TEMPERATURE DEPENDENCE STUDY OF STRUCTURE AND DYNAMICS OF N-METHYL ACETAMIDE AT TWO ISOBARS

A

Thesis Submitted

in partial fulfillments of requirements for the

Degree of

Master of Science in Chemistry

Submitted by

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June 2009

Acknowledgement

The key elements concentration, dedication, hard work and application are not the only essential factors for achieving the desired goals but also guidance, assistance and co-operation of people is necessary.

I would like to express my deep and sincere gratitude to my supervisor **Dr. Snehasis Chowdhuri ,** Lecturer . His wide knowledge and logical way of thinking have been of great value for me. His understanding and personal guidance have provided a good basis for the present thesis. Especially the strict and extensive comments and many discussions and the interactions with Dr. Chowdhuri had a direct impact on the final form and quality of this thesis. I could never imagine to have better mentor than him.

I owe my sincere thanks to **Dr. Susheel Mittal**, Head of School of Chemistry and Biochemistry, for providing facilities.

I wish to express my sincere thanks to all Research Scholars for the possible help extended especially, whenever needed.

I also thank to all the faculty and staff members of School of Chemistry and Biochemistry, Thapar University, Patiala, for their co-operation and support throughout the project work.

I would like to specially acknowledge my classmates and juniors, who have been always there for me as a source of constant motivation and support.

I was very fortunate to have unconditional support from my family and Dr. Chandrika Chowdhuri throughout this time. Without their encouragement and suggestion, this work would indeed have been very difficult for me to tackle.

Last but not least, thanks to God for giving me inner peace and strength. May your name be exalted, honored and glorified.

Finally, I offer my regards to everybody who was important to the successful realization of thesis, as well as expressing my apology that I could not mention personally one by one.

Nidhi Prashar

Candidate's Declaration

I hereby declare that the work being presented in the dissertation entitled **"Temperature dependence study of structure and dynamics of N-methyl acetamide at two isobars",** in partial fulfillment of the requirements for the award of the degree of Masters in Chemistry, School of Chemistry and Biochemistry (SCB), Thapar University, Patiala, is my own work during the period of Jan 2009 to May 2009, under the supervision of Dr. Snehasis Chowdhuri, Lecturer, School of Chemistry and Biochemistry, Thapar University, Patiala. I have not submitted the matter embodied in this dissertation for the award of any other degree.

Patiala
Date: 9-06-09

Nidhi Prashar

This is to certify that the above statement made by the candidate is correct and true to the best of our knowledge.

Dr. Snehasis Chowdhuri
Project Supervisor,
Lecturer (SCB),
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Dr. Susheel Mittal
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Thapar University,

Certificate

This is to certify that the project entitled **""Temperature dependence study of structure and dynamics of N-methyl acetamide at two isobars",** being submitted by Ms. Nidhi Prashar in partial fulfillment of the requirement for the award of degree of Master of Science in the School of Chemistry and Biochemistry, Thapar University, Patiala, is a bonifide work carried out under the supervision of Dr. Snehasis Chowdhuri and that no part of this project has been submitted for the award of any other degree.

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INTRODUCTION

Proteins, quite simply, make us who we are. Proteins is a polymer of amino acids joined together by peptide linkage. Protein functions include acting as structural building blocks, catalyzing chemical reactions or defending our bodies from attack by alien molecules. These functionalities are impaired if the shape of the protein molecule is changed by heating, cooling or dehydration. A molecular-level description of protein-protein and protein-water interactions and their temperature-pressure dependence is crucial for understanding protein folding and function.

Computer simulation has become an important tool in understanding the dynamics of condensed phases at the molecular level. Computer simulations act as a bridge between microscopic length and time scales and the macroscopic world of the laboratory: we provide a guess at the interactions between molecules, and obtain `exact' predictions of bulk properties. The predictions are `exact' in the sense that they can be made as accurate as we like, subject to the limitations imposed by our computer budget. At the same time, the hidden detail behind bulk measurements can be revealed. An example is the link between the diffusion coefficient and velocity autocorrelation function (the former easy to measure experimentally, the latter much harder). Simulations act as a bridge in another sense: between theory and experiment. Different simulation techniques that have been applied so far to investigate the dynamics of various liquids. In classical molecular dynamics simulations the force on a single atom is the sum of its pairwise interactions with other atoms. The parameters describing these interactions are empirical: determined either from experiment or from more exact ab initio calculations. Amides provide the simplest model for the structure and conformational characteristics of the backbones of proteins.

N-methylacetamide (NMA) is one of the simplest molecules containing the peptide linkage which is ubiquitous in biological molecules and therefore it has intrinsic value as a model peptide system. It contains a single peptide bond (O=C-N-H) terminated by methyl moieties on the carbonyl carbon and on the amino nitrogen. Its internal

dergrees of freedom and intermolecular bonding are therefore locally similar those of polypeptide segments. Further, distinguishing feature of NMA is that it has one of the highest static dielectric constants of any liquid (≈180 at T = 30 °C)(1). The molecular origin of this high dielectric constant and its steep decline upon heating (2) is assumed to arise from the strongly temperature-dependent, orientational correlations of a molecule that possesses a large intrinsic dipole moment and forms hydrogen bonds. The molecule N-methylacetamide (NMA) is the minimal model of the peptide linkage in proteins and its behaviour captures the essential elements of protein - protein and protein -water interactions whilst its structural simplicity renders it experimentally, computationally and theoretically tractable.

LITERATURE SURVEY

A key issue underlying the success of the simulation methods is the need for potential functions that properly describe the interatomic interactions in the modeled systems. Great effort has gone into the development of force fields for peptides (3-9). However, the focus has often been on local conformational results,while the functions' abilities to represent intermolecular interactions have generally received only modest testing. The Hagler- Lifson (7) and EPEN/2 (5) potentials are exceptions and involved parameterization with lattice constants and energies for amide crystals, though the latter are not well reproduced with EPEN/2 (5).

