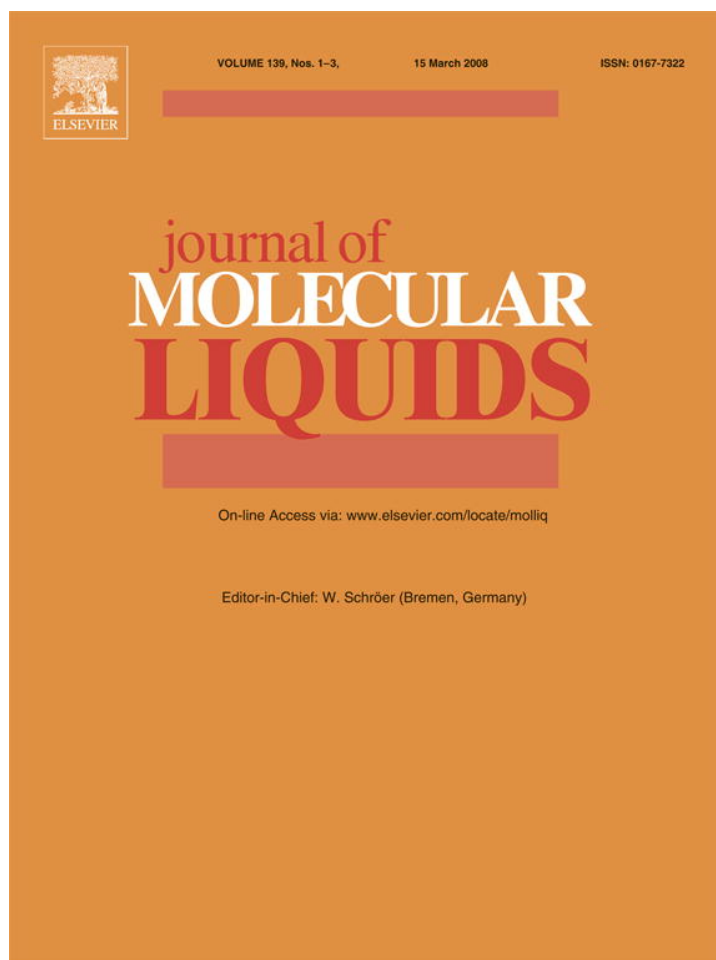


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A study of cyclohexane, piperidine and morpholine with X-ray diffraction and molecular simulations

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Abstract

In this work, the EDXD/molecular dynamics approach to the study of molecular liquids, is applied to cyclohexane and two substituted analogues, piperidine and morpholine. The Structure Functions and Radial Distribution Functions obtained from EDXD (Energy Dispersive X-ray Diffraction) scattered intensity data are interpreted with the same theoretical model recently used for unsaturated liquids. The agreement obtained is satisfactory, although a bit lower in this case. The models are then refined through least-squares fitting to experimental data.

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1. Introduction

The use of simulation methods to assist the interpretation of diffraction data has a long history. Since the pioneer works of Schommers [1,2], several authors have formulated methods to solve the so-called “inverse problem” (i. e. when experimental diffraction data, like pairwise correlation functions are known, and interaction functions are sought). Among all the methods, we should cite the “Reverse Monte-Carlo” technique [3] and the LWR approach [4]; moreover, the problem has been thoroughly studied by Soper and coworkers, who have discussed the matter in a few papers [5–7]. An exhaustive review on the subject has recently been written by Toth [8].

In two recent papers by our group [9,10] we showed that molecular dynamics simulations with an all-atom force field (MMFFX94 [11]) produced trajectories whose ensemble of molecular configurations yielded model curves (structure functions and radial distribution functions) that reproduced correctly the data obtained with our EDXD (Energy Dispersive X-ray

Diffraction) experiments for pyrrole, furan and thiophene, three etheroaromatic analogues of benzene. The models were built by replicating the molecule structure in three dimensions (up to a distance of the order of the highest peak in the experimental RDF), by energy minimizing such “pseudo-crystal” (thus making it more disordered, or “liquid-like”) and then by thermalizing the system with molecular dynamics at room temperature for 1 ns. Among all the force fields tested, MMFF94X [11] proved to be a suitable choice for those etheroaromatic systems.

