A Computational and Experimental Study on the Relative Stabilities of Cis and Trans Isomers of *N*-Alkylamides in Gas Phase and in Solution

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The cis/trans ratio of *N*-methylformamide (NMF), *N*-methylacetamide (NMA), and *N*-(2-*endo*-norbornyl)-formamide (NNF) in dilute solutions in chloroform, methanol, and water have been experimentally measured by ^{1}H NMR. Unlike NMA and NMF, the cis/trans ratio of NNF is sensitive to the solvent environment. To understand the anomalous behavior of NNF, we have performed calculations of ΔG and other observables between the cis and trans isomers of NMA, NMF, and NNF both in gas phase and in solution using several ab initio and DFT methods and SCRF models. The strikingly predominance of the trans isomers of *N*-alkyl substituted formamides can be rationalized in terms of close contact interactions between the formyl group and the C−H bond of the *N*-alkyl group. The molecular geometries and dipole moments of the studied amides using the RHF and B3LYP theoretical levels and split valence sets are in good accordance with the experimental values. The rotational barriers (ca. 7.0 kcal/mol) around the C2−N bond of *cis*- and *trans*-NNF were determined with the RHF/3-21G and B3LYP/6-31G* methods. On the other hand, the PCM model of the SCRF theory offers a satisfactory explanation of the different solvent dependence of NMA and NNF but fails in the computation of the cis/trans ratio of NMF in polar solvents.

Introduction

The importance of the amide functional group is demonstrated by the fact that the amide peptide bond is the basic linkage in peptides and proteins. The geometric constraints of the amide bond, such as the nearly planar structure around the C−N bond because of its partial double-bond character, define the conformational freedom of motion for many small molecules as well as for peptides and proteins.[1] Virtually, no cis-peptide bond occurs in the X-ray structure for proteins when the nitrogen is secondary,[2] where cis refers to the relative orientation of the substituents on the amide nitrogen and carbonyl carbon. It is unclear how the preference for trans-peptide bonds in proteins is partitioned between intrinsic and environmental effects.[2] To help elucidate these fundamental questions, several studies have been undertaken on models. Some of the simplest models for the main chain of proteins are *N*-methylformamide (NMF) and *N*-methylacetamide (NMA). The properties of isolated (gas phase) NMF and NMA, including the geometry, dipole moment, and energy differences between cis and trans isomers, have been extensively studied using ab initio methods.[1]

For the understanding of the structural properties and biological functions of amides and proteins, it is important to know how they interact with solvents, particularly water. So far, most theoretical investigations concerned with solvent interactions feature Monte Carlo (MC) statistical mechanics,[3] molecular dynamics simulations, and water complexes[3,4] as well as continuum models using ab initio methods.[5] There is, however, less experience with density functional theory (DFT) calculations coupled with continuum models to investigate structural and energetic aspects of amides and their interactions with solvents.[6]

Cis/trans isomerism of secondary amides in solution has been experimentally studied by NMR methods. Thus, the trans isomers in a series of *N*-monosubstituted alkylamides were the preferred geometry.[7,8] In the *N*-alkylformamides, a slightly increase in the proportion of the cis form with the bulk of the *N*-alkyl group (R) has been observed by ^{1}H NMR (R = CH_3, 8% cis, R = *i*Pr, 12% cis, both as pure compounds) as well as by ^{13}C NMR (R = *n*Pr, 15% cis; R = *t*Bu, 24% cis, both in d_6-DMSO) methods.[7] However, several complexities are encountered in the interpretation of NMR results because of solute−solvent interactions and self-association of the solute. Thus, the cis/trans ratio of formanilide is concentration-dependent in $CDCl_3$ and increases from 27% to 55% cis as the molar fraction of the amide decreases from 0.525 to 0.015.[9] On the other hand, the persistence of self-association with dilution in the cis isomer was attributed to the formation of cyclic dimers.[9−11]

The alkyl amides NMF and NMA have been characterized with respect to equilibrium constants of cis/trans isomerization by NMR methods at low concentrations in different solvents (20 °C, 0.025M). At the concentration indicated, there were no signs of aggregation of these solutes in any of the solvents examined.[12] The resulting constants cover a range of cis fraction from 1.39% (NMA in D_2O) to 10.5% (NMF in $CDCl_3$), but remain nearly constant for NMA and NMF in several solvents.[12] The remarkable insensitivity of the cis/trans equilibria of NMA

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TABLE 1: Abundance of the Trans Isomers of NMF, NMA, and NNF in $CDCl_3$ and MeOH-d_4 at 20 °C

amide	solvent	% trans	M (mol/L)
NMF	$CDCl_3$	88.8 ± 0.1	0.12
	CD_3OD	94.1 ± 0.1	0.12
NNF	$CDCl_3$	76.4 ± 1.0	0.05
	CD_3OD	91.8 ± 0.1	0.05
NMA	$CDCl_3$	97.9 ± 0.1	0.05
	CD_3OD	99.2 ± 0.1	0.05

and NMF to changes in solvent and the preponderance of the trans isomer agree with the preference of peptide bonds for the trans configuration.[1,2] This fact is also consistent with high level MC statistical mechanic simulations using the MP2/6-31G*//HF/6-31G* method,[13] as well as the aqueous solvation thermodynamics by integral equation theories and molecular dinamics (MD) simulations, carried out on NMA.[14]

It is unclear the origin of the preference for trans peptide bonds in proteins (vide supra). This question can be extended to the strikingly preference of formamides for the trans form,[7,10] since cis and trans isomers would appear to have comparable steric crowding between the carbonyl oxygen or the formyl hydrogen and the *N*-alkyl substituents.[9] The marked preference for the trans isomer of *N*-alkylformamides was supposed to be a combination of steric and charge interaction factors.[15] However, it could be interesting to find a more detailed description of these interactions.

In the course of our study on the mechanism of the Leuckart reaction of 2-norbornanones,[16] we have isolated *N*-(2-*endo*-norbornyl)formamide (NNF). When doing the spectroscopic characterization, we have observed an anomalously high proportion of cis isomer that changes significantly with the solvent when measured by ^{1}H NMR at low concentration (Table 1). To elucidate this unprecedented sensitivity of the cis/trans ratio to solvent effects, as well as the preference of all amides for the trans isomer, we have carried out in this paper experimental determinations of the cis/trans ratios of NMF, NMA, and NNF in apolar ($CDCl_3$) and polar (MeOH-d_4; NNF is not soluble in water) solvents. The experimental results (Table 1) have been compared with computational estimations of the cis/trans energy differences of the three amides at different theoretical levels and basis sets both in the gas phase and in solution.