Previous simulation studies have been performed both on NMA in water at infinite dilution and on neat liquid NMA. The work has been focused on optimization of potential functions (9-13) (including polarizable models, 13-16), comparison between ab initio and empirical predictions for cis-trans isomerization (17,18) in the gas phase and in water solution, hydrogen bonding in water (17,19) charge polarization effects using QM/MM methods (20), solid NMA (21), liquid NMA (22) and isolated molecule (23)

vibrational properties, isolated dimmers (24-26) larger clusters (27) and other intramolecular properties including the dipole moment (13).

The most widely used OPLS functions were developed by Jorgensen and co-workers for the use in fluid simulations of amides and peptides (9). The OPLS model for intermolecular interactions has also been combined with the intramolecular parameters of Weiner et.al (8) to derive a force field for peptides and proteins that has proven useful in studying heterogeneous systems. Then, James W. Caldwell and Peter A. Kollman presented the first nonadditive molecular dynamics simulation of organic liquids, studying the structure and energetics of N-methylacetamide (16). Later on Jiali Gao et.al (14) constructed a set of polarisable intermolecular potentioal function (PIPF) through a series of Monte Carlo simulations which provides the insight into condensed phase polarization effects.

Thus NMA and aq. NMA have been studied by a wide range of computational and theoretical techniques. As a model peptide NMA has been used in the optimisation of the CHARMM (12) and OPLS (9) forcefields. The majority of theoretical studies investigate small clusters of molecules in vacuum using ab initio techniques: isolated NMA (23), NMA dimmers (24,26), short oligomers (27,38) and NMA-nH_2O complexes (20,38). Combined QM/MM techniques have also been used to model NMA-nH_2O complexes in vacuum, implicit and explicit solvent (20,39). The cis-trans isomerisation pathway has been studied using both ab initio and empirical potentials in vacuum and in explicit water solvent (17,40). Classical molecular dynamics simulations have concentrated on the pure liquid (41)or the infinite dilution limit (22) although Zhang et. al have recently considered the full concentration range of the aqueous solution using the OPLS-AA and SPC force fields.

But no work has been done theoretically to study the structural and dynamical changes of neat N-methyl acetamide over a wide range of temperatures at a particular pressure. In this thesis, the structure and dynamics of neat NMA at five different

temperatures (305.5 K to 454 K) at two different isobars (0.1 MPa and 200 MPa) is investigated and the results are compared with experimental data (43), wherever available.

METHODOLOGY

Molecular Dynamics (MD) techniques simulate the movement of individual particles in a deterministic fashion. This is in contrast to Monte Carlo (MC) techniques where successive states are generated stochastically and accepted probabilistically. While both MD and MC methods yield information about instantaneous structure only MD can be used to investigate system dynamics.

During a classical molecular dynamics simulation a set of particles is allowed to evolve in time according to the laws of classical mechanics. Each individual particle trajectory is not particularly informative but the strength of the technique lies in the fact that the complete set of trajectories is distributed according to a statistical ensemble and thus the rules of statistical physics can be applied to obtain macroscopic thermodynamic averages from the microscopic behaviour of the simulated particles.

Our calculations are based on OPLS functions. In particular, the N-methyl acetamide molecules are characterized by the multisite interaction potential and the atoms are modeled as charged Lennard-Jones particles . In these models, the interaction between atomic sites are expressed as

$$U(r_i, r_j) = 4\varepsilon_{ij}\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \frac{q_i q_j}{r_{ij}} \qquad \ldots\ldots\ldots\ldots\ldots \quad (1)$$

where, q_i is the charge of the *i*-th atom . The Lennard-Jones parameters σ_{ij} and ε_{ij} are obtained by using the combination rules $\sigma_{ij} = (\sigma_i+\sigma_j)/2$ and $\varepsilon_{ij}=\sqrt{\varepsilon_i \varepsilon_j}$. The values of the potential parameters q_i , σ_i , and ε are given in Table 1.

The simulations were carried out in a cubic box with a total of 256 particles (N-methyl acetamide). The simulations were performed at two different pressures : 0.1 MPa and 200 MPa and at five different temperatures: 305 K, 333 K, 373 K, 423 K and 454 K.

We employed the minimum image convention for calculation of the short range Lennard-Jones interactions. The long range electrostatic interactions were treated using the Ewald method (44) and, for the integration over time, we adapted the leap-frog algorithm with time step of 10–15 s (1 fs). The production phase of all the simulations was run in microcanonical ensemble but with varying box size. In order to find the appropriate box size for a desired pressure at a given temperature, we first carried out MD runs of 400–600 ps at constant pressure by employing the weak coupling scheme of Berendsen *et. al* (42). During this initial phase of the simulations, the volume of the simulation box was allowed to fluctuate and the average volume was determined at the end of the simulation. Subsequently, we carried out simulations in microcanonical ensemble keeping the box size fixed at the average value obtained previously for a given system at a given temperature and pressure. While carrying out the simulations in microcanonical ensemble, each system was equilibrated for 400 ps and the simulations were run for another 1.5–2 ns for the calculation of the structural and dynamical quantities. The average values of the pressure and temperature of a system during the production phase of each simulation were found to be very close to the previously chosen pressure and temperature for that particular system.

Table 1. OPLS parameters for N-methyl acetamide.

Atoms	charge, q (*e*)	σ (Å)	ε (kcal/mol)
N	-0.57	3.25	0.170
H	0.37	0.00	0.00
C	0.50	3.75	0.170
O	- 0.50	2.96	0.210
CH_3 (N)	0.20	3.80	0.170
CH_3 (C)	0.00	3.91	0.160

RESULT AND DISCUSSION

STRUCTURAL PROPERTIES

The pressure and temperature induced changes of the structural properties are investigated by calculating various radial distribution functions.

Radial distribution functions, g(r)

The radial distribution function is one method of quantifying the average structure of a solid or liquid and is particularly important in that it can be extracted from neutron scattering measurements and derived by theory as well as calculated from simulations. Essentially the radial distribution function says whether or not two particles are likely to be found with a separation distance of r. It can be constructed by considering a central particle and asking how many particles there are in an annulus of width dr at a distance of r from the central particle. Varying the distance r generates a histogram of the number

of particles as a function of distance, n(r). It is clear that this function increases without bound, therefore it is logical to normalise by the number of expected neighbours for a system where the particle positions are uncorrelated. This normalised distribution is known as the radial distribution function g(r) and for a liquid has the general form as shown in figure1. First of all it can be seen that there is no contribution at short distances since two particles cannot occupy the same space. There is a peak at a distance corresponding to the first neighbour shell.

