

# Ab initio MO and density functional studies on *trans* and *cis* conformers of *N*-methylacetamide

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## Abstract

The effect of basis sets on the structures and energetics of the rotation for the peptide bond of *N*-methylacetamide (NMA) has been investigated at high levels of theory. The structures, dipole moments and thermodynamic properties for *trans*- and *cis*-NMA have been determined at the HF, MP2 and B3LYP levels with 6-31G(d), 6-31G(d,p), 6-31+G(d), 6-31+G(d,p), 6-31++G(d,p), 6-311+G(d,p) and 6-311++G(d,p) basis sets. By comparing the calculated structure and dipole moment of *trans*-NMA and the relative enthalpy ( $\Delta H$ ) of *cis*-NMA in the gas phase with corresponding experimental data, the B3LYP level with 6-31G(d) or 6-31G(d,p) basis sets appears to be the most appropriate among several levels of theory and basis sets considered here. *Trans*-NMA is computed to be favored by a total free energy of 2.7 kcal/mol than *cis*-NMA in water at the B3LYP/6-31G(d,p) level with the SCI-PCM method, which corresponds to 1.1% population of *cis*-NMA. This is consistent with the results of NMR experiments in aqueous solution that estimate the *cis* population to be  $1.5 \pm 0.1\%$  and the free energy difference of  $2.5 \pm 0.3$  kcal/mol. In addition, the change in relative solvation free energies is computed to be  $-0.1$  kcal/mol at the HF and B3LYP levels with the 6-31G(d,p) basis set as transferred from water to chloroform, which corresponds to the increase of the *cis* population by about 0.3%, consistent with the value from NMR measurements. Therefore, the SCRf method with proper levels of theory and basis sets seems to be reasonable to describe the solvation of NMA. Our calculated results confirmed that the relative distribution of *trans* and *cis* conformers of NMA is insensitive to the solvent polarity. © 2001 Elsevier Science B.V. All rights reserved.

**Keywords:** *N*-methylacetamide; Ab initio calculations; Cis-trans equilibrium; Solvation

## 1. Introduction

*N*-methylacetamide (NMA) is the simplest model for the peptide linkage in proteins and has been extensively studied, both experimentally and theoretically. Recent studies have focused on the *trans*–*cis* equilibrium around the C–N bond (*trans* and *cis* refer to the configuration of C=O and N–H with respect to the C–N bond) [1–5], solvation [1,2,4,6–10], vibrational

properties [3,11–15], characteristics in hydrogen bonds [5,10,11,13,14,16–18] and electronic states [19]. However, due to the very small population of the *cis* conformer of NMA, experimental data are quite limited for the *cis*–*trans* isomerization. In particular, the experimental and/or theoretical barriers for internal rotation and vibrational frequencies of NMA have recently been used to derive the potential parameters for the peptide backbone [20–24].

The structures of *trans*-NMA in crystal and in the gas phase were determined by X-ray [25] and electron [26] diffraction experiments, respectively. NMR

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studies on NMA estimate the population of the *cis* conformer in water to be 1.5–7% [2,27–29], which corresponds to the free energy difference in the range of 1.5–2.5 kcal/mol in favor of *trans*-NMA. A rough estimate of the enthalpy change of 2.3 kcal/mol between two conformers has been made from an infrared spectroscopic measurement of NMA in a nitrogen matrix at different nozzle temperature [30].

The solvation thermodynamics of two conformers of NMA and the internal rotational barrier about the C–N bond have been investigated by NMR experiments [2,28,29] and theoretical approaches [1,4,6–10]. NMR measurements predict the increase of *cis*-NMA by about 1.3% as transferred from water to chloroform [2]. The relative hydration free energy between two conformers is estimated to be  $0.13 \pm 0.30$ ,  $-0.4$  and  $-0.41 \pm 0.35$  kcal/mol from MC simulations [1], integral equation calculations [6], and MD/free energy perturbation simulations [8], respectively. The ab initio self-consistent reaction field (SCRF) calculations at the HF/6-31G(d) level predict that the *cis* conformer has the favored hydration by 0.5 kcal/mol than the *trans* conformer [4]. These previous results indicate that the relative distribution of two conformers is insensitive to the solvent polarity and that the dominant population of *trans* peptide bonds in *N*-methylated amides can be ascribed to the intrinsic stability of the *trans* conformer in the gas phase.

Recent theoretical studies on NMA using quantum mechanical methods have mostly focused on the relative thermodynamics [1,2,4,5,16,31] and vibrational frequencies [11,13,14] of *trans* and/or *cis* conformers in the gas phase. The ab initio calculations have been carried out at the HF and/or MP2 levels with 4-31G(d) [11], 6-31G(d) [1,2,4,16], 6-31G(d,p) [18] and 6-31++G(d,p) [14] basis sets. For *trans*-NMA, Markham and Hudson [13] employed the HF or MP2 levels with 6-31+G, 6-31+G(d) and 6-31++G(d,p) basis sets to calculate resonance Raman spectra in the gas phase and in water. Mirkin and Krimm [31] have investigated the structure of *trans*-NMA at the HF level with 6-31G(d), 6-311G(d), 6-31+G(d), 6-311+G(d), 6-31+G(2df,2pd) and 6-311+G(2df,2pd) basis sets, the MP2 level with 6-31G(d) and 6-31+G(d) basis sets, and the MP3, MP4 and CISD levels with the 6-31+G(d) basis set. In addition, the DFT functionals B3LYP and/or BLYP with the basis set 6-311++G(d,p)

have been used to study the conformation and hydrogen-bonding effect of NMA and its complexes with water molecules [5,10], which are consistent with the corresponding experimental data and/or ab initio results at high basis sets.