Experimental Results

Leuckart Reaction. The reaction of commercially available (±)-2-norbornanone with formamide and formic acid at 150 °C (24 h), followed by extraction in CH_2Cl_2/H_2O, gives (±)-*N*-(2-norbornyl)formamide as a mixture of endo/exo isomers with a 9:1 ratio (measured by ^{1}H NMR).[16] Pure NNF was isolated after crystallization from hexane (mp 65.3−67.4 °C, ref 17 66 °C), in an overall yield of 84%. NMF, NMA, and (±)-2-norbornanone were purchased from Aldrich Chemicals Co.

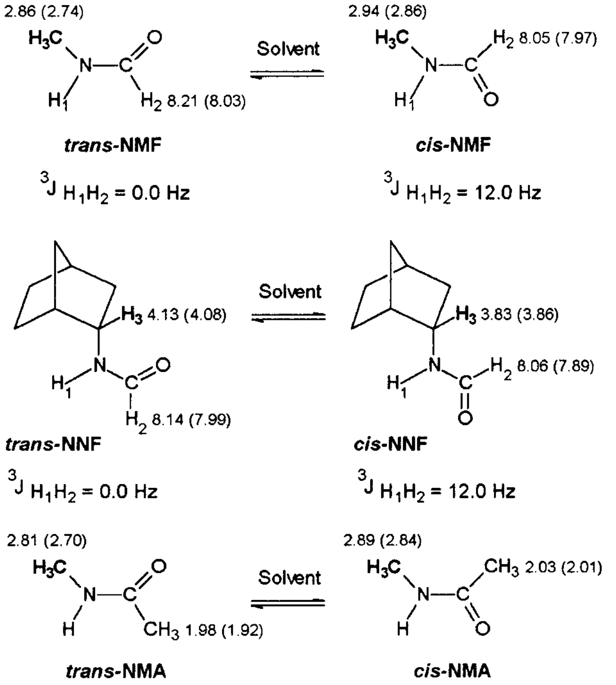


Figure 1. Interesting *J* (in Hz) and δ (in ppm) of NNF, NMF, and NMA (300 MHz, ^{1}H NMR) in $CDCl_3$ (0.05 M). The data in parentheses correspond to the equilibrium in MeOH-d_4 (0.05 M). Cis/trans ratios were calculated through integration of the bolded signals.

The most interesting features of the ^{1}H NMR spectra (250 MHz) of the *cis*- and *trans*-NNF equilibrium mixture are given in Figure 1. ^{1}H NMR measurements carried out at different concentrations of NNF (0.6 M to 0.0025 M in $CDCl_3$ and MeOH-d_4) showed similar cis/trans ratios, which reveal no signs of aggregation of the solute in any of the solvents examined. The IR spectra showed only sharp bands in the free N−H bond stretching region (3400−3300 cm^{-1}) in $CDCl_3$, whose aspect remains also constant in the 0.12−0.025M concentration range.[11] The cis/trans ratios of NMF, NMA, and NNF in equilibrium in $CDCl_3$ and MeOH-d_4 solution were determined by integration of the ^{1}H NMR signals of the two conformers and are listed in Table 1.

Computational Results and Discussion

Energy Differences of Cis/Trans Isomers in the Gas Phase. The energetic differences of *cis*- and *trans*-NMF, NMA, and NNF in gas phase were determined at several theoretical levels and basis sets. Our results are summarized in Table 2; other related data reported in the literature are also included.

The molecular mechanics calculation of steric energies differences of the cis and trans amides (ΔE_{M}) was performed using the MMX force field implemented in the PCMODEL package.[18] The electrostatic interactions were calculated with the charge−charge electrostatic model at the default dielectric constant ($\epsilon = 1.5$).[18] The differences in binding energy (heat of formation) ΔE_{A} were calculated with the semiempirical AM1 method implemented in HyperChem,[19] using default parameters. The Gaussian 98W package[20] was used to perform the ab initio and DFT molecular orbital calculations. The standard 3-21G

TABLE 2: Computed Energy Differences [$\Delta E = E$ (Cis) − E (Trans), kcal/mol] of Amides in Gas Phase

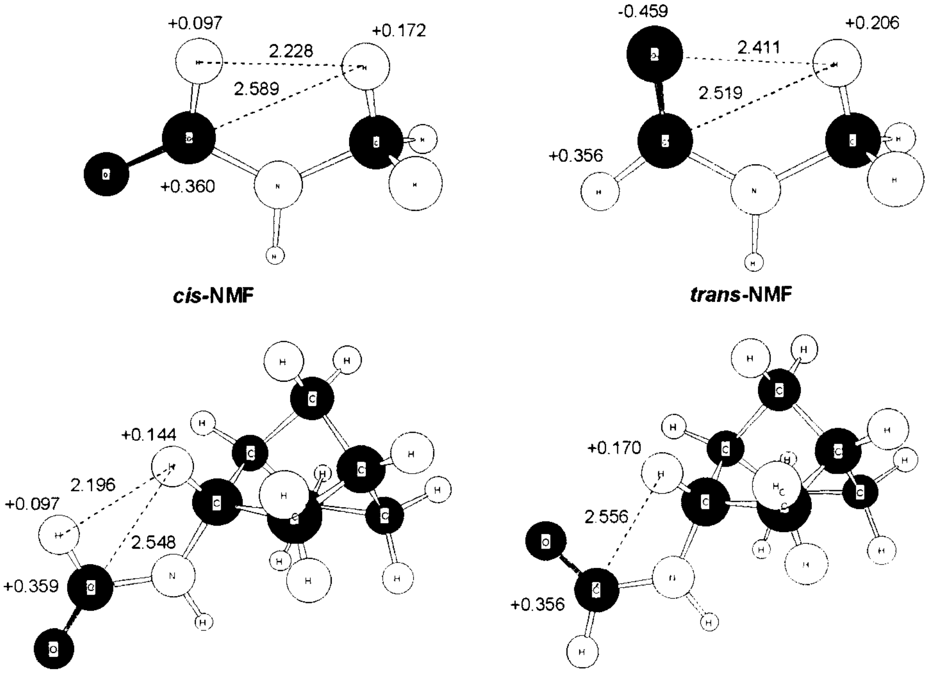
amide	ΔE_{M}[a]	ΔE_{A}[b]	ΔE_{H}(I)[c]	ΔE_{B} (I)[d]	ΔE_{B} (II)[e]	ΔE_{B}(III)[f]	ΔE_{B} (IV)[g]	ΔE_{MP} (II)[h]
NMA	0.66	−0.18	3.07	3.08	2.50	2.46	2.52	2.15[i]; 2.22[j]
NMF	−0.27	−0.48	1.52	1.63	0.93	1.07		
NNF	−0.52	−0.44	1.55	1.32	0.84			

