

Molecular dynamics of *cis/trans* *N*-methylformamide liquid mixture using a new optimized all atom rigid force field

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Abstract

The properties of the liquid *N*-methylformamide (NMF) at normal conditions are studied by means of NVT and NPT molecular dynamics (MD) simulation techniques. The liquid has been modeled for the first time via MD as a mixture of two conformers (*cis* and *trans*) with mole fraction $X_{trans} = 0.94$. A new all atom interaction potential model has been constructed and its reliability in predicting certain properties of the system has been presented. The results obtained reveal the existence of some differences regarding the dynamic and structural properties of the two conformers in the fluid.

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1. Introduction

Among several classes of organic solvents, the lower substituted liquid amides appear to be very interesting molecular systems for several reasons. Concerning the structure of these liquids, several studies have shown that they represent two different classes of solvents. Specifically, in the protic systems formamide (FA), *N*-methylformamide (NMF) and *N*-methylacetamide (NMA) hydrogen bonds of the type $C=O \cdots H-N$ may be formed among the molecules at liquid conditions. On the other hand, *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA) are polar aprotic solvents. It has been suggested that the $C=O \cdots H-N$ type of hydrogen bond leads to the formation of the ordered intramolecular structures of peptides and proteins in aqueous solution [1]. For this reason, investigating the structural and dynamic properties of *N*-monomethyl amides (NMF, NMA) becomes a very interesting task since these molecules contain a peptide linkage and therefore may be used as the simplest models for the main chain of proteins. One should add that NMF is of considerable medical interest since previous studies have revealed that this solvent has an antitumor activity [2].

In view of the importance of NMF, a number of its properties have been explored experimentally so far. Specifically, to help elucidate fundamental questions on the structure of NMF, a number of experimental studies have been reported in the past based on several techniques such as X-ray and electron diffraction (XD, ED) [3–5], nuclear magnetic resonance (NMR) [6], synchrotron radiation (SR) and neutron diffraction (ND) with two isotopic substitutions [7,8]. In the aforementioned ND studies, the authors investigated the intramolecular rather than the intermolecular structure of the liquid.

Theoretical considerations, via high level *ab initio* methods [9–12] and computer simulation (CS) techniques [13–18], have also been employed to study NMF. In a recent MD treatment [13], the authors reported results concerning the intermolecular structure of liquid FA, NMF and DMF in conjunction with experimental data. In the case of NMF the calculated total pair radial distribution functions were compared with corresponding functions derived from XD and ND experimental data partially reported in that MD treatment. Note however that the aforementioned structural experimental studies on liquid NMF in [13] have not yet completely presented in any further publication until the time this paper was written. The results obtained from all the above-mentioned computational studies complement the experimental investigations of the system,

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and they have led to a better understanding of its behavior. It should be emphasized, however, that despite the research effort on NMF and some of its mixtures, a deeper and quantitative understanding of the behavior of this liquid has not been achieved. It is important to notice here that, the existence of hydrogen bonding in liquids generally causes a very short range ordering among the molecules and presumably a slowing down of the molecular motions. Recently, Barthel et al. [19] have published an experimental investigation devoted to the dynamics of liquids FA, NMF, DMF and DMA using dielectric relaxation spectroscopy (DRS). In that study the comparison of the estimated molecular volumes and dielectric relaxation times of FA and NMF, with respect to DMF and DMA, reveals some influence of the hydrogen bonding on the dynamics of the former liquids.

As far as we know, the fundamental question to what extent the hydrogen bonds in NMF could affect the structural and dynamic properties in the liquid has not yet been definitively answered. Therefore, a thorough investigation of the structure in liquid NMF, extended to the hydrogen-bonding network and dynamics, becomes indispensable.