To figure out the dependence of structures, dipole moments and thermodynamic properties of *trans*- and *cis*-NMA on the basis sets at high levels of theory, we carried out the HF, MP2 and B3LYP calculations at several basis sets, up to 6-311++G(d,p). The results obtained here may provide us useful information to choose adequate levels of theory and basis sets for conformational study of amides and peptides.

## 2. Computational methods

All ab initio and density functional calculations were carried out using the GAUSSIAN 94 package [32] run on the Cray-XMP C90 supercomputer. Geometry optimizations for *trans* and *cis* conformers of NMA were carried out at the HF, MP2 and B3LYP levels with 6-31G(d), 6-31G(d,p), 6-31+G(d), 6-31+G(d,p), 6-31++G(d,p), 6-311+G(d,p) and 6-311++G(d,p) basis sets. Because the orientation of the methyl groups in NMA has known to be important to have the conformational preference [16], four combinations of *trans*- and *cis*-methyl torsions (represented by  $\phi$  and  $\psi$  in Fig. 1) were included in starting points for optimization. Vibrational frequencies were calculated for fully optimized conformations at all levels, which were used to compute the enthalpy change ( $\Delta H$ ) and the free energy change ( $\Delta G$ ) for the *trans*-to-*cis* isomerization at 298.15 K in the gas phase. Scale factors for vibrational frequencies used

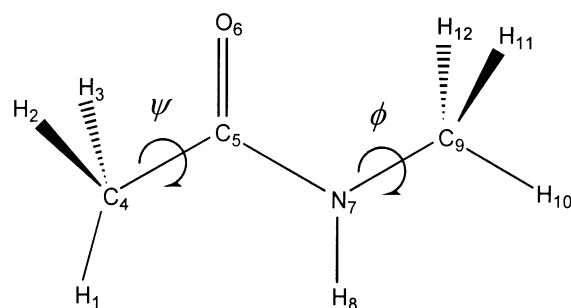


Fig. 1. Atomic definitions for *trans*-NMA with *trans*  $\phi = 180^\circ$  (C5–N7–C9–H10) and *cis*  $\psi = 0^\circ$  (H1–C4–C5–N7).

Table 1

Calculated frequencies ( $\text{cm}^{-1}$ ) of amide I mode for *trans*-NMA at different basis sets (experimental values are 1708 and 1706  $\text{cm}^{-1}$  in Ar and  $\text{N}_2$  matrices, respectively [14])

Basis sets	HF		MP2		B3LYP	
	Unscaled	Scaled <sup>a</sup>	Unscaled	Scaled <sup>a</sup>	Unscaled	Scaled <sup>a</sup>
6-31G(d)	1957	1709	1797	1705	1789	1709
6-31G(d,p)	1955	1706	1799	1708	1787	1707
6-31+G(d)	1924	1712	1750	1704	1751	1713
6-31+G(d,p)	1922	1711	1752	1707	1749	1710
6-31++G(d,p)	1922	1710	1751	1706	1749	1710
6-311+G(d,p)	1912	1702	1757	1711	1742	1703
6-311++G(d,p)	1912	1702	1756	1711	1741	1703

<sup>a</sup> Scale factors used are 0.873, 0.949 and 0.955 for the former two basis sets, and 0.890, 0.974 and 0.978 for the latter five basis sets at the HF, MP2 and B3LYP levels of theory, respectively.

in computing thermal energy corrections [33] were derived to reproduce experimental frequencies of the amide I mode for *trans*-NMA in Ar (1708  $\text{cm}^{-1}$ ) and  $\text{N}_2$  (1706  $\text{cm}^{-1}$ ) matrixes [14]. We have employed three SCRF methods at the HF and B3LYP levels with 6-31G(d,p) and 6-31+G(d) basis sets to include the solvent effect, implemented in the GAUSSIAN 94, which are the polarizable continuum model (PCM), the isodensity polarizable continuum model (IPCM) and the self-consistent isodensity polarizable continuum model (SCI-PCM) [33]. The solvation free energies ( $\Delta G_s$ ) were calculated for optimized conformations of *trans*- and *cis*-NMA in chloroform and water, whose dielectric constants used are 4.71 and 78.36 at 298.15 K, respectively [34]. In chloroform, the solvation free energies were calculated only with the SCI-PCM method because convergence problems were encountered with the PCM and IPCM methods in water.