[a] MMX steric energies. [b] AM1 binding energies (heat of formation). [c] RHF/3-21G total energies. [d] B3LYP/3-21G total energies. [e] B3LYP/6-31G* total energies. [f] B3LYP/6-31G** total energies (ref 12). [g] B3LYP/3−111++G** total energies (ref 4d). [h] MP2/6-31G* total energies. [i] Reference 13. [j] References 23 and 24.

TABLE 3: Computed Cis−Trans Differences of Free Energies and Enthalpies of Amides at Different Theoretical Levels and Basis Sets in Gas Phase (kcal/mol, 20 °C, 1 atm)

Amide	ΔG_H (I)[a]	ΔH_H (I)[a]	ΔG_H (II)[b]	ΔG_B (I)[c]	ΔH_B (I)[c]	ΔG_B (II)[d]	ΔH_B (II)[d]	ΔG_{MP}(II)[e]	ΔH_{MP}(II)[e]	ΔH_{exp}[f]
NMA	3.48	3.09		3.76	3.29	2.35	2.36	2.50[g] 2.53[h] 3.69[i]	2.07[g] 2.22[i]	2.3
NMF	1.42	1.45	1.81	1.43	1.58	1.02	0.85			
NNF	1.35	1.50		1.59	1.30	1.11	0.81			

[a] RHF/3-21G. [b] RHF/6-31G*, ref 36. [c] B3LYP/3-21G. [d] B3LYP/6-31G*. [e] MP2/6-31G*. [f] Experimental value, ref 25. [g] Reference 13. [h] Reference 23. [i] Reference 24.



***cis*-NMF** ***trans*-NMF**

***cis*-NNF** ***trans*-NNF**

Figure 2. Fully optimized structures of NMF and NNF in gas phase, calculated by using the B3LYP/6-31G* method. The attractive (O−H) and repulsive (H−H and C−H) close contacts found are in Å.

and 6-31G* split-valence basis sets were used at the Restricted Hartree−Fock (RHF) and B3LYP (Becke's three parameter exchange and the LYP correlation functional) theoretical levels. The B3LYP[21] is a gradient-corrected functional method including some of the effects of electron correlation. This DFT method achieves greater accuracy than RHF with only a modest increase in computational time and disk usage, far less than Møller−Plesset perturbation theory at the second-order level including all electrons [MP2 (full)].[22] In each case, the total energies (*E*) of the cis/trans isomers and the corresponding vibrational frequencies were calculated at the same theoretical level and basis set as the geometry optimizations.

The free energy (*G*) and enthalpy (*H*) of the most stable conformations of the amides have been calculated by us in all the cases as sum of thermal (at 20 °C and 1 atm) and electronic terms without scaling factors. The differences ΔG and ΔH are given in Table 3. As comparison, related values calculated for NMA using the MP2/6-31G* method are also included.[13,23,24] On the experimental side, only an estimation of $\Delta H_{ex} = 2.3$ kcal/mol was made for NMA in a nitrogen matrix (see Table 3).[25] This value is in better agreement with the value calculated by us using the B3LYP/6-31G* method than the value computed with the MP2/6-31G* method.[23,24]

In contrast with the results obtained with the MMX and AM1 methods, all ab initio and DFT methods predict the trans isomer to be more stable than the cis isomer (see Tables 2 and 3). This notorious failure of both molecular mechanics and semiempirical methods in the very important case of the amide linkage prompted us to identify the interactions responsible for the marked preference of *N*-alkylformamides for the trans isomer. With this purpose, we have calculated the nonbonded interactions of both isomers detected as close contacts by the Chem3D interface[20b] from the distance matrix computed with the B3LYP/6-31G* method. This procedure can offer merely a qualitative explanation because when using quantum-mechanical methods only the total energy is decisive. The atom charges were calculated from a Mulliken population analysis of the self-consistent field (SCF) density determined with the B3LYP/6-31G* method.[20a] The close contacts and the charges of the involved atoms are given in Figure 2. The total nonbonded interaction potential of the formamides NMF and NNF [*V*(tot)] is given by the sum of the electrostatic interaction potential [*V*(el)] and the van der Waals potential [*V*(w), see eq 1].[26]

$$V(\text{tot}) = V(\text{el}) + V(\text{w}) \qquad (1)$$

We have calculated *V*(el) by means of the charge−charge model [Coulomb potential, $V(\text{el})_C$][27] and also according to the distance-dependent dielectric model [$V(\text{el})_{DM}$],[28] (Table 4). The $V(\text{el})_C$ values are very high because the dielectric constant for gas phase (1.5) seems to be too low for close-contact interactions.[28] A more realistic potential should be $V(\text{el})_{DM}$, because in this case the potential varies as the inverse square of the internuclear distance.[29] The van der Waals interactions were calculated using

TABLE 4: Calculated Interaction Energy of Close Contacts (in kcal/mol)

amide	interaction	V(w)	$V(\mathrm{el})_\mathrm{C}$	$V(\mathrm{tot})_\mathrm{C}$	$V(\mathrm{el})_\mathrm{DM}$	$V(\mathrm{tot})_\mathrm{DM}$
cis-NMF	H---H	0.64	1.66		1.12	
	H---C═O	0.52	5.32		3.08	
	sum	0.96	6.98	7.94	4.20	5.16
trans-NMF	H---O	0.63	6.47		3.85	
	H---C═O	0.64	−8.72		−5.43	
	sum	1.27	−2.25	−0.98	−1.58	−0.31
cis-NNF	H---H	1.45	1.41		0.96	
	H---C═O	1.26	4.51		2.66	
	sum	2.71	5.92	8.63	2.65	6.33
trans-NNF	H---C═O	0.61	5.26		3.09	
	sum	0.61	5.26	5.87	3.09	3.70

the MM2 variation of the Lennard-Jones potential,[26,27] which combines attractive and repulsive components at the distances computed with the B3LYP/6-31G* method uncorrected for vibrational motion. Despite the limitations of our calculations, the V(tot) values (Table 4) clearly show that the preference for the trans formamides is due to electrostatic interactions. Thus, the cis formamides display more repulsive close contacts between the formyl group and the C−H hydrogen of the *N*-alkyl group than the trans isomers.