In the present work, we turned to three aliphatic molecular liquids, cyclohexane (C₆H₁₂), piperidine (C₅H₁₁N) and morpholine (C₄H₁₀ON). In piperidine and morpholine, one and two CH₂ groups of the cycloalkane ring are substituted by one NH and one NH and one O, respectively. The three compounds show an upward trend in boiling points and densities (see next paragraph). This observation makes the three compounds an interesting benchmark for X-ray analysis from an experimental point of view, too. Thus, the aim of this work is twofold:

- Verifying if the simple theoretical model (as it uses a generic all-atom force field taken from the literature without further modifications) can easily be extended to other liquids (non-aromatic);

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- Assessing if our experimental technique can readily account for the observed trend in the physical properties.

Apart from a purely academic significance, the three molecules are interesting from an industrial viewpoint, as well. Cyclohexane is one of the most widely used solvents in chemistry, as well as one of the most important scaffolds for organic reactions, owing to its renowned conformational isomerism properties. The basicity/reactivity of piperidine (and morpholine) nitrogen, in turn, makes them an important structural motif shared by many pharmacophores [12].

Among the three systems, cyclohexane is the one most papers in the literature dealt with. The molecule was studied with electron diffraction in the gas phase by Ewbank et al. [13] and in liquid phase in a few works, both in the deuterated form (C_6D_{12}) with neutron diffraction [14] and in the natural form (C_6H_{12}) with traditional X-ray diffraction (ADXRD, Angular Dispersive), using $Cu_{K\alpha}$ radiation with maximum $q \approx 7 \text{ \AA}^{-1}$ (see next)[15]. In both studies, a significant degree of local order was pointed out; the intermolecular pair correlation functions derived from neutron diffraction measurements show spatial features up to 25 Å. Some measurements on mixtures with benzene [16] or other alkanes [17], and of solutions of alcohols (n-butanol-1 [18] and 2-methyl-2-propanol [19]) were reported. Among theoretical works, we cite a molecular dynamics study [20], a charge distribution force field study [21] and an ab initio investigation[22]. As for piperidine and morpholine, not many structural papers exist in the literature. A recent (2004) crystallographic study by A. Parkin et al. [23] should be cited. Noteworthy is the molecules capability of inducing mesophases in liquid crystals [24]. Piperidine was the subject of several theoretical calculations, too. [25,26].

The liquids were studied at room temperature ($\approx 25^\circ\text{C}$).

2. Experimental

2.1. Material

Liquid cyclohexane (b.p. 80.7°C , density 0.779g/cm^3), piperidine (b.p. 106°C , density 0.862g/cm^3) and morpholine (b.p. 129°C , density 0.996g/cm^3) were purchased from Aldrich.

2.2. X-ray diffraction: data treatment

We performed our experiments using the non-commercial energy-scanning diffractometer built in the Department of Chemistry, Rome University. Detailed description of both instrument and technique can be found elsewhere [27–30]. The experimental protocol (instrument geometry and scattering angles) of the data acquisition phase is analogous to that used for pyrrole [9]. The appropriate measuring time (i. e. number of counts) was chosen so as to obtain scattering variable (q) spectra with high signal to noise ratio (500,000 counts on average). The expression for q is:

$$q = \frac{4\pi \sin \theta}{\lambda} = E \cdot 1.014 \sin \theta \quad (1)$$

when E is expressed in keV and q in Å^{-1} . The various angular data were processed according to the procedure described in the literature [31–33] and in a few papers from our group [27,29,30], and normalized to a stoichiometric unit of volume containing one molecule. From the measured density values (see above), we obtain the following concentration values: 9.27mol/L (cyclohexane), 10.01mol/L (piperidine) and 12.29mol/L (morpholine). The corresponding molecular volumes (in cubic Ångstroms) are 179.40, 164.10 and 144.81, respectively. Merging of all angular data yielded the total “(static) structure function”, $I(q)$, which is equal to:

$$I(q) = I_{e.u.} - \sum_{i=1}^n x_i f_i^2 \quad (2)$$

where f_i are the atomic scattering factors, x_i are the number concentrations of i -type atoms in the stoichiometric unit and $I_{e.u.}$ is the observed intensity in electron units. Fourier transformation of $I(q)$ led to radial distribution functions (RDF)

$$D(r) = 4\pi r^2 \rho_0 + \frac{2r}{\pi} \int_0^{q_{\max}} q I(q) M(q) \sin(rq) dq \quad (3)$$

In this equation, ρ_0 is the bulk number density of stoichiometric units and

$$M(q) = \frac{f_C^2(0)}{f_C^2(q)} \exp(-0.01q^2) \quad (4)$$

is the sharpening factor (i.e. carbon was used as the “sharpening atom”). We used the value of 17 \AA^{-1} as the upper limit of integration.