### 3. Results and discussion

#### 3.1. Scale factors

We need scale factors for vibrational frequencies, zero-point energies, and use in computing thermal energy corrections because they are slightly different from experimental values depending on the level of theory and basis set [33]. The amide I mode is known to be useful in interpreting backbone structures of peptides and proteins [35]. Recently, Torii et al. [14]

reported the vibrational frequencies of the amide I mode of *trans*-NMA to be 1708 and 1706  $\text{cm}^{-1}$  in Ar and  $\text{N}_2$  matrixes, respectively. To reproduce these experimental frequencies, scale factors were chosen. Because scale factors for 6-31G(d) and 6-31G(d,p) basis sets are found to be quite similar each other and the same is true for 6-31+G(d) to 6-311++G(d,p) basis sets, the averaged scale factor is used for each of two groups of basis sets. That is, scale factors used are 0.873, 0.949 and 0.955 for the former two basis sets, and 0.890, 0.974 and 0.978 for the latter five basis sets at the HF, MP2 and B3LYP levels of theory, respectively. They are quite close to the values recommended by Foresman and Frisch [33]. The scale factor of 0.890 for the HF/6-31+G(d) level has been successfully used to reproduce the observed results for the *cis*-*trans* equilibrium and rotational barrier for the prolyl peptide bond of proline dipeptide [36] and its 5-methylated dipeptides [37] in various solvent. Table 1 lists the unscaled and scaled frequencies of the amide I mode of *trans*-NMA at the HF, MP2 and B3LYP levels with different basis sets. All scaled frequencies are within  $\pm 5 \text{ cm}^{-1}$  from experimental values of 1708 and 1706  $\text{cm}^{-1}$  [14].

#### 3.2. Structural parameters

The structural parameters for NMA are defined in Fig. 1. The computed structural parameters for *trans*- and *cis*-NMA at the HF, MP2 and B3LYP levels with various basis sets are shown in Tables 2–4. Overall,

Table 2  
Optimized structural parameters of NMA at the HF level

	6-31G(d)		6-31G(d,p)		6-31+G(d)		6-31+G(d,p)		6-31++G(d,p)		6-31++G(d,p)		6-31++G(d,p)			
	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>		
<b>Geometrical parameters<sup>a</sup> ED<sup>b</sup></b>																
<b>Bond lengths (Å)</b>																
C4–C5	1.520	1.515	1.514	1.514	1.513	1.513	1.513	1.513	1.512	1.513	1.512	1.513	1.512	1.513	1.512	
C5–N7	1.386	1.350	1.357	1.350	1.356	1.350	1.349	1.349	1.355	1.349	1.355	1.350	1.356	1.350	1.356	
N7–C9	1.469	1.447	1.445	1.447	1.444	1.448	1.446	1.448	1.447	1.448	1.447	1.449	1.447	1.449	1.447	
C5=O6	1.225	1.201	1.200	1.201	1.201	1.204	1.204	1.204	1.204	1.204	1.204	1.198	1.198	1.198	1.198	
N7–H8		0.992	0.995	0.991	0.994	0.993	0.996	0.991	0.995	0.991	0.995	0.990	0.994	0.990	0.994	
C–H	1.107	1.083	1.084	1.083	1.084	1.083	1.083	1.083	1.084	1.083	1.084	1.084	1.084	1.084	1.084	
<b>Bond angles (°)</b>																
C4–C5–N7	114.1	116.3	116.6	116.3	116.8	116.5	116.8	116.5	116.9	116.5	116.9	116.3	116.8	116.3	116.8	
O6=C5–N7	121.8	122.2	121.4	122.2	121.3	122.1	121.3	122.1	121.2	122.1	121.2	122.2	121.3	122.2	121.3	
C4–C5=O6	124.1	121.5	122.0	121.5	121.9	121.4	121.9	121.4	121.8	121.4	121.8	121.4	121.9	121.4	121.9	
C5–N7–C9	119.7	121.4	127.4	121.2	127.4	121.7	127.3	121.6	127.2	121.6	127.2	121.7	127.2	121.7	127.2	
C5–N7–H8	110.0	119.6	114.0	119.6	113.9	119.3	114.2	119.3	114.1	119.3	114.1	119.2	114.2	119.2	114.2	
H–C–H	110.4	108.7	108.4	108.7	108.4	108.8	108.5	108.8	108.5	108.8	108.5	108.8	108.5	108.8	108.5	
<b>Torsion angles (°)</b>																
O6=C5–N7–H8	180.0	0.4	180.0	0.3	180.0	0.3	180.0	0.3	180.0	0.3	180.0	0.3	180.0	0.3	180.0	0.4
O6=C5–N7–C9	0.0	179.4	0.0	179.4	0.0	179.5	0.0	179.5	0.0	179.5	0.0	179.5	0.0	179.4	0.0	179.4
C4–C5–N7–H8	0.0	–179.7	0.0	–179.7	0.0	–179.8	0.0	–179.8	0.0	–179.8	0.0	–179.8	0.0	–179.8	0.0	–179.8
C4–C5–N7–C9	180.0	–0.7	180.0	–0.6	180.0	–0.6	180.0	–0.6	180.0	–0.6	180.0	–0.6	180.0	–0.7	180.0	–0.7

<sup>a</sup> Defined in Fig. 1.