The dipole moments (μ) of the most stable conformations of the amides NMA, NMF, and NNF were computed by Mulliken population analysis using the SCF density[20] computed with different methods. The results and the reported values are listed in Table 5. The more recent experimental result for *trans*-NMA is 3.85 D in benzene.[30] Our result with the B3LYP/6-31G* method agrees with the experimental values in the same extent as the one computed with the B3LYP/6-311++G**[4d] method, which adds diffuse functions on both heavy atoms and hydrogen and two sets of p and d functions on the hydrogen and heavy atoms, respectively. According to all ab initio calculations, the dipole moments of cis amides are larger than those of the corresponding trans isomers. The calculated $\Delta\mu$ values are similar in NMA and NMF, but considerably lower than the value of NNF (see Table 5).

Important observables in gas phase are the molecular geometries. Experimental data about the geometry of *trans*-NMA and *trans*-NMF in gas phase were determined by electron diffraction[31] (see Table 6 for *trans*-NMA and Table 7 for *trans*-NMF). The geometry of *trans*-NMA in gas phase has been extensively studied by ab initio methods; the more relevant results are summarized in Table 6. To supplement the reported data obtained with the RHF and B3LYP theoretical levels, we have calculated the geometry of the most stable conformer of *trans*-NMA with the RHF/3-21G, B3LYP/3-21G, and B3LYP6-31G* methods (see Table 6). The vibrational analysis verified that the geometry calculated by us corresponds to stationary structures, because there were no imaginary frequencies.

The agreement between the computed bond lengths and angles and the experimental values (excluding torsional angles) was measured by the correlation coefficient ρ (Table 6). The accordance is excellent in all cases, but the best ρ value corresponds to the B3LYP/6-31G* and RHF/6-31G* methods. All the computed values for the C′−N−H angle are higher by ca. 10° than the observed value. The torsional angles corresponding to the most stable conformations for the CH_3 torsions of *trans*-NMA are given in Table 6. The indicated C−H bond is in each case the nearest to the C−N−C′−O plane. Very shallow potential surfaces with respect to the CH_3 torsions [ΔE (N−CH_3) ≈ 0.1 kcal/mol and ΔE (C′-CH_3) ≈ 0.3 kcal/mol] were reported in the literature[4d,13,32] and are in agreement with the rotational barriers computed by us with the B3LYP/6-31G* method.

Strikingly, the predicted most stable conformation around the *C*- and *N*-methyl groups is more dependent on the basis set than on the theoretical level. Thus, the 3-21G* basis set at the

TABLE 5: Computed Dipole Moments μ with Different Methods in Gas Phase (in D)

	RHF/3-21G		RHF/6-31G**[b]		B3LYP/3-21G		B3LYP/6-31G*		B3LYP/6-311++G**[c]		MP2/6-31G*[b]		exp[d]
amide	μ	$\Delta\mu$[a]	μ	$\Delta\mu$[a]	μ	$\Delta\mu$[a]	μ	$\Delta\mu$[a]	μ	$\Delta\mu$[a]	μ	$\Delta\mu$[a]	μ
cis-NMF	4.38	0.4	4.30	0.27	3.96	0.27	4.00	0.19					
trans-NMF	3.98		4.03		3.69		3.81						
cis-NNF	4.57	0.73			4.21	0.66	4.39	0.58					
trans-NNF	3.84				3.55		3.81						
cis-NMA	4.35	0.30	4.21	0.18	3.93	0.34	3.91	0.27	4.315	0.34	4.21	0.17	
trans-NMA	4.05		4.03		3.59		3.64		3.971		4.04		3.85

[a] $\Delta\mu = \mu$ (cis) − μ (trans). [b] Reference 13. [c] Reference 4d. [d] Reference 30.

TABLE 6: Ab Initio Computed Versus Experimental Structural Parameters of *trans*-NMA in Gas Phase (Distances in Å, Angles in Degrees)

	exp[a]	RHF/ 3-21G	RHF/ 6-31G*[b]	RHF/ 6-311++G**[c]	B3LYP/ 3-21G	B3LYP/ 6-31G*	B3LYP/ 6-311++G**[c]	MP2/ 6-31G*[d]
C′═O	1.224 (3)	1.218	1.200	1.1981	1.241	1.224	1.2216	1.233
C′−N	1.386 (4)	1.356	1.353	1.3498	1.374	1.370	1.3642	1.367
N−C	1.468 (6)	1.461	1.447	1.4486	1.468	1.451	1.4558	1.450
C′−C	1.520 (5)	1.517	1.515	1.5128	1.529	1.529	1.5191	1.516
N−C′═O	121.8 (0.4)	123.0	122.2	122.20	122.8	122.9	121.89	
C−N−C′	119.6 (0.8)	121.8	121.5	121.70	120.7	122.8	121.45	122.1
C−C′−N	114.1 (1.5)	113.9	115.2	116.34	113.5	114.4	116.06	115.0
C′−N−H	110.4 (5)	119.6	119.4	119.20	119.4	118.6	119.35	118.8
C′−N−C−H	180[e]	0.5	168.7[f]	180.0	0.0	0.0	180.0	
N−C′−C−H	180[e]	179.7	143.4[f]	0.0	180.0	0.0	0.0	
O═C′−NH	180[e]	179.9	186.0[f]	180.0	179.9	180.0	180.0	
ρ		0.99902	0.99941	0.99921	0.99895	0.99929	0.99912	

[a] Reference 29. [b] Reference 13. [c] Structures with different methyl orientations (C′−N−C−H torsional angle) have similar energies with a difference of only 0.1 kcal/mol (ref 4d). [d] Reference 24. [e] Assumed values. [f] Reported in ref 32 but not in ref 13.