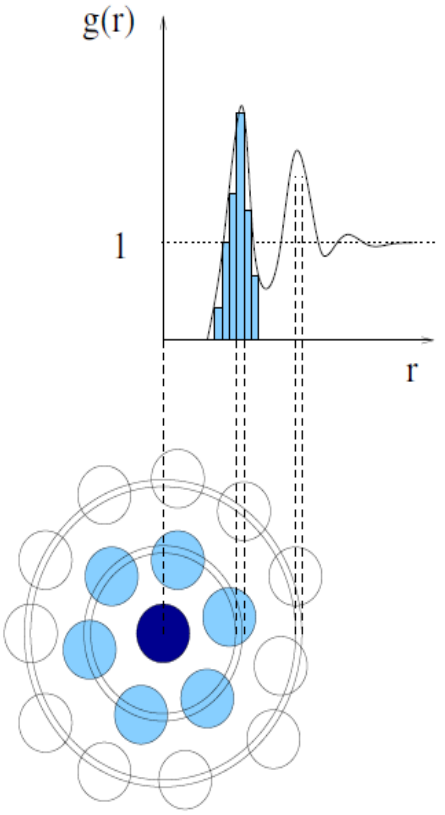

Figure 1. The radial distribution function, g(r) and its relation to interparticle structure

Note that although this peak is sharp it is not a rdf-function since liquid particles have some freedom of movement. Naturally after this peak there is a minimum in the distribution as the second neighbour particles cannot occupy them same space as the first neighbours. Since liquid particles are uncorrelated at large separations it is clear that the normalised distribution g(r) for liquids must tend to 1 for large r. For molecular systems

such as the neat NMA solution investigated in this thesis it is insuffcient to simply consider the correlations between molecules, instead the radial distribution functions between specific atom types are calculated .The coordination number (n_c) is calculated from the radial distribution function by integrating it up to the first minimum as follows

$$n_c = \int_0^{r\,\min} 4\pi\rho g(r) r^2 dr$$

where, ρ is the density of NMA molecules.

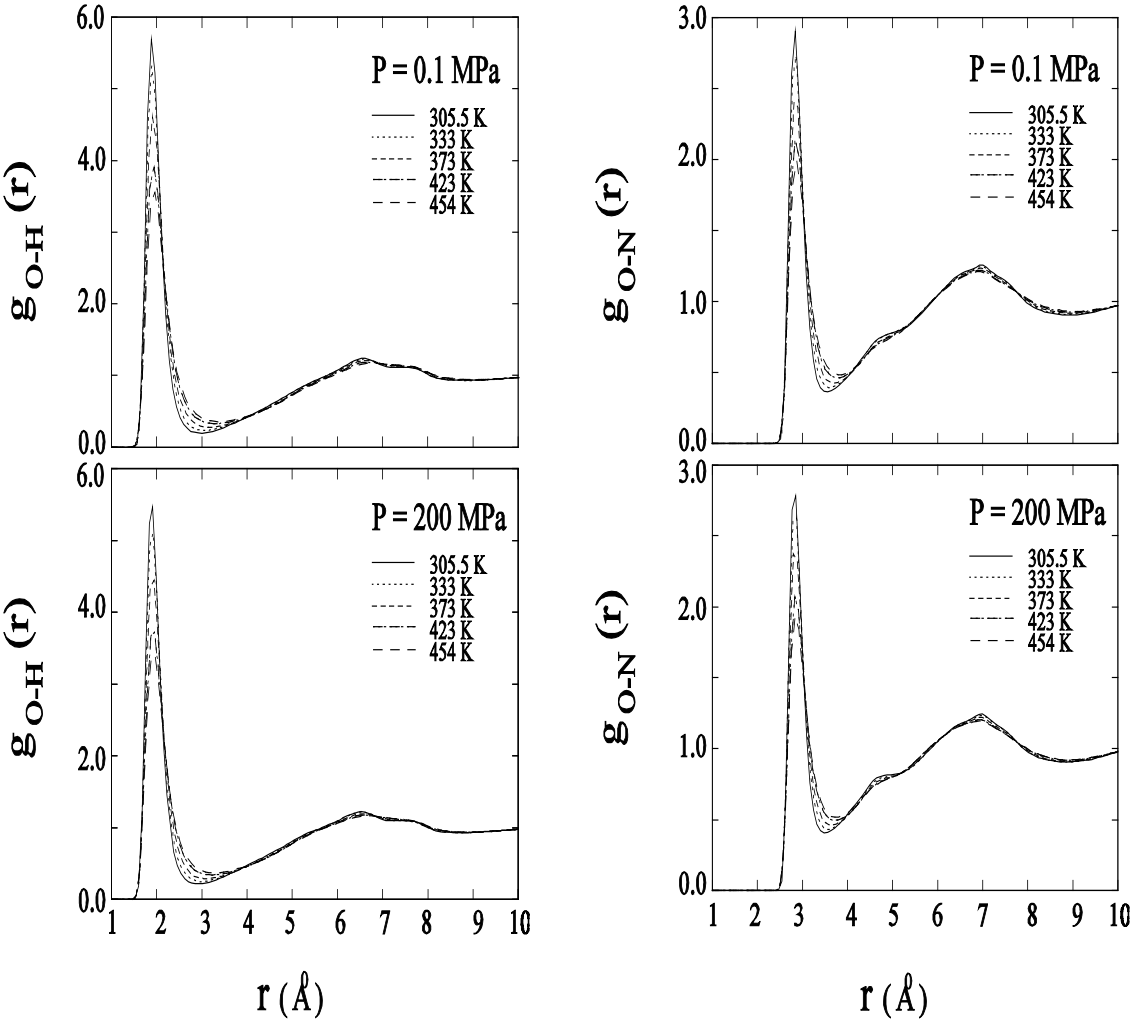

Figure 2. The temperature dependence of the oxygen-hydrogen and nitrogen-oxygen radial distribution functions between N-methyl acetamide molecules at P = 0.1 MPa and 200 MPa.