<sup>b</sup> Electron diffraction data, taken from Ref. [26].

Table 3  
Optimized structural parameters of NMA at the MP2 level

Geometrical parameters <sup>a</sup> ED <sup>b</sup>	6-31G(d)		6-31G(d,p)		6-31+G(d)		6-31+G(d,p)		6-31++G(d,p)		6-31++G(d,p)		6-31++G(d,p)		
	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	
<b>Bond lengths (Å)</b>															
C4–C5	1.520	1.515	1.514	1.515	1.514	1.513	1.513	1.513	1.513	1.513	1.513	1.517	1.517	1.517	1.516
C5–N7	1.386	1.363	1.373	1.363	1.373	1.364	1.372	1.364	1.372	1.364	1.372	1.365	1.375	1.365	1.375
N7–C9	1.469	1.452	1.452	1.450	1.449	1.455	1.453	1.454	1.453	1.454	1.453	1.454	1.453	1.453	1.454
C5=O6	1.225	1.233	1.232	1.233	1.232	1.239	1.238	1.237	1.238	1.237	1.237	1.226	1.225	1.226	1.225
N7–H8	1.009	1.014	1.014	1.004	1.009	1.011	1.016	1.006	1.011	1.006	1.011	1.007	1.012	1.007	1.012
C–H	1.107	1.092	1.093	1.088	1.089	1.093	1.093	1.088	1.089	1.088	1.089	1.092	1.093	1.092	1.093
<b>Bond angles (°)</b>															
C4–C5–N7	114.1	116.0	116.1	115.9	116.0	116.5	116.3	116.3	116.3	116.3	116.3	115.8	115.8	115.8	115.8
O6=C5–N7	121.8	121.7	121.2	121.7	121.3	121.5	121.2	121.6	121.2	121.6	121.2	121.8	121.5	121.8	121.5
C4–C5=O6	124.1	122.3	122.7	122.4	122.7	122.0	122.4	122.1	122.5	122.1	122.5	122.4	122.7	122.4	122.7
C5–N7–C9	119.7	120.2	126.0	120.1	126.0	120.7	125.8	120.7	125.7	120.6	125.7	120.5	125.1	120.5	125.1
C5–N7–H8	110.0	120.1	112.9	120.1	112.9	119.7	113.4	119.6	113.3	119.6	113.3	119.5	112.9	119.6	113.0
H–C–H	110.4	108.8	108.6	108.8	108.6	108.9	108.7	109.0	108.7	108.9	108.7	108.9	108.6	108.9	108.6
<b>Torsion angles (°)</b>															
O6=C5–N7–H8	180.0	7.8	180.0	180.0	7.9	180.0	7.5	180.0	7.8	180.0	7.8	180.0	9.4	180.0	9.4
O6=C5–N7–C9	0.0	167.6	0.0	167.6	0.0	168.4	0.0	168.1	0.0	168.1	0.0	168.1	0.0	165.4	0.0
C4–C5–N7–H8	0.0	–173.9	0.0	–174.0	0.0	–174.5	0.0	–174.2	0.0	–174.2	0.0	–174.2	0.0	–172.7	0.0
C4–C5–N7–C9	180.0	–14.2	180.0	–14.2	18.0	–13.5	180.0	–14.0	180.0	–14.0	180.0	–14.0	180.0	–16.8	180.0

<sup>a</sup> Defined in Fig. 1.

<sup>b</sup> Electron diffraction data, taken from Ref. [26].