As a part of our MD studies of liquid amides, we have recently reported results concerning the properties of liquid DMF using optimized force fields [20]. The focus in that work was to investigate the molecular interactions in the system. In the course of that study, we derived a new optimized potential model (OPLS) for DMF, based on a scaling parametrization procedure. In a subsequent MD treatment, we reported results concerning the properties of various potential models used to describe the DMF–water mixtures [21].

In connection to the above-mentioned CS studies of liquid amides, we demonstrate here the first MD treatment aimed to simulate the liquid NMF as a mixture consisted of *cis*- and *trans*-conformers. It should be stressed that our main motivation to study this system as a mixture has relied on the results reported in previous experimental studies of this fluid. Concretely, according to several experimental observations, liquid NMF consists of *cis*- and *trans*-conformers. At normal conditions the mole fraction of *trans* conformers in the fluid, X_{trans} , has been found to be about 0.94 [22]. From a theoretical point of view, only a limited number of CS studies on liquid NMF have been reported so far [13–18]. Eventually, there is only one CS study of NMF where the fluid has been modeled as a mixture consisted of two conformers [17,18]. Therefore, a more comprehensive MD simulation of this molecular liquid becomes a very interesting task.

In this Letter, we present a part of the results obtained from our MD simulation of liquid NMF using an all atom potential model. The proposed potential has been constructed in the framework of the present in-

vestigation to yield reliable descriptions of the interactions among the species in the mixture.

2. Computational details

As mentioned in the Introduction, only a limited number of CS studies on liquid NMF have been reported up to date. In a Monte Carlo (MC) treatment devoted to liquid amides FA, NMA, NMF and DMF, Gao et al. [14] developed a polarizable potential function (PIPF) of each liquid consisted of a pair-wise additive term (Lennard-Jones (L-J) plus Coulomb terms) and a nonadditive polarization part. The potential functions were derived by the adjustment of the empirical parameters in order to reproduce the experimental thermodynamic data for the pure liquid, and the polarization energies were optimized to be consistent with the results obtained from combined QM/MM simulations [23]. In a subsequent MC investigation [15], Cordeiro used optimized rigid force field to determine the hydrogen bonding in liquid NMF. Torii and Tasumi [16] performed MD simulations and instantaneous normal mode (INM) analysis of liquid NMF. In that treatment the authors employed the six-site potential model developed by Jorgensen and Swenson [24] to calculate the Raman spectral profiles and the optical Kerr effect (OKE) in the liquid. Before proceeding any further, however, we should remark that all the above-mentioned CS treatments were based on the assumption that liquid NMF consists of *trans*-conformers. Finally, quite recently Krienke et al. [17,18] performed a MC study of liquid NMF in which the system has been modelled as a mixture of two conformers. In that treatment the authors employed a polarizable force field to represent the interactions in the system. However, a closer inspection of the thermodynamic results obtained from that study indicates clearly the existence of some deviations from experiment. Concerning the potential energy of the system, U_{sim} , at 298 K and normal pressure, we see that this property is overestimated by about 10% compared with experimental results [17]. The predicted pressure, P_{sim} , deviates also significantly from the experimental one at the same conditions.

Taking into consideration all the above arguments, we decided to extend these previous computational studies on liquid NMF by employing the MD technique to simulate the fluid as a mixture of *cis*- and *trans*-conformers and by using a new all atom (9-site) optimised model to describe the interactions among the species in the system.

Note that among several computational techniques, the MD method is advantageous due to its ability to provide information underlying not only the thermodynamics and structure, but also the dynamic properties of the system under investigation.

In what follows we will present the new optimized potential employed in this study to model the liquid.

The used model consists of site–site pair-wise additive potentials which contain the short-range L-J (12-6) plus Coulombic terms. The L-J interaction parameters between sites of different types are set by the usual Lorentz–Berthelot combining rules. Note also that the fractional charges on the molecules coincide with the L-J sites. Also, the long-range part of the Coulombic interactions was treated by the Ewald method.

