LETTER

Combined ab initio and classical molecular dynamics simulations of alkyl-lithium aggregates in ethereal solutions

**Hassan K. Khartabil · Marilia T. C. Martins-Costa ·
Philippe C. Gros · Yves Fort · Manuel F. Ruiz-López**

Abstract Molecular dynamics simulations of organolithium aggregates in solution are reported for the first time. We use a combined quantum/classical force field (the so-called QM/MM approach) and study ethyl-lithium aggregates in dimethyl ether (DME) solvent. The solutes are described at the Density Functional Theory level while solvent molecules are described using molecular mechanics. NVT Molecular Dynamics simulations at 200 K are carried out in the Born–Oppenheimer approximation. After equilibration, the production phase was run for 80 ps (monomer), 40 ps (dimer) and 26 ps (tetramer). The analysis of the results focuses on Li coordination as a function of aggregate size and we show that the total Li coordination number is always 4. No decoordination has been observed along the simulations. Fluctuations of the structures are predicted to be large in some cases and possible implications on reactivity are discussed.

Keywords Organolithium compounds · QM/MM ·
Molecular dynamics simulations · Solvent effects

H. K. Khartabil · M. T. C. Martins-Costa · M. F. Ruiz-López (✉)
Equipe de Chimie et Biochimie Théoriques,
SRSMC, Nancy-University, CNRS, Boulevard des Aiguillettes,
BP 239, 54506 Vandoeuvre-lès-Nancy, France
e-mail: Manuel.Ruiz@cbt.uhp-nancy.fr

H. K. Khartabil
e-mail: Hassan.Khartabil@cbt.uhp-nancy.fr

M. T. C. Martins-Costa
e-mail: Marilia.Martins-Costa@cbt.uhp-nancy.fr

P. C. Gros · Y. Fort
Equipe de Synthèse Organométallique et Réactivité,
SRSMC, Nancy-University, CNRS, Boulevard des Aiguillettes,
BP 239, 54506 Vandoeuvre-lès-Nancy, France
e-mail: philippe.gros@sor.uhp-nancy.fr

Y. Fort
e-mail: Yves.Fort@sor.uhp-nancy.fr

1 Introduction

Organolithium compounds are widely employed in synthetic organic chemistry [1–4]. They exhibit a marked trend to aggregate making the elucidation of their reaction mechanisms difficult, both from the experimental and the theoretical points of view. Moreover, large solvent effects on aggregation have been observed. For instance, nBuLi is known to exist as hexamers in hexane solution [5,6], whereas in THF solution, tetramers and dimers are present [7]. In general, the experimental analysis of aggregate concentrations is extremely difficult due to the complexity of the NMR signals. As a consequence, the choice of the system and the optimal conditions to carry out new experiments are complex and remain often based on accumulated empirical information and trial-and-error approaches. Theoretical chemistry can provide valuable assistance and not surprisingly a large number of papers have been published on different systems and reactions (see for instance [8–10]). Some of these works have been devoted to the analysis of solvation effects in coordinating solvents using quantum chemical methods and microsolvation models, i.e. carrying out electronic energy calculations for a system that consists of the aggregate plus a few solvent molecules in the first solvation shell. It has been shown in this way that aggregation in ethereal solutions is strongly influenced by solvent coordination and that the coordination degree, i.e. the number of solvent molecules bonded to the aggregate plays a crucial role. On one hand, it is responsible for the largest part of the total solute–solvent interaction energy. On the other hand, it largely contributes to the overall entropy balance in speciation equilibria.

A precise determination of this number is therefore fundamental in order to estimate the concentration of aggregates. It depends on several factors such as the chemical

nature of the organolithium compound, steric interactions, temperature, etc. Standard quantum chemical methods are well-adapted to obtain equilibrium geometries and total energies but thermal contributions to free energy cannot be obtained with high accuracy. For instance, entropy computations using the harmonic frequencies of vibration for a single energy minimum is clearly inappropriate for flexible systems. Molecular Dynamics (MD) is a suitable tool in this respect but due probably to technical difficulties, no simulation of organolithium compounds in solution has been reported to date. Classical MD approaches are impractical because of the lack of appropriate force-fields to describe Li–X bonds (though some efforts have been done [11]). Ab initio molecular dynamics could be envisaged but unfortunately the high computational cost of this technique limits its application to simple systems and short simulation times (typically a few picoseconds). Thus, Car–Parrinello simulations have been reported for simple gas-phase aggregates [12] or simple organolithium compounds [13,14]. A quite interesting work has recently been reported on CH_3Li interacting with three dimethylether molecules [15] though the dynamics of such complexes in gas phase is not necessarily representative of the dynamics in the condensed phase.

