7	0.8	0.8
TSN1	4.6	4.3	0.6	4.6	4.6	4.6
TSN2	14.1	13.9	0.6	14.1	15.9	15.3
TSN3	1.5	1.1	0.9	1.6	1.6	1.6
TSN4	8.8	8.4	−0.8	7.4	7.6	7.5
TSN5	17.3	16.9	0.1	16.7	18.2	17.7

[a] ZPVE and thermal corrections were evaluated at 1 atm and 298.15 K from B3LYP/6-31+G(d,p) frequency calculations. $\Delta G_{solution} = \Delta G_{gas} + \Delta G_{solvation}$, where $\Delta G_{solvation}$ was calculated at the B3LYP/6-31+G(d,p) level.

TABLE 4: MP2-FC/6-311+G(d,p)//B3LYP/6-31+G(d,p) Relative Electronic Energies, ZPVE Corrections, Entropic Contributions, and ΔG Values in Gas Phase and in DMSO and Chloroform (kcal mol^{-1}) for *N*,*N*-Dimethylnaphthamide[a]

N,*N*-dimethyl-naphthamide structures	ΔE	ΔE + Δ(ZPVE)	$-T\Delta S$	ΔG_{gas}	DMSO ($\epsilon = 46.7$) $\Delta G_{solution}$	chloroform ($\epsilon = 4.9$) $\Delta G_{solution}$
MDN1	0.0	0.0	0.0	0.0	0.0	0.0
MDN2	−0.3	−0.3	0.2	−0.1	0.2	0.0
TSDN1	14.4	14.9	2.4	16.6	16.1	16.1
TSDN2	14.1	14.0	2.3	15.5	17.3	16.7
TSDN3	0.0	0.0	1.8	1.2	1.7	1.5
TSDN4	16.9	16.8	2.2	18.3	20.1	19.4

[a] ZPVE and thermal corrections were evaluated at 1 atm and 298.15 K from B3LYP/6-31+G(d,p) frequency calculations. $\Delta G_{solution} = \Delta G_{gas} + \Delta G_{solvation}$, where $\Delta G_{solvation}$ was calculated at the B3LYP/6-31+G(d,p) level.

of 2.126 Å) and between the nitrogen atom and the hydrogen atom on C2 (N···H distance of 2.291 Å). From **MN1**, the system may also reach the minimum energy conformation **MN2** ($\alpha = 137.5°$; $\beta = -4.4°$), very like **MN1** in energy**,** through the TS **TSN3** ($\alpha = 94.3°$; $\beta = 0.0°$) of C_1 symmetry with an energy barrier of 1.1 kcal mol^{-1}. In **TSN3**, the NH_2 group is planar and the amidic moiety is almost orthogonal to the rings plane. **MN2** is only 0.7 kcal mol^{-1} less stable than **MN1** and presents a C(amide)−C1−C8a angle of 124.5° favoring the hydrogen-bond interaction between the oxygen atom and the hydrogen atom on C2 while reducing the repulsion between one of the amidic hydrogen atoms and the hydrogen on C8. In **MN2**, the NH_2 group displays a slight pyramidalization ($\omega = 355.1°$) with the hydrogen atoms oriented outward. **MN2** is connected with its enantiomer **MN2'** in two different ways. The first one takes place through α rotation and inversion at N through the TS **TSN4** ($\alpha = 180.0°$; $\beta = 0.0°$) of C_s symmetry with an energy barrier of 8.4 kcal mol^{-1}. The second one corresponds to concerted α and β rotations without inversion at N through the TS **TSN5** ($\alpha = 180.0°$; $\beta = 90.0°$) of C_s symmetry with an energy barrier of 16.9 kcal mol^{-1}. In **TSN5**, the nitrogen atom, which presents a strong pyramidalization ($\omega = 316.8°$), is interacting with the hydrogen atom on C8 (N···H distance of 2.151 Å), and the hydrogen atoms on N are oriented outward. The oxygen atom is also interacting with the hydrogen atom on C2 at a distance of 2.286 Å.