In Figure 2, the radial distribution functions between NMA molecules for different temperature at two pressures are shown. The first peak of g_{OH} (r) is sharp with well-defined minima at r = 3.15 Å. Integration over this peak gives a co-ordination number n (r = 3.15 Å) = 1.02 . The change in g (r) with temperature is appreciable at lower values of r but at high r values it becomes negligible.

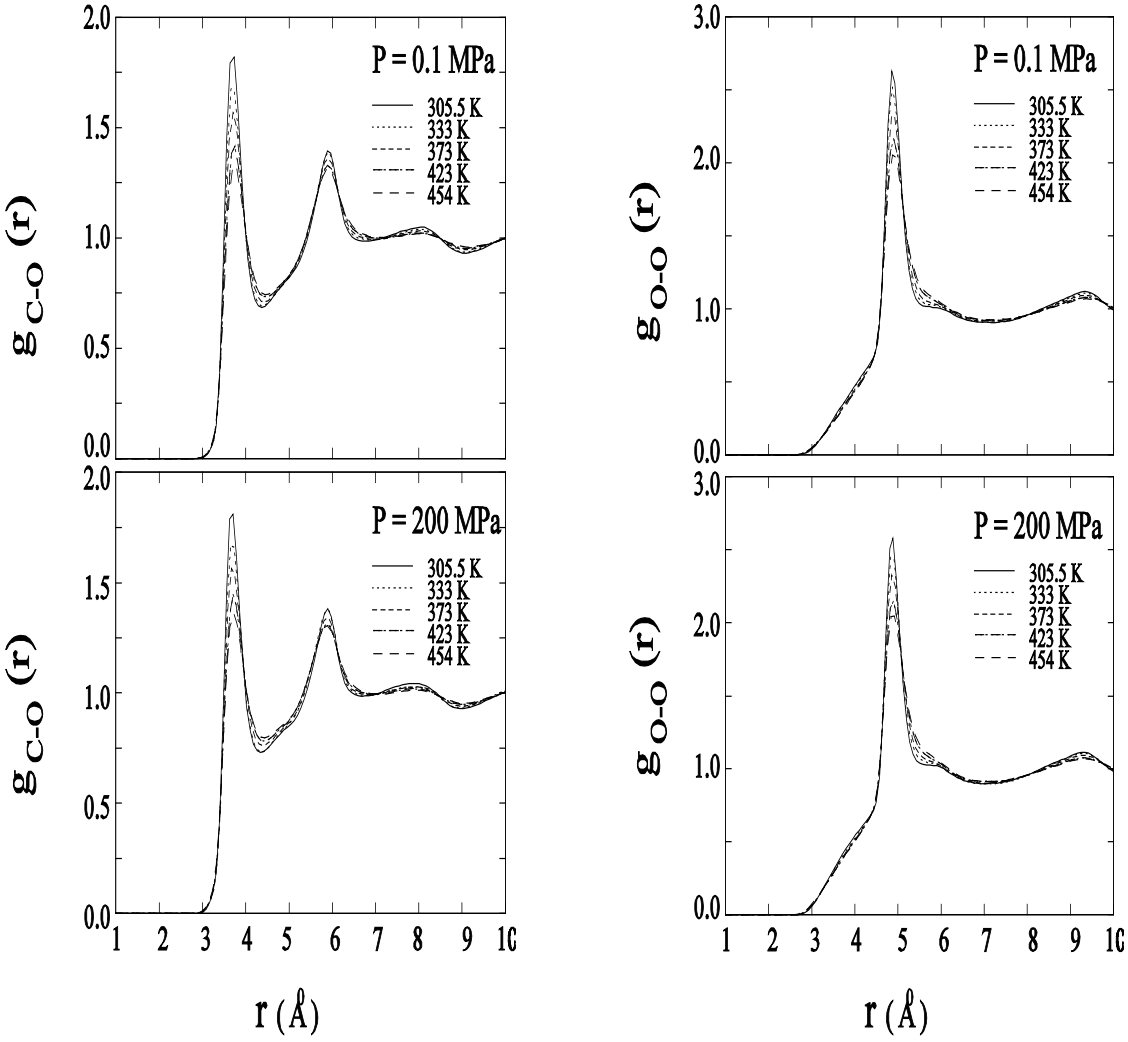

Figure 3. The temperature dependence of the carbon-oxygen and oxygen-oxygen radial distribution function between n-methyl acetamide molecules at P=0.1MPa and 200MPa.

With the increasing temperature the peak height decreases and thus area under the curve decreases slightly resulting in decrease in co-ordination number. A slight shift of the first peak is seen to occur at higher pressures indicating a more compact packing. The $g_{ON}(r)$ shows a distinct contact peak, the co-ordination number, integrated to the first minima at r = 3.65 Å, yields n = 1.06