TABLE 7: Ab Initio Computed Geometries for *cis*-NMA

	RHF/3-21G	RHF/6-31G*[a]	B3LYP/3-21G	B3LYP/6-31G*	MP2/6-31G*[b]
C=O	1.200	1.218	1.240	1.224	1.232
C′−N	1.357	1.359	1.376	1.372	1.372
N−C	1.445	1.459	1.467	1.452	1.451
C′−C	1.514	1.515	1.527	1.522	1.514
N−C′=O	121.4	121.9	121.9	121.3	
C−N−C′	127.4	126.5	126.3	127.3	126.1
C−C′−N	116.6	115.6	114.7	116.1	116.1
C′−N−H	114.0	115.1	115.0	113.8	112.9
C′−N−C−H	180	179.4	179.4	180.0	
N−C′−C−H	180	179.8	0.1	179.7	
O=C′−N−H	0	0.1	0.1	0.3	

[a] Reference 13. [b] Reference 24.

TABLE 8: Ab Initio Computed Versus Experimental Structural Parameters of *trans*-NMF in Gas Phase (Distances in Å, Angles in Degrees)

	exp[a]	RHF/3-21G	RHF/4-31G[b]	RHF/6-31G*[c]	B3LYP/3-21G	B3LYP/6-31G*
C′=O	1.219 (5)	1.225	1.219		1.224	1.219
C′−N	1.366 (8)	1.355	1.343		1.361	1.362
N−C	1.459 (6)	1.454	1.453		1.471	1.453
C′−H	1.125[d]	1.108	1.081		1.103	1.108
N−C′=O	124.6 (5)	126.0	124.4		125.5	125.6
C−N−C′	121.4 (9)	123.6	121.6	123.28	121.3	122.9
H−N−C′	118.7[d]	117.9	119.2	117.75	119.7	118.0
N−C′−H	112.7[d]	111.6	114.1		111.4	111.8
C′−N−C−H	180[d]	0.0	180		0.0	0.0
O=C′−N−H	180[d]	180.0	180		180.0	180.0
ρ		0.99986	0.99998		0.99994	0.99992

[a] Reference 31. [b] Reference 33. [c] Reference 12. [d] Assumed values.

TABLE 9: Optimized Computed Geometries of *cis*-NMF, *cis*-NNF, and *trans*-NNF (Distances in Å, Angles in Degrees)

	RHF/3-21G		RHF/6-31G*[a]	B3LYP/6-31G*		
	cis-NNF	*trans*-NNF	*cis*-NMF	*cis*-NMF	*cis*-NNF	*trans*-NNF
C′=O	1.214	1.216		1.218	1.218	1.220
C′−N	1.353	1.350		1.363	1.363	1.362
N−C	1.454	1.462		1.449	1.452	1.456
C′−H	1.085	1.085		1.110	1.109	1.109
N−C′=O	125.5	124.7		125.0	125.1	125.2
C−N−C′	124.1	121.3	125.22	125.3	125.5	122.9
H−N−C′	116.9	119.6	115.52	115.4	115.1	118.0
N−C′−H	112.3	113.0		111.9	112.0	112.1
C′−N−C−H	21.4	60.0		0.0	9.9	30.4
O=C′−N−H	−0.4	−179.7		0.3	0.0	178.1

[a] Reference 12.

RHF and B3LYP levels predicts the most stable conformation for *trans*-NMA that is different from the computed one using the 6-311++G** basis set. The assumed conformation for the intensity analysis[31] (see Table 6) is not the most stable one according to the B3LYP/6-31G* and B3LYP/6-311++G** methods. This could be the ground for the discrepancy between the experimental and computed values of the C′−N−H angle.

The structures computed by us for *cis*-NMA as well as the reported values are given in Table 7. The main changes between both isomers appear to be due to steric hindrance between the methyl groups of the cis isomer. Thus, the C−N−C′ angle is wider by ca. 10° and the C′−N−H angle is narrower by ca. 5° in the cis isomer. Hence, the higher energy of *cis*-NMA is due to angle deformations to accommodate steric congestion for the methyl groups.[7a,13]

In comparison to NMA, there are few computational studies of the geometry of NMF in gas phase. The structure of *trans*-NMF determined by electron diffraction[31] is given in Table 8. The geometry of the most stable conformer (with no imaginary frequencies) computed by us with the RHF/3-21G, B3LYP/3-21G, and B3LYP/6-31G* methods is summarized in Table 8. Some reported data are also included.[12,31,33] As in NMA, the accordance between computed structural parameters and experimental data is excellent, although the assumed conformation in the literature[31] is not the most stable (see Table 8). The highest ρ value corresponds to the RHF level with the 3-21G basis set. Using the RHF level with a contracted 2s,1p/1s basis set,[32] the most stable conformation for *trans*-NMF does display a C′−N−C−H torsional angle of 180° and a torsional barrier of 0.88 kcal/mol. By contrast, we have found with the B3LYP/6-31G* method that the most stable conformation has a torsional angle of 0.0° (see Table 8) and a barrier of 0.59 kcal/mol.

The geometries of *cis*-NMF, *cis*-NNF, and *trans*-NNF have also been computed with the B3LYP/6-31G* method. A summary is given in Table 9 besides the few reported data for *cis*-NMF.[12] The only noticeable structural differences between cis and trans isomers of both formamides are minor changes in the C−N−C′ and C′−N−H angles (by ca. 3°). Moreover, the bond lengths of the cis and trans isomers are very similar. Thus, it can be concluded that neither steric (van der Waals) nor bonding−antibonding interactions[34] play any significant role in the ΔE between cis and trans formamides. This conclusion agrees with the low van der Waals interactions calculated by us listed in Table 4.

TABLE 10: Conformational Energies of *cis*-NNF and *trans*-NNF (*E* (rel) in kcal/mol; Angles in Degrees)

	cis-NNF		*trans*-NNF	
C′−N−C−H	E_H(I) (rel)[a]	E_B(II) (rel)[b]	E_H(I) (rel)[a]	E_B(II) (rel)[b]
0	0.27		0.61	
9.9		0.00		
21.4	0.00			
30.4				0.00
44.3			0.00	
60	0.92		0.31	
120	5.31		6.44	
145			8.37	6.45
150	8.57	6.98		
180	5.21		4.91	
207.1	3.28			
208.8			2.43	
240	3.76		3.62	
290	1.81			
300	1.86		1.74	
306.2			1.71	

[a] RHF/3-21G. [b] B3LYP/6-31G*.