3. Results and discussion

3.1. X-ray diffraction: Structure functions and RDF

Experimental structure functions and radial distribution functions (in the form $\text{Diff}(r) = D(r) - 4\pi r^2 \rho_0$) for liquid cyclohexane, piperidine and morpholine are reported in Fig. 1, top and Fig. 1, bottom, respectively (notice that piperidine and morpholine curves are down-shifted of 800 units (structure function) and 2 units ($\text{Diff}(r)$) to accommodate all data in a single plot). As it can be seen, all three liquids are moderately “ordered” at 25°C ; in fact, all the structure functions (Fig. 1, top) show four well-defined peaks besides the “molecular” peak at high values of the scattering variable q , namely

- (1) A sharp peak (principal peak) whose maximum falls at 1.24 \AA^{-1} in cyclohexane, 1.28 \AA^{-1} in piperidine and 1.32 \AA^{-1} in morpholine. The most important contributions to this peak are long range interactions (periodic in crystals);
- (2) A peak between 4 and 7 \AA^{-1} (centered at about 5.5), followed by a broader one in the range $7.5\text{--}11 \text{ \AA}^{-1}$, usually attributed to mid-range interactions;
- (3) A small (but always noticeable) peak at 3 \AA^{-1} for cyclohexane and piperidine; this peak is absent in morpholine function.