In each conformer, the H–CO–NH–C(Me)– group is planar. Also, one of the three methyl hydrogens is coplanar with the H–CO–NH–C(Me)– group and this plane dichotomizes the angle $\angle H_2(\text{Me})C(\text{Me})H_3(\text{Me})$ of the methyl carbon with the other two methyl hydrogens which are out of the plane. We also mention that, in contrast to all previous models, we have used different conformations in the methyl groups for the two conformers (see Fig. 1). This comes in agreement with recently reported high level ab initio calculations [9–11], according to which the most stable conformations of the methyl groups in each conformer are different. The intramolecular geometries for the two conformers used in our model are summarized in Table 1 and depicted in Fig. 1. By comparing the intramolecular geometries for the two conformers proposed in this study with those employed in previous models, we clearly see that the

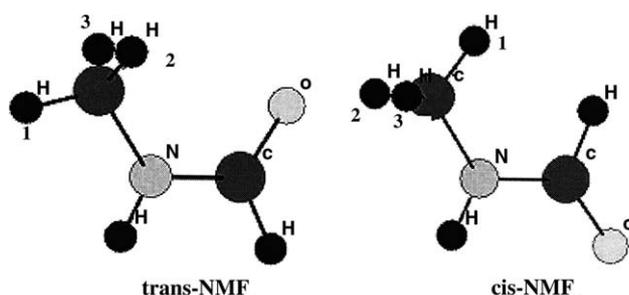


Fig. 1. Intramolecular geometries of *cis*- and *trans*-NMF I.

Table 1
Parameters of the intramolecular geometry of *cis*- and *trans*-NMF

Bond lengths and angles	
$r_{\text{N-C(Me)}} \text{ (nm)}$	0.1449
$r_{\text{C(O)-H}} \text{ (nm)}$	0.1123
$r_{\text{C(Me)-H}} \text{ (nm)}$	0.1090
$r_{\text{C(O)-N}} \text{ (nm)}$	0.1335
$r_{\text{N-H(N)}} \text{ (nm)}$	0.0960
$r_{\text{C(O)-O}} \text{ (nm)}$	0.1230
$\angle \text{C}_{(\text{Me})}\text{NC}_{(\text{O})} \text{ (deg)}$	120.0
$\angle \text{OC}_{(\text{O})}\text{N} \text{ (deg)}$	122.9
$\angle \text{HC}_{(\text{O})}\text{N} \text{ (deg)}$	114.5
$\angle \text{H}_{(\text{N})}\text{NC}_{(\text{O})} \text{ (deg)}$	119.0
$\angle \text{NC}_{(\text{Me})}\text{H}_{(\text{Me})} \text{ (deg)}$	109.5
$\angle \text{H}_{(\text{Me})}\text{C}_{(\text{Me})}\text{H}_{(\text{Me})} \text{ (deg)}$	120.0

corresponding bond lengths and angles used differ slightly but not insignificantly from those assigned to other models.

In our treatment, the fractional charge distribution on each conformer was taken from the model proposed in [17,18] and has been re-evaluated. Our parametrization procedure has led to obtain slightly modified fractional charges on the conformers in comparison with their corresponding initial values. The new fractional charge distributions used for the *trans*- and *cis*-conformers of NMF models yield effective dipole moments sufficiently higher than the gas phase one. This is in agreement with the consideration that point charge distributions need to provide permanent dipole moments greater than gas-phase values in potential models constructed for liquid simulations [20]. Note that the corresponding modified dipole moments for the *cis*- and *trans*-conformers are 4.29 and 4.13 D, respectively. The experimental gas-phase value for the system assuming to be consisted of only *trans*-conformers is about 3.78 D [25]. These values are also comparable with the results obtained from density functional quantum mechanical calculations by Desfrancois et al. [9]. It must be emphasized that, earlier molecular mechanics (MM) calculations for the two conformers also yielded different dipole moment values for the *cis*- and *trans*-molecules and specifically a higher value μ_{cis} compared with μ_{trans} [26] as in our model and in contrast with the previous *cis*- and *trans*-NMF model. The modified point charge distributions on each NMF conformer are depicted in Table 2.