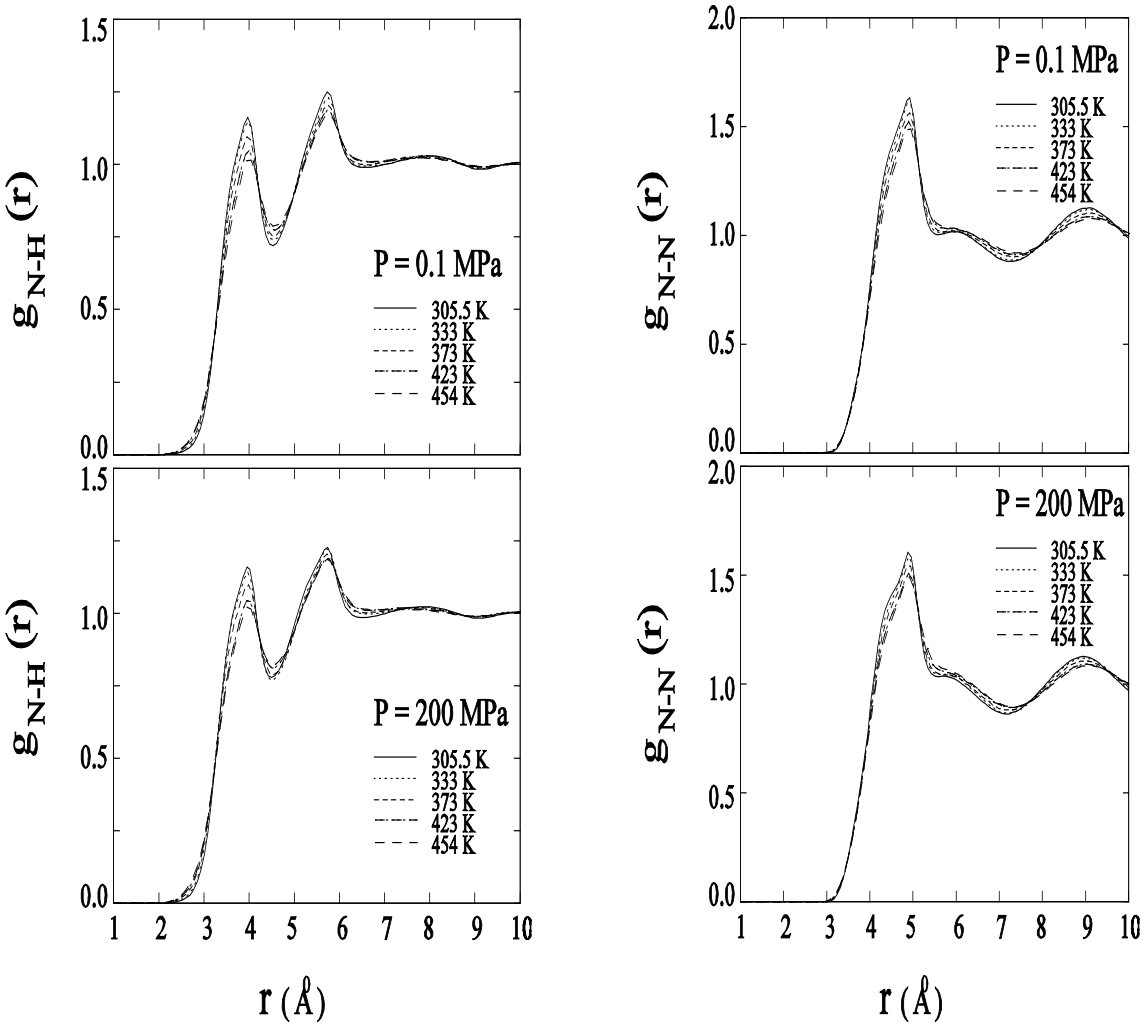

Figure 4. The temperature dependence of the nitrogen-hydrogen and nitrogen-nitrogen radial distribution function between N-methyl acetamide molecules at P= 0.1MPa and 200MPa.

In contrast to other distribution functions, the oxygen-oxygen radial distribution function (in Fig.3) shows unusual features : it has a main peak at r = 4.9Å above a high background but also exhibits a long and otherwise featureless tail extending down to much shorter distance. The $g_{OO}(r)$ distribution has a shallow minima between the first and second maxima. A significant number of oxygen-oxygen contacts must be therefore arise for non-hydrogen-bonding molecules. This conclusion is supported by the large O-O coordination number, n (r = 5.6Å) = 4.9.