We have explored the six-fold potential energy surface generated by rotation around the N−C bond of the chiral amides *cis*-NNF and *trans*-NNF with the RHF/3-21G method because the accordance between the observed and computed geometries of formamides using this method is as good as those computed using the B3LYP/6-31G* method (see Table 8). The energy of the six eclipsed bisected conformations was computed by optimization with frozen C′−N−C−H torsional angle at 0°, 60°, 120°, 180°, 240°, and 300°. Only three energy minima corresponding to staggered conformers were found by optimization of the six eclipsed conformers with unfrozen torsional angle at 21.4°, 207.1°, and 290.0° for *cis*-NNF and 44.3°, 208.8°, and 306.2° for *trans*-NNF. The maximum energy conformations (transition states) were determined by scanning the potential energy surface around the bisected conformation at 120°. The computed conformational energies (in hartrees) and relative energies (in kcal/mol) are given in Table 10. The rotational barriers were calculated to be 8.57 and 8.37 kcal/mol for the cis and trans isomers, respectively. These barriers are the highest ones reported for chiral formamides and, hence, are promising for the application of these compounds in asymmetric synthesis.[35] The global energy minimum and the transition state for both isomers were also optimized with the B3LYP/6-31G* method. According to the data in Table 10, the rotational barriers are mainly due to the interaction of the *endo*-C6−H with the C═O bond of *trans*-NNF or the formyl C−H bond of *cis*-NNF. The C′−N−C−H torsional angles computed with the B3LYP/6-31G* method, 9.9° and 30.4° for the minimal energy conformations of *cis*- and *trans*-NNF respectively (see Table 9), show that, as a consequence of the chirality of the 2-norbornyl group, the nonplanar structure of *cis*- and *trans*-NNF is preferred. On the other hand, the B3LYP/6-31G* computed rotational barriers are ca. 1 kcal/mol lower than those computed with the RHF/3-21G method.

The actual value of the C′−N−C−H torsional angle is not only determined by the interactions of the hydrogen atom of the C−H bond with the formyl group but also by interactions between the N−H bond and the 2-norbornyl moiety. The very shallow potential curve in the 0−60° range (see Table 10) can explain that even minute differential interactions provoke the different values of the C′−N−C−H torsional angle computed for both isomers of NNF using the B3LYP/6−331G* and RHF/3-21G methods.

Computations in Solution. We have seen that the B3LYP/6-31G* method success in predicting ΔH values of amides in gas phase. We will now try to extend this DFT method to the study of cis/trans populations in solution, which is of fundamental interest in the experimental field.

The principal approaches for computing free energies of compounds in solution employ either a continuous description of the solvent or the use of discrete solvent molecules.[5] The discrete models feature Monte Carlo (MC) statistical mechanics or molecular dynamics (MD) simulations for computing free-energy changes.[36] The main drawbacks of the discrete model are as follows: (1) the sensitivity of the calculated free energies of hydration to the details of the intermolecular potential function;[13] (2) the calculations are rooted in force-field methods, whose parameters are of questionable generality for fine calculations; (3) the election of the geometries of the solvent−solute complexes, which are needed for specific interactions such as hydrogen bonding, is rather intuitive in the case of few solvent molecules;[4d] (4) high computational demand in the case of solvent boxes; (5) the discrete model proper methods to compute free-energy changes, like the free-energy perturbation theory and thermodynamic integration,[37] yield relative rather than absolute free energies of solvation.[36] An interesting approach to avoid this drawback[36] is the adoption of a linear response theory[38] to estimate free-solvation energies, a characteristic method of continuum models; (6) no separation between electrostatic and hydrogen-bonding components is carried out using discrete models.[36]

To probe the reliability of the periodic box model for solvation implemented in the HyperChem package,[19] we have placed the MM+ optimized structure for the cis and trans isomers of NMA in a periodic box (18.7 × 18.7 × 18.7 Å) containing 216 TIP3P water molecules. The optimization of the solvated molecules was performed using standard cutoff options[19] with the MM+ molecular-mechanics method implemented in HyperChem.[19] Under these conditions, an energy difference of 5.2 kcal/mol favoring the trans isomer was found. In contrast with our result, a higher stability of the cis isomer in water was reported performing Monte Carlo simulations on the cis and trans isomers of NMA using two sets of potential functions including OPLS for the amides with TIP4P water.[39] However, the opposite conclusion is reached using another set of OPLS parameters for both cis and trans conformers, because *trans*-NMA is computed to be better hydrated by 2.2 ± 0.3 kcal/mol.[13] On the other hand, the employment of refined ("ad hoc") charge distributions yields no statistically significant difference in the free energies of hydration (0.1 ± 0.3 kcal/mol favoring the trans-isomer were calculated).[13] Thus, the sensitivity of the results in aqueous solution to the details of the charge distribution limits the general use of the Monte Carlo simulations for computing amidic cis/trans populations. The predicted total free-energy difference between the cis and trans isomers of NMA in water is 2.6 ± 0.3 kcal/mol, as given in Table 11 under ΔG^{S}(MC).[13]

The self-consistent reaction field (SCRF) theories calculate the electrostatic component of solvation energies treating the solvent as continuous, characterized only by a fixed cavity within the solvent field. In the present paper, we shall employ three SCRF models: the DIPOLE model,[5,40] the polarizable continuous model (PCM),[5] and the self-consistent isodensity polarizable continuous model (SCI−PCM)[5] at different levels and basis sets to determine the solvent effects on ΔE^{S} and ΔG^{S} using Gaussian 98W.[20] In each case, the computations were performed using as input the most stable conformation in gas phase.