For *N*,*N*-dimethyl-1-naphthamide, the **MDN1** conformer appears at $\alpha = 57.5°$ and $\beta = 7.5°$. In this structure, the oxygen atom is 2.593 Å away from the hydrogen atom on C8. The nitrogen atom is hardly pyramidalized ($\omega = 359.2°$). The three TSs connecting **MDN1** and its enantiomer **MDN1'**, **TSDN1** ($\alpha = 10.4°$; $\beta = -13.5°$), its enantiomer **TSDN1'**, and **TSDN2** ($\alpha = 0.0°$; $\beta = 90.0°$), have now similar energy barriers of 14.9 kcal mol^{-1} (both enantiomers) and 14.0 kcal mol^{-1}, respectively. In **TSDN1** and **TSDN1'**, the oxygen atom is interacting with a hydrogen atom of one of the methyl groups and with the hydrogen atom on C8 at distances of 2.303 and 1.999 Å, respectively, while two of the hydrogen atoms of the other methyl group are 1.984 Å away from the hydrogen atom on C2. The $N(CH_3)_2$ group is slightly pyramidalized ($\omega = 357.9°$). In **TSDN2**, the oxygen atom is interacting with the hydrogen atom on C8 at a distance of 2.124 Å and the nitrogen atom is situated at 2.296 Å from the hydrogen atom on C2. In this structure, N is strongly pyramidalized ($\omega = 332.4°$) with the methyl groups oriented outward. **MDN2** ($\alpha = 109.2°$, $\beta = -4.0°$) is very like **MDN1** in energy (only 0.3 kcal mol^{-1} more stable than **MDN1**) and presents the $N(CH_3)_2$ group slightly pyramidalized ($\omega = 359.7°$). **MDN2** and its enantiomer **MDN2'** are connected only through **TSDN4** ($\alpha = 180.0°$, $\beta = 90.0°$) of C_s symmetry with an energy barrier of 16.8 kcal mol^{-1}. No TS was found analogous to **TSN4** directly connecting the minimum energy structure **MN2** and its enantiomer **MN2'** through α rotation and inversion at N. **MDN2** is also connected with **MDN1** through the TS **TSDN3** ($\alpha = 93.9°$, $\beta = 0.0°$), which has almost the same energy as **MDN1**.

Comparison with Experiment. The molecular structure of benzamide has been experimentally determined by single-crystal X-ray analysis at room temperature.[21] A neutron diffraction refinement at low temperatures has been reported more recently.[22] Our theoretical results are in good agreement with the figures from neutron diffraction. In effect, we see from **MB1** in Figure 1 that DFT bond distances agree with the experimental ones within ±0.01 Å except for the C−O and C−N bonds owing to the presence of hydrogen bonding in the solid phase, which decreases the double-bond character of the C−O bond and increases the double-bond character of the C−N bond. Our results for these two bonds are in much better agreement with the experimental data from electron diffraction in the gas phase (C−O = 1.225(3) Å; C−N = 1.380(11) Å).[23] This good agreement of our results with experimental data can be considered as a support of the adequacy of the theoretical method employed in the present work.

To more readily compare our results with experimental data, we performed the calculation of ΔG_{gas} at 1 atm and 298.15 K. The effect of solvent was also taken into account by means of PCM calculations to obtain $\Delta G_{solution}$. The corresponding values obtained for all of the critical structures found in this work are presented in Tables 1−4.

When thermal corrections and entropy are taken into account all of the TSs in general become less-stabilized than the corresponding minimum structures owing to the entropy contribution to ΔG (see Tables 1−4). This destabilization is more important when the hydrogen atoms bonded to N are substituted by methyl groups. The only exceptions to this general behavior are **TSN4** and **TSN5**.

The effect of solvent causes the TSs through concerted rotations to become destabilized by 1.0−1.9 kcal mol^{-1} in chloroform and by 1.5−2.6 kcal mol^{-1} in DMSO relative to the most stable minimum structure, while ΔG for the other critical structures varies between −0.4 and +0.4 kcal mol^{-1} in both solvents relative to the gas-phase values. This dependence of the energy barrier for rotation on the polarity of solvent is in agreement with the interpretation of the experimental behavior found for aromatic amides.[10] In effect, it has been suggested that a TS in which amide conjugation is lost would become destabilized by polar solvents with respect to the conjugated ground state whereas a TS with an amide conjugation similar to that of the minimum structure would determine a barrier to rotation similar to that in gas phase. Our computational results are in accordance with this interpretation given that the TSs through concerted rotations present a larger negative charge on N and a less negative charge on O compared with the minimum structures, and a lower dipole moment, μ (see Figures 1−4). It has been also suggested that the loss of amide conjugation would be partially compensated by an increase of conjugation of the carbonyl group with the aromatic rings. Our computational results clearly show that the aryl−CO conjugation presents its largest extent in the TSs through concerted rotations as displayed in Figure 5 for the case of 1-naphthamide.