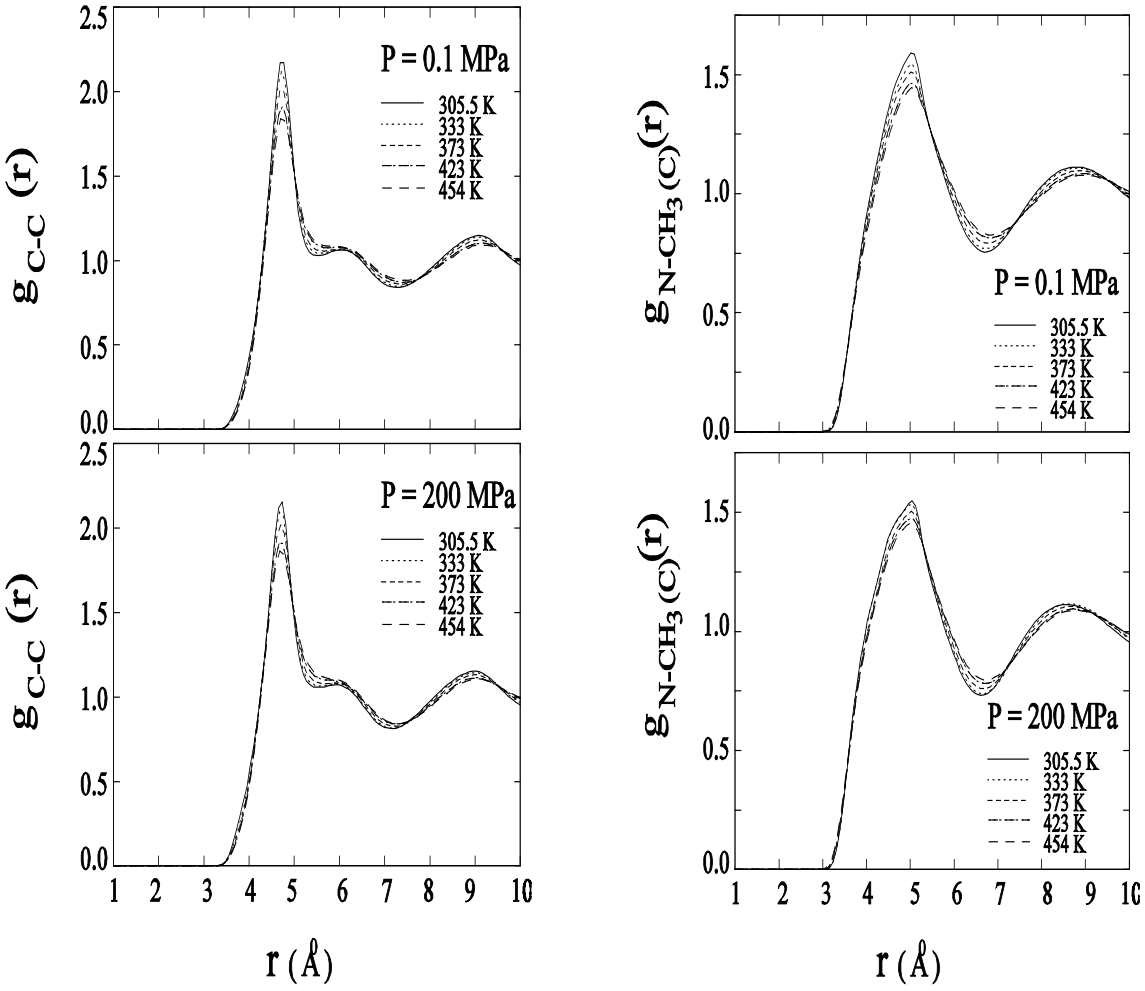

Figure 5. The temperature dependence of the carbon-carbon and nitrogen-methyl group on carbonyl carbon radial distribution function between N-methyl acetamide molecules at P= 0.1MPa and 200MPa.

The various radial distribution function of NMA at different temperature and pressures are given and the coordination number of some of them are calculated in a similar way by integrating the radial distribution functions upto their first minimum and the results are shown in Table 2.

Table 2. The average coordination number of NMA molecules at varying temperatures and pressures

Temp. →		305.5 K	333.0 K	373.0 K	423.0 K	454.0 K
n_{OO}	0.1MPa	4.90	4.80	4.60	4.50	4.20
	200MPa	5.15	5.02	4.85	4.68	4.54
n_{OH}	0.1MPa	1.005	1.00	0.98	0.94	0.889
	200MPa	1.03	1.03	1.00	0.96	0.93
n_{ON}	0.1MPa	1.006	1.048	1.01	0.944	0.92
	200MPa	1.11	1.10	1.075	1.02	0.99
n_{NN}	0.1MPa	4.75	4.60	4.45	4.30	4.07
	200MPa	5.30	5.20	4.97	4.90	4.69
n_{NH}	0.1MPa	1.75	1.70	1.6	1.48	1.44
	200MPa	1.88	1.885	1.81	1.71	1.60

DYNAMICAL PROPERTIES

Diffusion

Diffusion is the process by which matter is transported in a fluid in spite of the absence of flow and is caused by the thermal motion of individual fluid particles. Particles diffuse due to a concentration gradient, $\partial c/\partial x$, in accordance with Fick's Law

$$j = -D \, \partial c / \partial x \qquad \text{…….....} \quad (2)$$

where, j is the flux of the diffusing species and the constant of proportionality D is known as the diffusion coeffcient.

A simple case to consider is the diffusion of a labelled particle through a solution of otherwise identical particles, a process known as self-diffusion. The pressure effects on translational motion are studied by calculating the diffusion coefficients of N-methyl actetamide. The self-diffusion coefficient *D* of a particle is related to the time integral of the velocity-velocity autocorrelation function (VAF) by

$$D = \frac{k_B T}{m} \int_0^\infty C_V(t) dt \qquad \text{…….. (3)}$$

Where, k_B is the Boltzmann constant, *m* is the mass of a particle and C_V(t) is the velocity-velocity time correlation function

$$C_V(t) = \frac{\langle V_i(t).V_i(0) \rangle}{\langle V_i(0).V_i(0) \rangle} \qquad \text{……} \quad (4)$$

where, $_{Vi}$ (t) is the velocity of a molecule at time *t* and the average is carried out over all the particles and over the initial time.

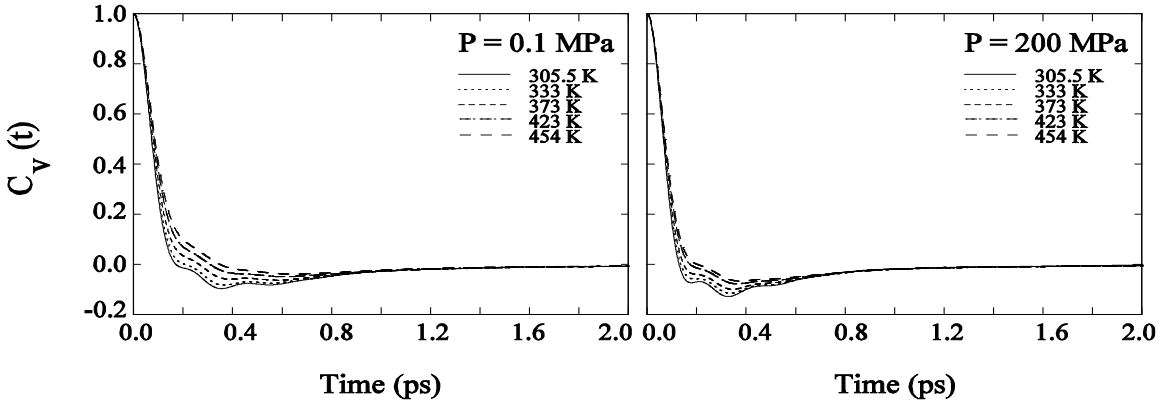

Figure 6. The decay of VAF for NMA at different temperatures and pressures.

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The self diffusion coefficient can also be calculated from the long-time limit of the mean-square displacement (MSD) by

$$D = \lim_{t\to\infty} \frac{\langle [r(t) - r(0)]^2 \rangle}{6t} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (5)$$

where, r (t) is the position of a of a particle at time t and again the average is carried out over all the particles and over the initial time.