Table 4  
Optimized structural parameters of NMA at the B3LYP level

	6-31G(d)		6-31G(d,p)		6-31+G(d)		6-31+G(d,p)		6-31++G(d,p)		6-31++G(d,p)		6-31++G(d,p)		
	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	
<b>Geometrical parameters<sup>a</sup> ED<sup>b</sup></b>															
<b>Bond lengths (Å)</b>															
C4–C5	1.520	1.523	1.521	1.522	1.521	1.521	1.520	1.519	1.520	1.519	1.519	1.518	1.519	1.518	1.518
C5–N7	1.386	1.365	1.372	1.365	1.371	1.365	1.370	1.365	1.370	1.370	1.364	1.370	1.364	1.370	1.370
N7–C9	1.469	1.453	1.452	1.453	1.452	1.456	1.455	1.456	1.455	1.455	1.456	1.455	1.456	1.455	1.455
C5=O6	1.225	1.225	1.224	1.225	1.224	1.229	1.229	1.229	1.229	1.229	1.229	1.222	1.221	1.222	1.221
N7–H8		1.008	1.011	1.007	1.010	1.009	1.013	1.008	1.011	1.008	1.011	1.006	1.010	1.006	1.010
C–H	1.107	1.094	1.095	1.094	1.094	1.095	1.094	1.094	1.094	1.094	1.094	1.092	1.092	1.092	1.092
<b>Bond angles (°)</b>															
C4–C5–N7	114.1	115.8	116.1	115.8	116.1	116.2	116.4	116.2	116.2	116.6	116.2	116.0	116.0	116.4	116.4
O6=C5–N7	121.8	121.9	121.2	121.9	121.2	121.8	121.1	121.8	121.1	121.8	121.1	121.9	121.9	121.2	121.2
C4–C5–O6	124.1	122.3	122.7	122.3	122.6	122.0	122.4	122.0	122.3	122.0	122.3	122.1	122.3	122.1	122.4
C5–N7–C9	119.7	121.0	127.3	120.9	127.3	121.6	127.1	121.5	127.1	121.5	127.1	121.5	127.1	121.5	127.1
C5–N7–H8	110.0	119.7	113.8	119.8	113.7	119.4	114.1	119.3	113.8	119.3	113.8	119.3	113.9	113.9	113.9
H–C–H	110.4	108.6	108.3	108.5	108.3	108.7	108.4	108.7	108.4	108.7	108.4	108.7	108.4	108.7	108.4
<b>Torsion angles (°)</b>															
O6=C5–N7–H8	180.0	0.4	180.0	0.4	180.0	0.4	180.0	0.3	180.0	3.2	180.0	3.4	180.0	3.3	3.3
O6=C5–N7–C9	0.0	179.4	0.0	179.4	0.0	179.4	0.0	179.5	0.0	175.3	0.0	175.3	0.0	174.8	0.0
C4–C5–N7–H8	0.0	–179.7	0.0	–179.7	0.0	–179.7	0.0	–179.7	0.0	–177.5	0.0	–177.5	0.0	–177.4	0.0
C4–C5–N7–C9	180.0	–0.7	180.0	–0.6	180.0	–0.6	180.0	–0.6	180.0	–5.4	180.0	–5.4	180.0	–5.9	–5.8

<sup>a</sup> Defined in Fig. 1.

<sup>b</sup> Electron diffraction data, taken from Ref. [26].

Table 5

Mean absolute deviations of calculated structural parameters of *trans*-NMA from electron diffraction data (taken from Ref. [26])

Basis sets	Bond lengths (Å)			Bond angles (°)		
	HF	MP2	B3LYP	HF	MP2	B3LYP
6-31G(d)	0.022	0.014	0.011	3.0	2.7	2.7
6-31G(d,p)	0.022	0.015	0.010	3.0	2.6	2.8
6-31+G(d)	0.022	0.014	0.010	3.1	2.8	2.9
6-31+G(d,p)	0.022	0.015	0.010	3.0	2.7	2.8
6-31++G(d,p)	0.022	0.015	0.010	3.0	2.7	2.8
6-311+G(d,p)	0.023	0.011	0.011	3.0	2.5	2.8
6-311++G(d,p)	0.023	0.011	0.011	3.0	2.6	2.8

the results for *trans*-NMA are consistent with experimental values from electron diffraction [26]. Table 5 includes mean absolute deviations (MAD) of calculated structural parameters of *trans*-NMA from electron diffraction data. For bond lengths and bond angles, MAD lies between 0.010 and 0.023 Å and between 2.6 and 3.1° at the HF, MP2 and B3LYP levels, respectively, irrespective of basis sets. Although there are no significant differences in MAD, the best results are obtained from the B3LYP functionals, followed by those of MP2 and HF levels. The deviations for the C5–N7 bond length and the C5–N7–H8 bond angle of the amide group contribute largely to the overall MAD.

Upon rotating around the bond C5–N7, the *trans* conformer becomes the *cis* conformer, which has the steric hindrance between terminal methyl groups. To reduce these steric interactions, the C5–N7 bond length of the *cis* conformer becomes longer by about 0.006 Å than that of the *trans* conformer. The C5–N7–C9 angle widens by about 6°, whereas the C5–N7–H8 angle narrows by about 5°. These general trends for structural parameters appear to be held for all levels of theory and basis sets.

Recently, Mirkin and Krimm [31] reported the structures of *trans*-NMA at the HF, MP2 and higher levels with various basis sets and concluded that the equilibrium structure of the isolated molecule has planar symmetry within the expected torsion angle variations. To check the planarity of peptide bond, our calculated torsion angles of *trans*- and *cis*-NMA are also shown in Tables 2–4, and the results of *trans* conformers are consistent with those of Mirkin and Krimm [31]. However, *cis* conformers optimized at

the HF and B3LYP levels still have the planar symmetry within about 5°, but the MP2 calculations result in non-planarity, irrespective of basis sets.