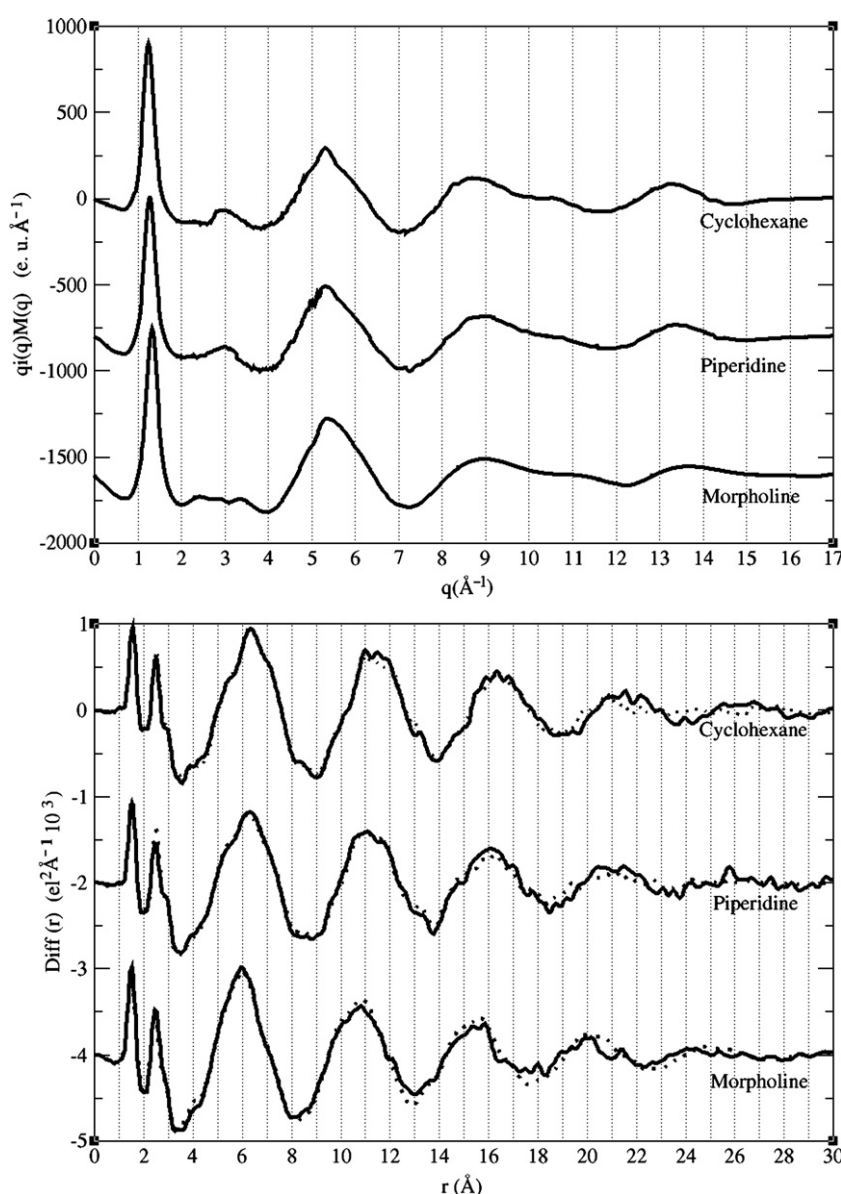


Fig. 1. Experimental structure functions (top) and radial distribution functions — in “Diff” form (bottom). Continuous: experimental; dotted: model.

From the analysis of the structure function peaks (Fig. 1 — top), some qualitative information can be inferred, namely:

- (1) All the three liquids share similar intramolecular interactions, since the functions are almost superimposable in the range $4\text{--}17 \text{\AA}^{-1}$;
- (2) Intermolecular interactions tend to occur at smaller distances when passing from cyclohexane to morpholine (the principal peak position is consequently shifted at higher q);
- (3) Piperidine shows a structure lying between those of cyclohexane and morpholine, although a little bit more similar to the former.

The increase in intermolecular interactions agrees with the upward trend in the physical properties (boiling points and

densities) observed for the three molecules, and is confirmed by the inspection of radial distribution curves (i.e. when passing from “reciprocal” to “direct” space), which are reported in Fig. 1 — bottom:

- (1) The first two peaks (intramolecular contacts) are sharp and fall at the same distances, approximately;
- (2) In the higher order peaks region (peaks 3–7 of RDF), corresponding to intermolecular interactions, the presence of etheroatoms gives origin to shorter distances than in the unsubstituted case (cyclohexane).
- (3) The effect propagates in an almost geometric fashion, so that the absolute difference of the peak positions (in the greatest difference case, cyclohexane–morpholine) passes from 0.3 (first intermolecular peak, around 6\AA) to 2 in the fourth peak (around 20\AA) (see Fig. 1 and Table 1 below).

Table 1
Intermolecular peak positions of experimental RDF (Å)

Cyclohexane	Piperidine	Morpholine
6.25	6.10	5.95
11.50	11.00	10.75
16.30	16.05	15.60
21.50	21.00	19.50

The shorter contacts found in the substituted compounds could be due to the formation of hydrogen bonds N–H---N between molecules, as postulated several years ago by Lutskii et al. in a study dealing with ultrasound speed in complex liquids [34] and more recently found by A. Parkin et al. [23] in the crystal phase; supplemental short range interactions involving morpholine oxygen atom O should be invoked to account for the difference between piperidine and morpholine.

Our experimental data for cyclohexane (both real and reciprocal-space) are in good agreement with the already cited neutron diffraction studies [14]. Peak positions are almost the same, the shifts being likely attributable to intrinsic differences between the two techniques.

3.2. Models

The first family of models used to interpret experimental data was built according to the protocol introduced in [9,10] that can be summarized as follows:

At first, the three molecules were drawn and “cleaned” (i.e. common structural parameters were assigned) using the graphical builder of the software MOE [35]. The structures were then replicated in three dimensions, using the routine “solvatebox” of leap (AMBER)[36]. A molecule (the “solute”) was placed in the center of a rectangular box of identical copies (the “solvent”). The box dimensions, and hence the number of molecules in the aggregate, were in the same range of the

longest distances found in the experimental radial distribution curves (see Fig. 1, bottom); a “pseudo-crystal” of 32 molecules was deemed appropriate for the system, the furthest peaks in RDF falling between 23 and 25 Å. (“crystal” models, Fig. 2).