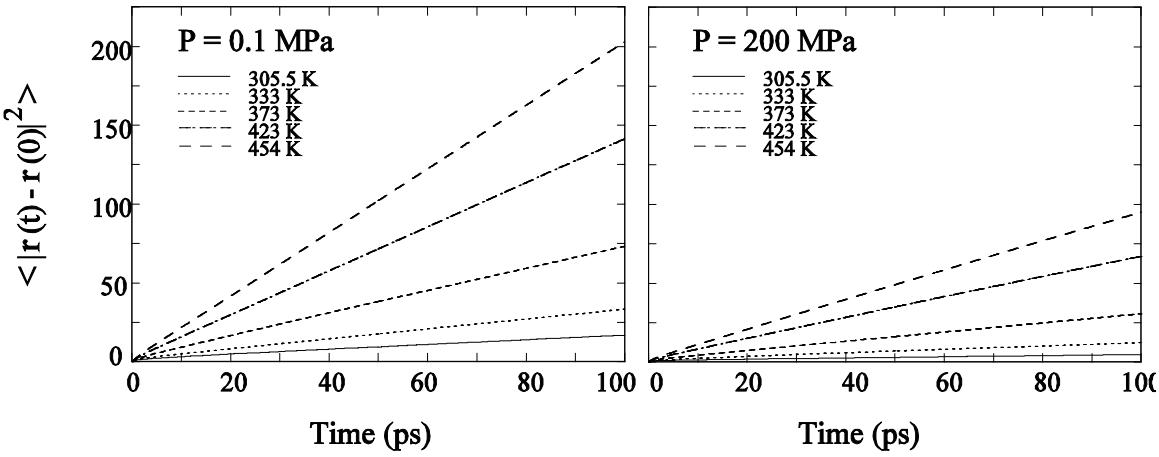

Figure 7. The time dependence of the mean-square displacement at different temperatures and pressures for NMA.

The diffusion coefficients calculated using these two different routes have been found to be quite close to each other as shown in Table 3. We have taken the average of the values obtained from these two routes as the simulation result of the diffusion coefficient at a given temperature and pressure and compare with experimental data in Figure 8.

Table 3. The self-diffusion coefficients (D) for neat NMA in 10^{-5} cm^2s^{-1}

Temperature (K)	Pressure					
	0.1 MPa			200 MPa		
	D_{VAF}	D_{MSD}	$D_{Expt.}$	D_{VAF}	D_{MSD}	$D_{Expt.}$
305.5	0.49	0.29	0.37	0.09	0.08	-
333.0	0.83	0.56	0.70	0.28	0.21	0.29
373.0	1.59	1.22	1.47	0.65	0.51	0.65
423.0	2.76	2.36	2.90	1.35	1.21	1.39
454.0	3.76	3.38	4.16	1.85	1.58	2.00

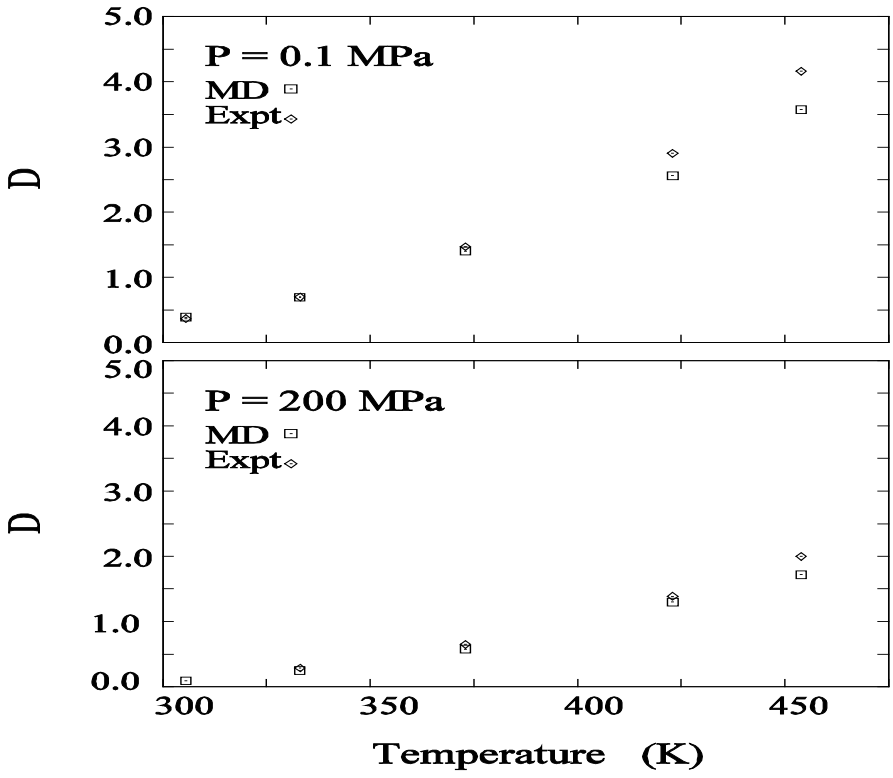

Figure 8. Temperature dependence of the diffusion coefficients of NMA at two different pressures.

CONCLUSION

In this thesis, we have presented the molecular level study of the effects of temperature and pressure on the structural and dynamical properties (self-diffusion coefficient) of neat NMA . Calculations are done at many different temperature (from 305.5 K to 454 K) and at two different pressures (0.1 MPa and 200 MPa) by using a combination of isobaric-isothermal and microcanonical molecular dynamics methods. We used this two-step methodology because the coupling with thermal and pressure baths can alter the true dynamics of a system, especially when the calculations are done at non-ambient high pressure conditions. The dynamical results presented here are averaged over the microcanonical part of the simulation without any coupling with bath Hamiltonians.

It is found that, with application of pressure, the co-ordination number of NMA molecules increases slightly due to packing effects in the compressed system and temperature dependent responses of structural properties are also observed. With the increasing temperature the co-ordination number of NMA molecules decreases due to increased disorder in system.

Due to increasing pressure the intermolecular interactions become more dominant thus affects the dynamical behviour of NMA molecules thereby decreasing the self-diffusion coefficients. On the other hand, with the increase in temperature the thermal motion of particles increases thus the self-diffusion coefficient increases.

We note that, to the best of our knowledge, the results of temperature- pressure dependence on the structural and dymanical properties of neat NMA are presented here for the first time theoretically and compared the results with experimental data where ever available . We hope that the present work will encourage further experimental studies in this area. Also, the present work can be extended in many different directions.