As mentioned above, in our treatment we used a planar configuration for the H–CO–NH–C(Me)– group to represent the ground-state intramolecular geometries for each conformer. In order to obtain better agreement with experiment, we modified slightly the bond lengths and angles derived from the aforementioned experimental and computational studies. These modifications were carried out throughout a series of trial simulations, while the L-J and point charge parameters were being each time also readjusted to predict reliable results. Note that the optimization method used in this study is

Table 2
Intermolecular potential parameters for *cis*- and *trans*-NMF

Site	$\sigma \text{ (nm)}$	$\epsilon \text{ (K)}$	$q_{\text{trans}} \text{ (e)}^{\text{a}}$	$q_{\text{cis}} \text{ (e)}^{\text{a}}$
C _(Me)	0.370	50.0	–0.055	–0.055
H _(Me) ^b	0.230	11.0	0.070	0.070
N	0.325	80.0	–0.510	–0.496
H _(N)	0.230	8.0	0.335	0.385
C _(O)	0.370	50.0	0.470	0.420
H	0.230	11.0	0.060	0.060
O	0.296	100.0	–0.510	–0.524

^a Dipole moments $\mu_{\text{trans}} = 4.13 \text{ D}$ and $\mu_{\text{cis}} = 4.29 \text{ D}$.

^b The point charges and L-J parameters for all the methyl hydrogens are the same.

commonly used in condensed phase simulations [27,28]. A summary of all the optimized potential parameters is given in Tables 1 and 2.

Finally, the liquid NMF was simulated at 298.15 K and corresponding density 0.9986 g/cm^3 in the NVT ensemble using the Nose-Hoover thermostat. The simulations were performed for a system consisted of 241 *trans*- and 15 *cis*-NMF species in the central simulation box using periodic boundary conditions. Also, some additional simulations were performed at the same state point in the NPT ensemble. In each case, the equilibration time was 200 ps, using a time-step of 0.001 ps. The liquid properties were obtained in a subsequent simulation of 800 ps, after the equilibration period. The equations of motion were integrated using modified Beeman algorithms [29].

3. Results and discussion

The most important thermodynamic results obtained for liquid NMF from our MD simulations are summarized and compared against previous CS studies and experimental values in Table 3. A closer inspection of the results depicted in this table indicates that our model exhibit a more realistic description of the thermodynamic behavior at this state in comparison with all the previous CS studies and with experiment. Concerning the mean potential energy, U_{sim} , on the basis of our model, we may conclude that the predicted value is quite close to the experimental one of 53.7 kJ mol^{-1} from both the NVT and NPT simulations. A similar conclusion may be drawn for the calculated pressure, as well as for the density. Therefore, with regards to the simulated potential energy, pressure and density our model can reproduce these quantities more accurately than the previous available potentials.

The self-diffusion coefficients of both the NMF conformers D_{cis} and D_{trans} were also studied in this treatment by integrating the corresponding linear velocity autocorrelation functions and also by using the mean square displacements of the particles. Interestingly,

Luedemann et al. also studied the self-diffusion in this liquid amide [17] by using the pulsed field gradient spin echo method [30,31]. By analyzing their data obtained at 298.9 K and normal pressure they found that the self-diffusion $D_{\text{trans}} (8.69 \times 10^{-10} \text{ m}^2 \text{ s}^{-1})$ is greater than $D_{\text{cis}} (7.95 \times 10^{-10} \text{ m}^2 \text{ s}^{-1})$. This experimental observation may be characterized as an unexpected one since it was generally assumed that such kind of conformers exhibit the same dynamical behavior in the liquid state. Unfortunately, this motional behavior in liquid NMF has not yet been explored in details. One possible origin of this effect might be the existence of different local intermolecular ordering and hydrogen bonding network around each conformer.