The aggregates were then processed with the energetic modules of MOE [35]. The force field MMFF94X (with atom types and point charges), that gave good results in the previous studies [9,10], was used to model morpholine and piperidine; unfortunately, the same force field is not suitable for cyclohexane, since several parameters are missing. Therefore, the force field PEF95SAC [37], a force field developed for hydrocarbons and sugars (of which cyclohexane is the basic structural motif), was employed. A molecular mechanics minimization (standard “conjugate gradient” protocol up to a gradient of 0.05kCal/Å) was subsequently run. (“min” models). Then, the systems were simulated with classical Molecular Dynamics (MD). A trajectory of 1100ps (100ps heating + 1000ps production) in NVT ensemble was produced, with coordinates dumping every picosecond (1100 frames in total). No periodic boundary conditions were applied, and SHAKE algorithm [38] was used to increase timestep duration. For every model, the Debye structure functions for pairs of interactions was calculated:

$$i_{mn}(q) = \sum f_m f_n \frac{\sin(r_{mn}q)}{r_{mn}q} \exp\left(-\frac{1}{2}\sigma_{mn}^2 q^2\right). \quad (5)$$

The same sharpening factor, the same q_{max} value and the same normalization method as for experimental data were used. σ_{mn} factors are normally added to the calculation to account for thermal fluctuations in the interatomic distance which result in peak broadening. The same σ values are generally attributed to distances falling within predefined ranges (see, for instance, [27]). Since we used molecular dynamics (which simulates the evolution of the system at a given temperature, and incorporates such effect) to build our models, all σ_{mn} values were put equal

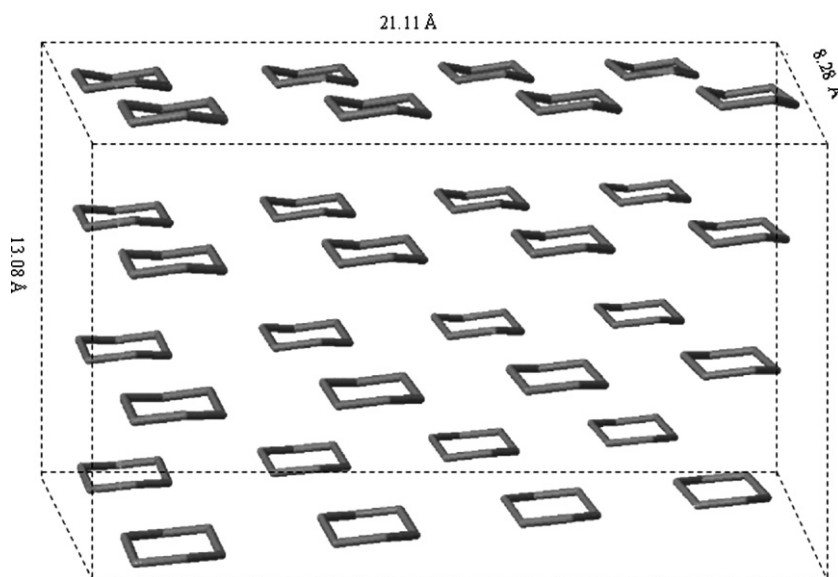


Fig. 2. Cyclohexane “crystal” model.