For example, it would be interesting to investigate similar temperature and pressure effects on aqueous NMA and NMA in the mixture of aqueous and non-aqueous solvents like water- methanol mixture and urea solutions etc. Also, the strength of hydrogen bonds can be tuned by changing the NMA concentration. It would be also interesting to look at such temperature-pressure effects using the method of *ab initio* molecular dynamics where, in addition to the diffusion properties, changes of electronic properties of the NMA systems on application of pressure and temperature could also be investigated.

REFERENCES

(1) G. R. Leader and J. F. Gormley, *J. Am. Chem. Soc.*, 1951, **73**, 5731.

(2) R.Y. Lin and W. Dannhauser, *J. Phys. Chem.*, 1963, **67**, 1805

(3) M. Levitt, *Annu. Rev. Biophys. Bioeng.*, 1982**, 11,** 251.

(4) (a) F. A. Momany, R. F. McQuire, A.W. Burgess and H. A. Scheraga, J. *Phys. Chem.*, 1975**, 79,** 2361. (b) L.G. Dunfield, A. W. Burgess, H. A. Scheraga, *Ibid.*, 1978, **82,** 2609.

(5) (a) R. A. Nemenoff, J. Snir and H. A. Scheraga, J. *Phys. Chem.*, 1978**, 82,** 2504. (b) J. Snir, R. A. Nemenoff, H. A. Scheraga, *Ibid.* 1978**, 82,** 2527.

(6) B. R. Gelin, M. Karplus, *Biochemistry*, 1979**, 18,** 1256.

(7) A. T. Hagler, E. Huler and S. Lifson, J. *Am. Chem.* Soc., 1974, **96,** 5319; A.T.Hagler and S.Lifson,**.** *Ibid.*, 1974, **96,** 5327.

(8) S. J. Weiner, P. A. Kollman, D. A. Case, U. C. Singh, C. Ghio, G. Alagona, S. Profeta, P. Weiner, J. *Am. Chem.* Soc., 1984, **106,** 765.

(9) W. Jorgensen and C. Swenson, *J. Am. Chem. Soc.*, 1985, **107**, 1489.

(10) P. Derreumauxa and G. Vergotenb, *J. Chem. Phys.*, 1995, **102,** 8586.

(11) G. Kaminski and W. L. Jorgensen, *J. Phys. Chem.*, 1996, **100,** 18010.

(12) A. D. MacKerell, D. Bashford, M. Bellott, R. L. Dunbrack, J. D. Evanseck, M. J. Field, S. Fischer, J. Gao, H. Guo , S. Ha, D. Joseph-McCarthy, L. Kuchnir, K. Kuczera, F. T. K. Lau, C. Mattos, S. Michnick, T. Ngo, D. T. Nguyen, B. Prodhom, W. E. Reiher, B. Roux, M. Schlenkrich, J. C. Smith, R. Stote, J. Straub, M. Watanabe, J. Wio´rkiewicz-Kuczera, D. Yin, M. Karplus, *J. Phys. Chem. B*, 1998, **102,** 3586.

(13) C. Langley and N. L. Allinger, *J. Phys. Chem. A*, 2002, **106,** 5638

(14) J. Gao, J. J. Pavelites and D. Habibollazadeh, *J. Phys. Chem.*, 1996, **100,** 2689.

(15) S. Iuchi, A. Morita, S. Kato, *J. Phys. Chem. B*, 2002, **106,** 3466.

(16) J. Caldwell and P. Kollman, J. *Phys. Chem.*, 1995, **99,** 6208

(17) Y. Mantz, H. Gerard, R. Iftimie, G. Martyna, *J. Am. Chem. Soc.*, 2004, **126,** 4080.

(18) K. Wibreg, D. Rush, *J. Org. Chem.*, 2002, **67,** 826.

(19) H. Guo and M. Karplus, *J. Chem. Phys.*, 1992, **96**, 7273.

(20) J. Gao and M. Freindorf, *J. Phys. Chem. A,* 1997, **101,** 3182.

(21) G. J. Kearley, M. R. Johnson, M. Plazanet, E. Suard, *J. Chem.Phys.*, 2001, **115,** 2614-2620.

(22) K. Kwac and M. Cho, *J. Chem. Phys.*, 2003, **119,** 2256.

(23) S. Gregurick, G. Chaban, R. Gerber, *J. Phys. Chem. A*, 2002, **106,** 8696.

(24) C. Langley, N. L. Allinger, *J. Phys. Chem.A*, 2003, **107,** 5208.

(25) C. I. Bayly, P. Cieplak, W. D. Cornell, P. A. Kollman, *J. Phys. Chem.*, 1993, **97**, 10269.

(26) M. Buck and M. Karplus, *J. Phys. Chem. B,* 2001, **105,** 11000.

(27) R. Ludwig, F. Weinhold, T. Farrar, *J. Phys. Chem. A*, 1997, **101,** 8861.

(35) T. Miyazawa, T. Shimanouchi, S. Mizushima, *J. Chem. Phys.*, 1956, **24,** 408.

(36) L. Markham and B. Hudson, *J. Phys. Chem.*, 1996, **100,** 2731.

(37) R. Schweitzer-Stenner, *J. Raman Spectrosc.*, 2001, **32,** 711.

(38) H. Torii, J. Phys. Chem. A, 2004, **108.,** 7272.

(39) B. Mennucci and J. Martinez , *J. Phys. Chem. B*, **2005**, 109, 9818.

(40) Y. Mantz, H. Gerard, R. Iftimie, G. J. Martyna, *J. Phys. Chem. B,* 2006, **110,** 13523.

(41) T. W. Whitfield, J. Crain, G. J. Martyna, *J. Chem. Phys*., 2006, **124**, 094503.

(42) H. J. C. Berendsen, J. P. M Postma, W . Fvan Gunsteren, A. Dinola and R. Haak, *J. Chem. Phys*., 1984, **81,** 3684.

(43) L. Chen, T. Grob and H. D. Ludemann, *Z. Phys. Chem.*, 200, **214,** 239.

(44) M. P. Allen and D. J. Tildesley, Compuer Simulation of Liquids, Oxford, New York, 1987.