According to our results, the predicted diffusion coefficients are $D_{\text{trans}} = 7.15 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ and $D_{\text{cis}} = 6.76 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$. As we can see, our diffusion results are in good agreement with experiment. The simulated D_{cis} is lower by about 5.5% than D_{trans} , while the percentage difference of the experimental values for D_{cis} and D_{trans} is about 8.5%.

Let us now investigate the local structure of liquid NMF in terms of the appropriate center of mass (COM) and site-site radial distribution functions (RDFs) calculated on the basis of our potential model. The RDFs have been evaluated for correlation distances up to about 1.8 nm with a resolution of 0.01 nm. The results obtained by the NVT-MD method at 298.15 K are depicted in the following figures.

The RDFs COM-COM *trans-trans* and *cis-trans* are shown in Fig. 2. From this figure it is obvious that these correlations are almost similarly shaped. However, the amplitude of the first peak in the *trans-trans* is higher than in the *cis-trans* correlation. These distributions yield about 12.2 *trans*-molecules in the first coordination shell of each conformer. Concerning the site-site RDFs, we mention that we have calculated the complete set of these functions and we will demonstrate here only the related ones to the hydrogen bonding of the fluid. The complete set of the calculated RDFs will be presented in a more extended paper about the structure of the system. The $\text{H}_\text{N}-\text{O}$ and $\text{H}_{\text{C}=\text{O}}-\text{O}$ *trans-trans* and *cis-trans*

Table 3
Thermodynamic results for liquid NMF from the present and previous CS studies

	A-MC	B-MC	C-MD	D-MD	E-MC			This work-MD		Exp.
	(<i>trans</i>)	(<i>cis</i>)	(mixt)	(mixt)	(mixt)					
Ensemble	NPT	NPT	NVE	NVT	NVT	NVT	NVT	NVT	NPT	
N (<i>trans</i>)	128	256	256	216	–	0	–	241	241	–
N (<i>cis</i>)	0	0	0	0	0	–	–	15	15	–
$-U_{\text{pot}}$	53.58	55.15	–	–	58.2	41.9	59.4	53.79	53.64	53.7
P	1	1	–	–	–	–	–	–0.9	1	1
ρ	0.969	1.00	0.9988	0.998	0.998	0.998	0.998	0.9986	0.9985	0.9986

Depicted are the number of *cis*- and *trans*-NMF molecules; the average potential energy, U_{pot} (kJ mol^{-1}); the pressure, P (bar) and the density, ρ (g cm^{-3}) of the system at 298.15 K and normal pressure.

A – [14], B – [15], C – [13], D – [16], E – [17], Exp. – [17].

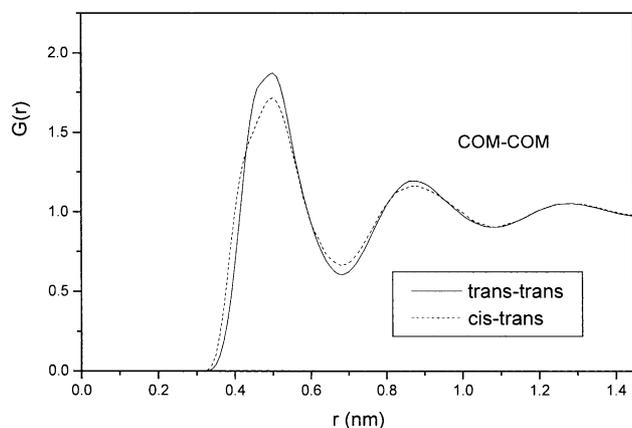


Fig. 2. Center of mass pair distribution functions *trans-trans* and *cis-trans* NMF.

RDFs are presented in Figs. 3, 4, respectively. By inspecting the H_N-O *trans-trans* and *cis-trans* RDFs from Fig. 3 we may observe that these functions are highly structured at relatively short intermolecular distances.