### 3.3. Dipole moments

Table 6 includes calculated dipole moments of NMA in the gas phase. The magnitude of dipole moment increases in the order of MP2 > HF > B3LYP levels. The experimental values of *trans*-NMA are 3.68 and 3.71 D [38]. The MP2 and HF calculations overestimate the dipole moment of *trans*-NMA. In particular, the calculated dipole moments of 3.73 and 3.71 D at the B3LYP level with 6-31G(d) and 6-31G(d,p) are in excellent agreement with experimental values. As found by the HF/6-31G(d) calculations of Jorgensen and Gao [1], the dipole moments for *cis* conformers are predicted to be larger by 0.2–0.3 D than those for *trans* conformers at all three levels. These small differences accord reasonably with the observed lack of a substantial solvent effect on the *cis*–*trans* equilibrium [2]. It may be noted that higher levels of theory with more split and diffuse functions do not reproduce well experimental dipole moments. The changes in dipole moments by introducing solvents will be discussed in the following section.

### 3.4. *Cis*–*trans* equilibrium and solvent effects

The calculated thermodynamic quantities for *cis*-NMA are summarized in Table 7. The electronic energy ( $\Delta E_e^0$ ) for the *cis* conformer relative to the *trans* conformer ranges from 2.15 to 2.83 kcal/mol. The values of  $\Delta E_e^0$  increase as the polarization and/or diffuse functions are added to hydrogen atoms at

Table 6  
Calculated dipole moments of NMA (units in D)

Basis sets	HF		MP2		B3LYP	
	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>	<i>cis</i>
6-31G(d)	4.01	4.21	4.17	4.34	3.73	3.92
6-31G(d,p)	4.00	4.22	4.15	4.35	3.71	3.92
6-31+G(d)	4.23	4.51	4.41	4.69	4.07	4.39
6-31+G(d,p)	4.21	4.53	4.40	4.70	4.05	4.38
6-31++G(d,p)	4.20	4.52	4.39	4.70	4.04	4.37
6-311+G(d,p)	4.13	4.46	4.27	4.55	3.98	4.31
6-311++G(d,p)	4.13	4.45	4.27	4.55	3.97	4.30

Table 7

Relative electronic energies, enthalpies and Gibbs free energies of *cis*-NMA in the gas phase (energies are in kcal/mol.  $\Delta H$  and  $\Delta G$  are calculated at  $T = 298.15$  K)

Basis sets	HF			MP2			B3LYP		
	$\Delta E_c^0$	$\Delta H$	$\Delta G$	$\Delta E_c^0$	$\Delta H$	$\Delta G$	$\Delta E_c^0$	$\Delta H$	$\Delta G$
6-31G(d)	2.50	2.45	3.73	2.15	3.35	1.90	2.19	2.13	2.73
6-31G(d,p)	2.53	3.08	2.25	2.19	3.39	1.97	2.20	2.13	2.75
6-31+G(d)	2.62	1.96	4.11	2.26	3.49	2.11	2.30	1.64	3.60
6-31+G(d,p)	2.67	2.02	4.19	2.35	2.99	3.59	2.33	2.86	1.98
6-31++G(d,p)	2.67	2.60	3.51	2.35	3.60	2.41	2.34	2.87	2.04
6-311+G(d,p)	2.83	2.18	4.44	2.26	2.99	3.64	2.49	3.03	2.21
6-311++G(d,p)	2.81	2.16	4.49	2.27	3.00	3.82	2.48	3.02	2.21

the HF, MP2 and B3LYP levels, except for the MP2 values with 6-311+G(d,p) and 6-311++G(d,p) basis sets. Except for these two basis sets, the values obtained by the B3LYP functionals are quite similar to those at the MP2 level, as expected from previous calculations (see Chapter 6 of Ref. [33]).

However, the thermal contributions from vibrational frequencies differ from each other, depending on the level of theory and basis set, even though they were scaled to produce the experimental frequency of the amide I mode of NMA (see Table 1). The best value of  $\Delta H$  is obtained at the B3LYP level with 6-31G(d) and 6-31G(d,p) basis sets, which is 2.13 kcal/mol and consistent with the experimental value of 2.3 kcal/mol from an infrared spectroscopic measurement in a nitrogen matrix at different nozzle temperatures [30]. In addition, the HF calculations with 6-31G(d), 6-31+G(d,p), 6-311+G(d,p) and 6-311++G(d,p) yield similar values of  $\Delta H$ . The B3LYP level of theory predicts the values of  $\Delta G$  to be 2.73 and 2.75 kcal/mol with 6-31G(d) and 6-31G(d,p) basis sets, respectively. These correspond to 1% *cis* populations, which are close to observed values in cyclohexane and water [2].

It should be noted that the computed entropic contributions ( $-T\Delta S$ ) for the *trans*-to-*cis* isomerization of NMA are 0.60 and 0.62 kcal/mol at the B3LYP level with 6-31G(d) and 6-31G(d,p) basis sets, respectively. However, the entropic contributions have accounted for  $-0.83$  to  $2.33$ ,  $-1.45$  to  $0.82$  and  $-0.88$  to  $1.96$  kcal/mol to the free energy difference at HF, MP2 and B3LYP levels, respectively. Since the vibrational modes having the lowest frequencies can exert the large contributions, the large entropic contri-

butions may be ascribed to the scaled frequencies by fitting the experimental amide I mode. The sign of  $\Delta S$  is the same as that obtained previously with the ECEPP force field [39], although the magnitudes of  $\Delta E$  and  $\Delta S$  from that study appear to be overestimated. From an ab initio energy calculation at the MP2/6-31G(d)//HF/6-31G(d) level and a vibrational frequency analysis at the HF/3-21G//HF/3-21G level, the values of  $\Delta H$  and  $\Delta G$  were reported to be 2.07 and 2.50 kcal/mol, respectively [2]. In addition, the values of  $\Delta H = 2.13$  kcal/mol and  $\Delta G = 2.53$  kcal/mol were found from the MP2/6-31G(d)//HF/6-31G(d) energies and the semiempirical AM1 frequencies [4].