According to our results in DMSO and chloroform, for benzamide the mechanism through inversion is, respectively, 14.1 and 13.2 kcal mol^{-1} more favorable than that through concerted rotations. This difference diminishes when a second ring is introduced and even more when the hydrogen atoms on N are substituted by methyl groups. Thus, for *N*,*N*-dimethyl-1-naphthamide in DMSO and chloroform, the route through inversion is only, respectively, 1.1 and 0.6 kcal mol^{-1} more favorable than that through concerted rotations so that in practice both mechanisms could be competitive. This is in agreement with the suggestion by experimentalists that the bulkier the substituents on N are the more favorable the route through concerted rotations becomes. The value obtained by us for the energy barriers for the enantiomerization of *N*,*N*-dimethyl-1-naphthamide (see Table 4) is within the 14−18 kcal mol^{-1} range experimentally found for 2-unsubstituted 1-naphthamides.[8,9] It is also interesting to note that, for steric reasons, in the minimum structures of the dimethylamides studied the amidic group is more separated from the rings plane (larger α values) than in

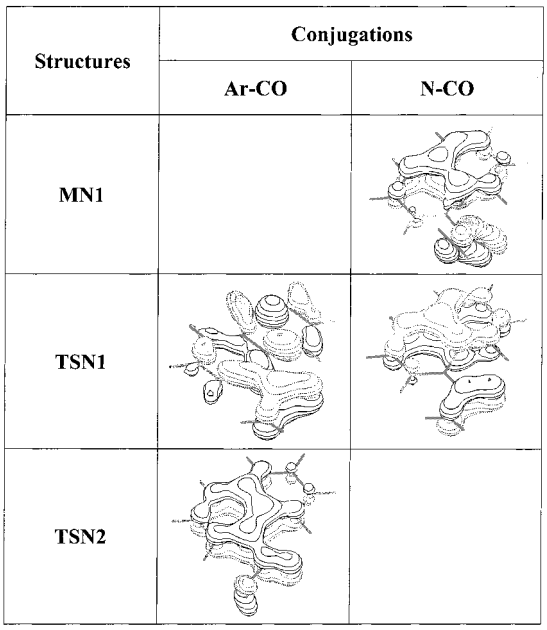


Figure 5. Computer plot of the MOs of the critical structures **MN1**, **TSN1**, and **TSN2** of 1-naphthamide showing the Ar−CO and N−CO conjugations when present.

those of the unsubstituted amides. The same trend is observed for the TSs through inversion at the N atom in naphthamides, which unlike those in benzamides do not display C_s symmetry. In the naphthamides, the two minima located on the same side of the rings plane present similar energy and can easily interconvert through energy barriers lower than 2 kcal mol^{-1}. As a consequence, the enantiomerization of the less-stable minima could take place more readily via the most stable minima rather than through the direct rotation across the rings plane.

In summary, MP2-FC/6-311+G(d,p)//B3LYP/6-31+G(d,p) calculations render two different kinds of mechanisms for enantiomerization in benzamide, *N*,*N*-dimethylbenzamide, 1-naphthamide, and *N*,*N*-dimethyl-1-naphthamide. The first kind proceeds through rotation about the Ar−CO bond and inversion at the nitrogen atom, while the second one consists of concerted Ar−CO and C−N rotations. Solvent effect destabilizes mostly the TSs with concerted rotations owing to the loss of amide conjugation in these structures. In all of the cases, the mechanisms through inversion are the most favorable ones, although for *N*,*N*-dimethyl-1-naphthamide the difference with respect to concerted rotations is only of 1.2 kcal mol^{-1} in DMSO and 0.6 kcal mol^{-1} in chloroform. While the energy barrier corresponding to the concerted rotations mechanism is not very dependent on the number of rings and the substituents on N, the barrier for the mechanisms through inversion increases when a second ring is introduced and even more when the hydrogen atoms on nitrogen are substituted by methyl groups so that for *N*,*N*-dimethyl-1-naphthamide both kinds of mechanisms could result practically competitively.

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