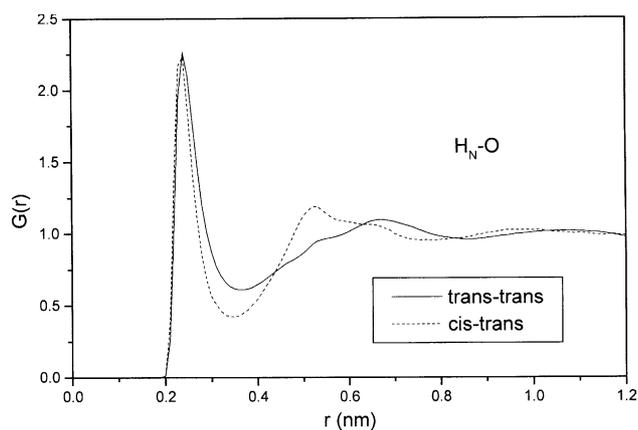


Fig. 3. Site-site pair distribution functions H_N-O *trans-trans* and *cis-trans* NMF.

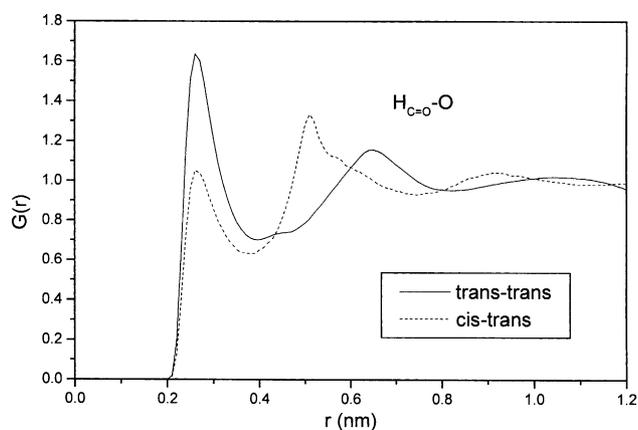


Fig. 4. Site-site pair distribution functions $H_{C=O}-O$ *trans-trans* and *cis-trans* NMF.

They provide a strong sharp-peaked first maximum around 0.24 nm. This feature indicates the existence of some kind of hydrogen bonding among the nearest *trans-trans* molecules. Moreover, concerning the behavior of the H_N-O *cis-trans* function we also see that it shows a comparable behavior at the first peak. However, beyond the first coordination shell the *cis-trans* function behaves quite differently than the *trans-trans*. Finally, as it can be seen from Fig. 4 the first peak of the $H_{C=O}-O$ *trans-trans* appears to be quite much more intense than the first peak of the $H_{C=O}-O$ *cis-trans* RDF. Moreover, the first maximum in the $H_{C=O}-O$ *cis-trans* correlation appears to be lower than the second one. On the basis of the above-discussed correlations we may conclude that the hydrogen bonding between oxygen and carbonyl hydrogen seems to be less favored in comparison with the $H_N \cdots O$ hydrogen bond. However, this weak correlation between O and carbonyl-H, especially in the case of *trans-trans* dimmers, contributes to the stabilization of such kind of dimer configuration.

4. Concluding remarks

In this study, we employed MD simulation techniques to study the liquid NMF, using a new optimized potential model. The simulations were performed in the NVT and NPT ensembles at normal conditions. In these simulations, the liquid was considered as a mixture of *cis*- and *trans*-conformers with mole fraction $X_{trans} = 0.94$. As a result we found that our 9-site new potential model is quite successful in predicting the bulk thermodynamic properties, as well as the translational behavior of the conformers in the liquid. The intermolecular structure was also studied and related, in some degree, with the hydrogen bonding in the system. Finally, the results obtained by the present MD study come in reasonable agreement with the experimentally observed ones. Further work to explore the hydrogen bonding of the system (static and dynamic) in more details is in progress.

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