In Table 8, calculated relative solvation free energies ( $\Delta\Delta G_s$ ) of *cis*-NMA and dipole moments ( $\mu$ ) of *trans*- and *cis*-NMA in water and chloroform are shown. Because convergence problems were encountered for the PCM and IPCM methods at the B3LYP level in water, the  $\Delta\Delta G_s$  at the B3LYP level was obtained only with the SCI-PCM method.

In water, the PCM method at the HF level (HF/PCM) with both 6-31G(d,p) and 6-31+G(d) basis sets predicts the favored hydration of the *cis* conformer by 1.2 kcal/mol than the *trans* conformer, but the HF/IPCM and HF/SCI-PCM result in different trends in  $\Delta\Delta G_s$ , depending on basis sets. The SCI-PCM model at the HF and B3LYP levels yields almost the same  $\Delta\Delta G_s$  in water with the same basis set. The calculated  $\Delta\Delta G_s$  by the HF/IPCM, HF/SCI-PCM and B3LYP/SCI-PCM methods at both basis sets agree well with the values of  $0.13 \pm 0.30$ ,  $-0.4$  and  $-0.41 \pm 0.35$  kcal/mol from MC simulations [1], integral equation calculations [6] and MD/free energy perturbation simulations [8], respectively. However,



Table 8

Calculated relative solvation free energies ( $\Delta\Delta G_s$ ) of *cis*-NMA and dipole moments ( $\mu$ ) of NMA (energies and dipole moments are in kcal/mol and D, respectively).  $\Delta\Delta G_s$  corresponds to the solvation free energy of the *cis* conformer relative to the *trans* conformer. In the second row for each SCRF model, the values correspond to dipole moments of *trans* and *cis* conformers, respectively)

Models		HF		B3LYP <sup>a</sup>	
		6-31G(d,p)	6-31+G(d)	6-31G(d,p)	6-31+G(d)
<i>Water</i>					
PCM	$\Delta G_s$	-1.23	-1.24		
	$\mu$	5.49, 5.99	5.69, 6.22		
IPCM	$\Delta G_s$	0.06	-0.03		
	$\mu$	5.28, 5.39	5.61, 5.78		
SCI-PCM	$\Delta G_s$	-0.10	0.22	-0.07	0.10
	$\mu$	5.01, 5.13	5.36, 5.45	4.73, 4.87	5.20, 5.40
<i>Chloroform</i>					
SCI-PCM	$\Delta G_s$	-0.23	-0.05	-0.17	-0.07
	$\mu$	4.68, 4.86	4.99, 5.19	4.40, 4.59	4.83, 5.11

<sup>a</sup> Convergence problems were encountered for the PCM and IPCM methods at the B3LYP level in water.

the favorable hydration of the *cis* conformer is expected from its larger dipole moment than the *trans* conformer at all levels of theory in water. Thus, the calculated  $\Delta\Delta G_s$  of -0.10 and -0.07 obtained by the SCI-PCM method with the 6-31G(d,p) basis set at the HF and B3LYP levels appear to be reasonable, which are in good agreement with the experimental finding that the  $\Delta\Delta G_s$  of the *cis* conformer appears to be less than 0.1 kcal/mol. On the other hand, the recent PCM calculations at the HF/6-31G(d) level resulted in that *cis*-NMA has the favored hydration by 0.5 kcal/mol than *trans*-NMA [4].

From the IPCM method at the HF level with 6-31G(d,p) and 6-31+G(d) basis sets, the solvation free energy ( $\Delta G_s$ ) of *trans*-NMA is determined to be -10.5 and -10.8 kcal/mol, respectively, which are consistent with the value of about -10.0 kcal/mol observed for NMA at 25°C in water [40]. However, the relative solvation free energies ( $\Delta\Delta G_s$ ) for *cis*-NMA at both levels appear to be underestimated, compared to the value of -0.1 kcal/mol determined experimentally for NMA in water [2]. On the other hand, the SCI-PCM calculations at the HF level with 6-31G(d,p) and 6-31+G(d) basis sets resulted in the  $\Delta G_s$  for *trans*-NMA to be -7.1 and -7.8 kcal/mol, respectively, and the corresponding values are -6.0 and -6.7 kcal/mol from the B3LYP level, respectively. Although these  $\Delta G_s$  with the SCI-PCM method

may be underestimated, the relative  $\Delta\Delta G_s$  for *cis*-NMA accords with the experimental value, as pointed out above. Recent HF/6-31G(d) calculations with the PCM method resulted in the  $\Delta G_s$  of *trans*-NMA equal to -7.0 kcal/mol [4]. From integral equation calculations [6] and free energy perturbation calculations [8,10] with MD simulations, the  $\Delta G_s$  for *trans*-NMA is estimated to be -9.8 and -9.6 kcal/mol, respectively.