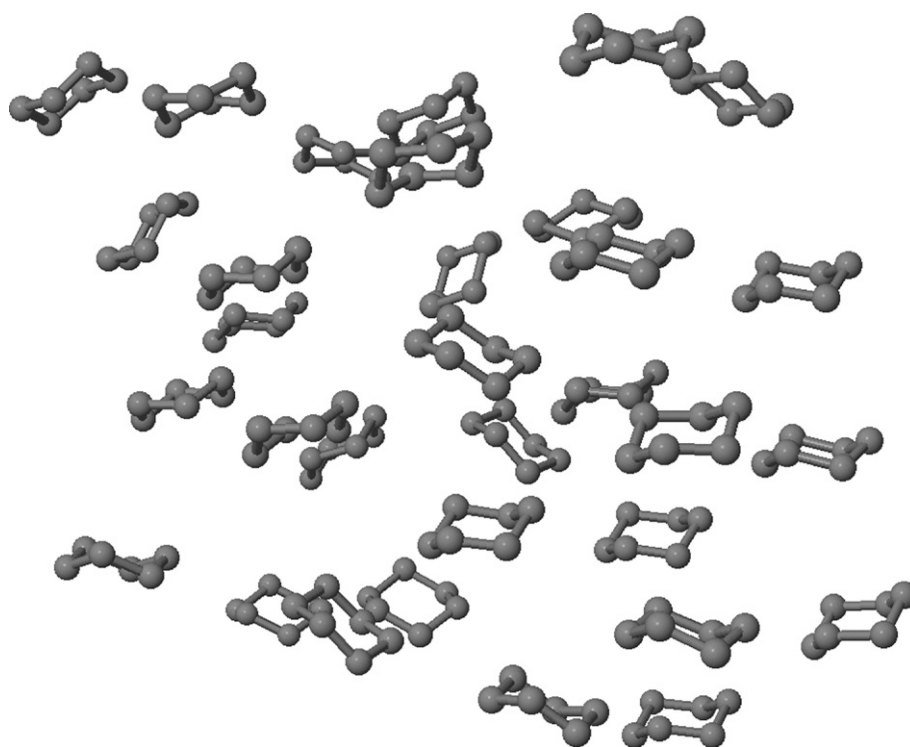


Fig. 3. Final frame (#1000) of cyclohexane MD trajectory.

to zero. Null sigma were used for all models (even ‘static’ ones), to generate an homogeneous set of data. All the 1100MD model functions were averaged, thus obtaining a single *ensemble* structure function. In Fig. 3, the last configuration of cyclohexane MD trajectory (#1000) is shown as an example of these “dyn” models.

The curve was extrapolated to zero below 0.9\AA^{-1} using experimental data, and then Fourier Transformed into the model radial distribution function (“Theoretical Peaks”). The agreement between model and experimental data obtained was fair, but less than that obtained with the liquids studied before (unsaturated). MMFF94X force field, that gave very good results, is probably not able to account for the increased conformational mobility of the molecules. Therefore, we decided to refine all the nine models by fitting their structure functions to experimental ones. For this analysis, an in-house software purposely written was used. The program moves the

particles attempting to minimize the difference between model and experimental functions. Two cycles of twenty iterations each were performed for every molecule. Deviation of model curves from experimental $q_i(q)M(q)$ is expressed with crystallographic residual factor[39,40] (R-factor).

$$R = \frac{\sum_q I(q)_{\text{exp}} - I(q)_{\text{model}}}{\sum_q I(q)_{\text{exp}}} \quad (6)$$

R values for the models, before and after fitting, are reported in the table below (Table 2).

The q range used for the computation is $0.9\text{--}17\text{\AA}^{-1}$, the former being the q value where extrapolation of model data (to model the “continuum”) was carried out, approximately. As it can be seen, the crystal models give unacceptable results, even after fitting; a certain degree of “thermal disorder” is needed to reproduce experimental data. The best agreement is found for cyclohexane after MD and fitting ($R \approx 8\%$). The fitting procedure can overcome force field limitations, but the physical correctness is lost for the sake of error reduction. The RDF of the best models for the three compounds (dyn + fitting) are reported in Fig. 1, bottom, where they are juxtaposed to experimental curves.

4. Conclusion

In this work, we report an EDXD (Energy Dispersive X-Ray Diffraction) study of three molecular liquids, cyclohexane, piperidine and morpholine. No liquid-phase experimental studies of the latter two have been reported, so far. Analysis of the structure and radial distribution functions shows that the

Table 2
R-factor values (%) of non-fitted and fitted models

Cyclohexane		
Crystal	29.36	22.71
Min	20.19	10.71
Dyn	13.97	8.02
Piperidine		
Crystal	38.28	30.08
Min	22.63	12.11
Dyn	24.06	14.17
Morpholine		
Crystal	49.18	41.14
Min	28.59	16.58
Dyn	27.27	16.03

intermolecular interactions occur at shorter distances, in the order morpholine < piperidine < cyclohexane. If the reverse order is assumed for the interaction strength (shorter distance = stronger interaction), the trend agrees with that observed in boiling points and densities. The experimental results are supplemented with models derived from molecular dynamics simulation employing the all-atom force field PEF95SAC (cyclohexane) and MFF94X (piperidine and morpholine). The theoretical curves obtained are only partially satisfactory; this fact may be due to the limitations of MMFF94X/PEF95SAC force fields in dealing with conformational flexibility of such systems. When the models are refined allowing the molecules to drift through least-square fitting to experimental data, very good agreements are obtained.

To recover the loss of physical correctness brought by mathematical fitting, new force fields and structure function-restrained molecular dynamics protocols are under development in our group.

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