TABLE 11: Computed Differences (Cis−Trans) in Total Energies (ΔE^S) and Free Energies (ΔG^S) of Amides in Solution (in kcal/mol)

amid e	solvent	ΔE_H^S (I)(D)[a]	ΔE_B^S (I)(D)[b]	ΔE_B^S (II)(D)[c]	ΔE_B^S (I)(S)[d]	ΔE_B^S (II)(S)[e]	ΔG_H^S (II)(P)[f]	ΔG_B^S (II)(P)[g]	ΔG_{MP}^S (II)(P)[h]	ΔG_{MP}^S (V)(P)[i]	ΔG^S (MC)[j]	ΔG^S (GF)[k]	ΔG^S_{ob}
NMA	D_2O	2.34	2.42	1.69	[l]	[l]	2.20	2.45	2.03		2.6	2.1	2.5 ±0.4[m]
	CD_3OD	2.36	2.58	1.72	[l]	[l]	2.22	2.46					2.80 ± 0.01
	$CDCl_3$	2.57	2.79	1.94	[l]	[l]	2.10	2.35					2.09 ± 0.01[m]
													2.23 ± 0.01
NMF	D_2O	0.90	1.17	0.85	2.10	1.45	0.96	0.69		3.9			1.4 ± 0.5[m]
	CD_3OD	0.43	1.19	0.85	2.24	1.61	0.92	0.64					1.61 ± 0.01
	$CDCl_3$	0.75	1.33	0.88	1.78	0.88	1.08	1.17					1.24 ± 0.01[m]
													1.20 ± 0.01
NNF	CD_3OD	0.71	0.82	0.31	[l]	[l]	1.63	1.02					1.40 ± 0.01
	$CDCl_3$	0.96	0.95	0.44	[l]	[l]	1.06	0.77					0.68 ± 0.03
ρ		0.865	0.884	0.877			0.853	0.880					

[a] DIPOLE//RHF/3-21G. [b] DIPOLE//B3LYP/3-21G. [c] DIPOLE//B3LYP/6-31G*. [d] SCI−PCM//B3LYP/3-21G. [e] SCI−PCM//B3LYP/6-31G*. [f] PCM//RHF/6-31G*. [g] PCM//B3LYP/6-31G*. [h] PCM//MP2/6-31G*, ref 38. [i] PCM//MP2/4-31G, ref 33. [j] Reference 13. [k] Reference 14. [l] No convergence of the trans isomer was achieved. [m] Reference 12.

TABLE 12: Computed Cavity Radius a_0 (in Å) and Molecular Volumes (V, in Å^3) of Amides Using the B3LYP/6-31G* Method with the DIPOLE and PCM Models, Respectively

amide	a_o	V (H_2O)	V (MeOH)	V ($CHCl_3$)
cis-NMA	3.62	116.4	116.4	168.1
trans-NMA	3.81	117.7	117.7	171.0
cis-NMF	3.51	92.3	92.3	135.2
trans-NMF	3.41	106.0	106.0	134.6
cis-NNF	4.54		213.3	296.9
trans-NNF	4.37		212.5	295.3

In the DIPOLE model, a spherical cavity of radius a_o is used. The a_o values were calculated with the standard method of the Gaussian 98W package, consisting of Monte Carlo simulations based on a 0.001 e/bohr^3 density envelope. From the a_o values (see Table 12) and the static dielectric constants (ϵ) of the solvents water, methanol, and chloroform, the differences in total energies in solution [ΔE^S(D)] were computed with several methods (see Table 11). According to calculations for NMA performed with integral equation theories,[14] the differences in hydration entropies (ΔS) between cis and trans conformers are negligible. This conclusion agrees with that reached with the Monte Carlo simulations using refined parameters (vide supra).[13] Thus, from the Gaussian fluctuation (GF) approximation a total ΔG^S for NMA in water of 2.1 kcal/mol was calculated [see Table 11, under ΔG^S (GF)].[14] Hence, the computed ΔE^S values in solution should be very similar to the corresponding observed ΔG^S_{ob} values calculated by us from the equilibrium data in Table 1 and other reported values (see Table 11). In fact, the ΔE^S values computed with the DIPOLE model are in fair accordance with the experimental ΔG^S_{ob} values, particularly using the B3LYP theoretical level. Thus, the corresponding correlation coefficients are near 0.9 (Table 11).

All the ΔE values computed in solution with the DIPOLE model are smaller than in gas phase, using the same computation method (compare Tables 2 and 11). Moreover, decreasing ΔE values were computed for solvents with increasing ϵ. These results are in agreement with classical electrostatics[14b] as well as the theoretical background of the DIPOLE model[5,40] since the cis isomers have a higher μ value than the corresponding trans isomers (see Table 5). However, the role of μ and consequent stabilization of the cis isomers seems to be overemphasized by the DIPOLE model.

A better definition of the cavity is given by the SCI−PCM model, because it takes into account the coupling of the isodensity surface with the electron density, that is, this procedure includes the effect of solvation in the solution of the SCF.[5] Unfortunately, the resulting Hamiltonian provokes serious computational problems. In our hands, the solvation energies of the cis isomers of NMA and NNF can be computed, but not the energies of the corresponding trans isomers because no convergence was achieved. In NMF, convergence in the computation of the energy of both cis and trans isomers was achieved in the three solvents; the computed ΔE^S values are listed in Table 11 under ΔE^S (S). The agreement with the experimental ΔG^S_{ob} data is excellent using the B3LYP/6-31G* method in the polar solvents.

The PCM energy defines the molecule-shaped cavity as the union of interlocking spheres, where radii were built by scaling the atomic van der Waals radii (default scaling factor 1.4 for chloroform, and 1.2 for methanol and water). The surface of each sphere was divided in 60 triangular tesserae (default value) for the calculation of the surface-charge distribution. The corresponding molecular volumes V are given in Table 12. The von Auwers−Skita rule (or conformational rule) states that the conformer of higher enthalpy has lower molecular volume.[15] This prediction is correct for NNF in all solvents because the computed a_0 and V values are higher in the more stable trans isomers, but not for NMF and NMA (see Table 12).

The PCM model is particularly interesting because it offers an estimation of the contributions of the free energy of solvation G(sol).[20] The total free energy of a molecule in solution (G^S) is given by eq 2:

$$G^S = G_{VAC} + G(\mathrm{sol}) \tag{2}$$

Where G_{VAC} is the molecular free energy in vacuo, computed from the molecular SCF electronic energy (E_{el}) with thermal and zero-point energy corrections.[33] G(sol) is the sum of electrostatic (G_{EL}) and nonelectrostatic (G_{NEL}) terms, that are defined by eqs 3 and 4:

$$G_{EL} = G_{US} + G_{PS} + G_{SP} \tag{3}$$

$$G_{NEL} = G_{CAV} + G_{DIS} + G_{REP} \tag{4}$$

Thus, G_{EL} includes the unpolarized solute−solvent (G_{US}), the polarized solute−solvent (G_{PS}), and the solute polarization (G_{SP}) energies. On the other hand, G_{NEL} is the sum of the cavitation (G_{CAV}), dispersion (G_{DIS}), and repulsive (G_{REP}) interactions.