By combining the  $\Delta G$  of 2.75 kcal/mol at the B3LYP/6-31G(d,p) level in the gas phase and the hydration free energies of -0.10 or -0.07 kcal/mol from the SCI-PCM/6-31G(d,p) method at the HF or B3LYP levels, respectively, *trans*-NMA is favored by a total free energy of 2.65 or 2.68 kcal/mol in water, which corresponds to 1.1% population of the *cis* conformer. This is consistent with the results of NMR experiments in aqueous solution that estimate the population of the *cis* conformer to be  $1.46 \pm 0.09\%$  [2] and the free energy difference of  $2.5 \pm 0.3$  kcal/mol [28] in favor of the *trans* conformer.

In chloroform, the SCI-PCM method at the HF and B3LYP levels results in the relative solvation free energies of *cis*-NMA to be -0.23 and -0.17 kcal/mol with the 6-31G(d,p) basis set, and -0.05 and -0.07 kcal/mol with the 6-31+G(d) basis set, respectively. From the values of  $\Delta\Delta G_s$  at the HF and B3LYP

levels with the 6-31G(d,p) basis set in water and chloroform, the solvation free energy change as transferred from water to chloroform is estimated to be  $-0.1$  kcal/mol, whereas the corresponding value with the 6-31+G(d) is  $-0.2$  kcal/mol. Combined with the  $\Delta G$  of 2.75 kcal/mol at the B3LYP/6-31G(d,p) level in the gas phase, the relative total free energy of *cis*-NMA is computed to be  $2.52 \pm 0.03$  kcal/mol at the HF and B3LYP levels in chloroform, which corresponds to 1.4% *cis* population. From *cis* populations with the 6-31G(d,p) basis set in water and chloroform, the change in the *cis* population as transferred from water to chloroform is computed to be about 0.3%, which is reasonably consistent with the value of 1.3% from NMR measurements [2].

The computed dipole moment of *trans*-NMA in water lies between 4.73 D at the B3LYP/6-31G(d,p) level and 5.36 D at the HF/6-31+G(d) level, which is smaller by 0.1–0.2 D than the corresponding value for *cis*-NMA. On the other hand, the PCM method at the HF/6-31G(d) [4] and HF/6-31++G(d,p) [13] levels results in 5.27 and 4.83 D for *trans*-NMA in water, respectively. In chloroform, the dipole moment of *trans*-NMA is calculated to be 4.40 D at the B3LYP/6-31G(d,p) level to 4.99 D at the HF/6-31+G(d), and *cis*-NMA is found to have a larger dipole moment by 0.2–0.3 D than *trans*-NMA. The dipole moments of 4.40 and 4.68 D for *trans*-NMA at the B3LYP and HF levels with the 6-31G(d,p) basis set are close to the experimental value of 4.22 D in 1,4-dioxane [41], but they are larger than experimental data of 3.85 and 3.87 D in benzene and carbon tetrachloride, respectively [42].

Recently, it has been shown that the SCRF calculations for a cluster involving hydrogen bonding of water molecules to the solute may provide an adequate description of the hydration effect on the resonance Raman spectra of NMA [13] and the rotational barrier for *N,N*-dimethylformamide [43]. However, the solvation effect on the *cis*–*trans* equilibrium in water studied here may support the reliability of the SCRF method with proper levels of theory and basis sets. Our calculated results may confirm that the relative distribution of two conformers is insensitive to the solvent polarity and that the dominant population of *trans* peptide bonds in *N*-methylated amides can be attributed to the intrinsic stability of the *trans* conformer in the gas phase.

#### 4. Conclusions

By comparing the calculated structure and dipole moment of *trans*-NMA and the  $\Delta H$  of *cis*-NMA in the gas phase with corresponding experimental data, the B3LYP level with 6-31G(d) or 6-31G(d,p) basis sets appears to be the most appropriate among several levels of theory and basis sets considered here. Our calculations may indicate that the B3LYP results are better than or close to the corresponding MP2 ones depending on basis sets.

The HF and B3LYP calculations with the 6-31G(d,p) basis set predict well the populations of the *cis* conformer in water and chloroform, and the dipole moment in chloroform. The SCRF method with proper levels of theory and basis sets seems to be reasonable to describe the solvation effect of NMA. It has been confirmed that the relative distribution of two conformers of NMA is insensitive to the solvent polarity.

The results obtained here may provide us useful information to choose adequate levels of theory and basis sets for conformational study of amides and peptides. The effect of basis sets at the HF, MP2 and B3LYP levels on the *cis*–*trans* equilibrium of proline dipeptide and 5-methylated proline dipeptides are now being carried out.

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