There are some contradictory reports about the success of the PCM model in predicting the solvent effect on the cis/trans population of amides. Thus, the total free-energy difference

TABLE 13: Computed Dipole Moments of Amides in Solution with the B3LYP/6-31G* Method and the PCM Model (in D)

amide	$CHCl_3$		CH_3OH		H_2O	
	μ_S	$\Delta\mu_S$	μ_S	$\Delta\mu_S$	μ_S	$\Delta\mu_S$
cis-NMA	4.43	0.24	4.92	0.11	4.95	0.09
trans-NMA	4.19		4.81		4.86	
cis-NMF	4.64	0.31	5.12	0.25	4.96	0.21
trans-NMF	4.33		4.87		5.17	
cis-NNF	4.86	0.52	5.26	0.21	5.29	0.16
trans-NNF	4.34		5.05		5.13	

TABLE 14: Computed Differences (Cis−Trans) in Free Energies of Solvation [Δ*G*(sol)] of Amides with the PCM Model Using the B3LYP/6-31G* Method (kcal/mol, 20 °C)

amide	solvent	ΔG_{US}	ΔG_{PS}	ΔG_{SP}	ΔG_{CAV}	ΔG_{DIS}	ΔG_{REP}	ΔG(sol)
NMA	D_2O	−0.29	0.33	−0.39	−0.16	0.01	0.12	−0.10
	CD_3OD	−0.30	0.25	−0.35	−0.12	0.01	0.10	−0.11
	$CDCl_3$	−0.23	−0.16	−0.04	−0.11	0.02	0.06	−0.23
NMF	D_2O	−0.92	−0.76	0.13	0.10	−0.14	0.17	−0.77
	CD_3OD	−0.91	−0.77	−0.11	0.08	−0.11	0.13	−0.79
	$CDCl_3$	−0.34	−0.30	−0.02	0.08	−0.07	0.05	−0.27
NNF	CD_3OD	−0.04	0.88	−0.59	0.05	−0.24	0.08	0.18
	$CDCl_3$	−0.07	0.04	−0.07	0.05	−0.15	0.05	−0.06

(ΔG^S) between the cis and trans isomers of NMA in water computed with the PCM//MP2/6-31G* method (2.03 kcal/mol)[23] is in good agreement with the observed value (2.5 ± 0.4 kcal/mol, see Table 11). However, the ΔG^S value computed for NMF in water with the PCM//MP2/4-31G method (3.9 kcal/mol)[33] is very different to the experimental value (1.4 ± 0.5 kcal/mol; see Table 11). This situation has prompted us to realize computations of ΔG^S with the PCM model of NMA, NMF, and NNF in different solvents using the RHF/6-31G* and B3LYP/6-31G* methods.

The computed ΔG^S (at 300 K) values using the RHF/6-31G* and B3LYP/6-31G* methods are listed in Table 11 as $\Delta G^S{}_H$(II)(P) and $\Delta G^S{}_B$(II)(P), respectively. The accordance between the experimental and reported values for NMA in water is excellent. Contrary to the reported values for NMF,[33] the ΔG^S values calculated by us are too low, especially in the polar solvents methanol and water. We were not able to reproduce the result of ref 4 because of the lack of computational details, but the MP2/4-31G method using the Hamiltonian implemented in GAUSSIAN 98 affords ΔG^S values similar to the ones obtained by us with the B3LYP/6-31G* method.

The dipole moments in solution (μ_S) computed with the PCM model using the B3LYP/6-31G* method are listed in Table 13. As expected,[5] the reaction field provokes an increase of μ_S, particularly in the trans isomers, and hence, a decrease of $\Delta\mu_S$. However, the cis isomers still display a larger μ_S value than the trans isomers except in NMA in water.

The contributors to Δ*G*(sol) computed with the PCM//B3LYP/6-31G* method are listed in Table 14. The Δ*G*(sol) values show that the cis amides are slightly better solvated than the trans amides, with the only exception of NNF in methanol, mainly because of the contribution of ΔG_{PS} (0.88 kcal/mol). This is the ground, according to the PCM model, for the anomalously high increase of $\Delta G^S{}_{ob}$ with the dielectric constant of the solvent. On the other hand, *cis*-NMF is predicted to be the most solvated cis isomer in polar solvents. This could lead to predict the ΔG^S of NMF to decrease with increasing the polarity of the solvent, which is not in accordance with the experimental $\Delta G^S{}_{ob}$ values for water and methanol.

Summary and Conclusions

The equilibrium populations of NMA, NMF, and NNF were determined by ^{1}H NMR in diluted solution in solvents of different dielectric constants, and we found that the cis/trans ratio on NNF is more sensitive to solvent changes than the other amides. The marked preference for the trans isomers in the case of *N*-alkylformamides in gas-phase is due to more repulsive electrostatic interactions between *N*-alkyl and formyl groups of the cis isomers.

Neither molecular mechanics (MMX) nor semiempirical (AM1) methods are adequate for the computation of cis/trans ratios of the (apparently) simple amide linkage. Despite it, both methods are implemented without warning in software to calculate conformational energies of even polypeptides.

The dipole moments, which are experimentally difficult to measure, can be satisfactorily computed using RHF and B3LYP theoretical levels even with split valence sets such as 3-21G. The molecular geometries in gas phase of NMA and NMF computed using all the ab initio and DFT methods listed in Tables 6−8 are in very good "statistical" accordance with the experimentally measured bond lengths and angles.

The very shallow potential surfaces for the torsions around the $N-CH_3$ and $C'-CH_3$ bonds computed by us and reported in the literature for NMA and NMF are in contrast with the c.a. 7.0 kcal/mol rotational barriers computed for the chiral NNF, whose most stable conformations around the N−C bond are not planar.

The cis/trans populations of NMA in water computed with the SCRF theory using the PCM//B3LYP/6-31G* and even the DIPOLE//B3LYP/3-21G are very similar to those computed with computational expensive high-level Monte Carlo simulations and are closer to experimental results than the computed ones with integral equation methods. Moreover, the PCM model offers a numerical explanation of the strikingly solvent dependence of the cis/trans ratio of NNF. However, the PCM model fails in the calculation of the cis/trans ratio of the simple NMF in polar solvents. This failure cannot be corrected either by inclusion of electron correlation contributions or by using a larger basis set. We believe that it could be rather attributed to errors in the calculation of the cavity in NMF in polar solvents. This failure indicates the need for improved solvation theories and implementations with more optional parameters.

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