In the present work, we report the first MD simulations for organolithium compounds in solution. We study the properties of ethyl-lithium aggregates $(EtLi)_n$ ($n = 1, 2, 4$) in dimethylether (DME) using a combined ab initio—classical MD simulation approach. DME has often been employed in theoretical studies as a suitable model for common ethereal solvents used in experimental work such as diethylether or THF.

2 Calculation method

Molecular dynamics simulations have been carried out using the so-called combined QM/MM (quantum mechanics/molecular mechanics) approach. The ethyl-lithium aggregates (the solutes) are described using Density Functional Theory (DFT) at the B3LYP/6-31G(d) level. We checked that the addition of diffuse functions on heavy atoms has a limited effect on the results (below 5% for aggregation energies, for instance). Solvent molecules are described through molecular mechanics (MM) using the OPLS force-field [16]. The solute–solvent QM/MM interactions involve electrostatic and non-electrostatic terms. The former are computed by introducing the MM charges (OPLS force-field) into the QM electronic Hamiltonian so that polarization effects are treated rigorously. Non-electrostatic terms are accounted for by using a Lennard–Jones potential. At each step of the simulation, a full SCF calculation is carried out for the QM subsystem in presence of the electric field created by the MM subsystem, and forces on QM and MM atoms are computed analytically.

Details on this combined DFT/MM force-field and its use in statistical simulations have been described before [17–21]. In this work, we have carry out MD simulations in the NVT ensemble at 200 K using a previously developed program interface [22,23] of Gaussian 03 [24] and Tinker [25]. We assume infinite dilution and a density for the solvent of 0.735 g/L [16]. We use a simulation box of 37.4 Å side length containing 500 solvent molecules plus one solute molecule (the $(EtLi)_n$ aggregate) and we apply periodic boundary conditions with a cutoff of 18.7 Å. Lennard–Jones parameters for the QM system (except for the Li atom) come from the OPLS force field [16]. Parameters for Li are taken from reference [26]. Note that van der Waals parameters for atoms in the QM subsystem, i.e. $(EtLi)_n$ aggregates, are only used to evaluate the non-electrostatic interaction with solvent DME molecules.

The suitability of the QM/MM force-field has been tested by comparison with full QM calculations for the (EtLi) (DME) complex in gas phase. The structure of the system is fully optimized at the QM level. In QM/MM calculations, the geometry of DME is assumed to be rigid. The optimized Li$\cdots$O distance amounts 1.846 Å at the DFT/MM level and is close to the value 1.909 Å obtained at the QM level. The difference is comparable to those obtained in other applications of the QM/MM approach [17–21]. The intramolecular LiC distances are very close: 2.014 and 2.018 Å at the DFT/MM and QM levels, respectively. The comparison of interaction energies is carried out using energies of monomers at their complex geometry, to account for the fact that geometry relaxation of DME is not considered in QM/MM calculations. The computed interaction energies are in perfect agreement and amount −18.2 kcal/mol in both methods (QM energy has been corrected for basis set superposition error). Further comparison between QM and QM/MM calculations is presented below for microsolvated aggregates.

The simulations have been done using an integration step of 0.5 fs. After minimization, the systems were equilibrated through classical MD simulations (aggregate geometry fixed) for at least 100 ps followed by at least 10 ps of DFT/MM MD simulation. Afterwards, the production phase was run for 80 ps (monomer), 40 ps (dimer) and 26 ps (tetramer). Note that some theoretical studies have already been reported for ethyl-lithium aggregates in gas phase [27] and microsolvated environments [28].

3 Results and discussion

In order to get a quick overview of the aggregate structures in solution, we have drawn in Fig. 1 an aligned superposition of equidistant 500 snapshots along the MD simulation. For simplicity in the figure, only the aggregate and solvent molecules in the first solvation shell are drawn. One notices two

Fig. 1 Position of non-hydrogen atoms (for the aggregate and first solvation shell DME molecules) using 500 snapshots along the simulation. One arbitrary structure is designed in *ball* and *stick* style for clarity
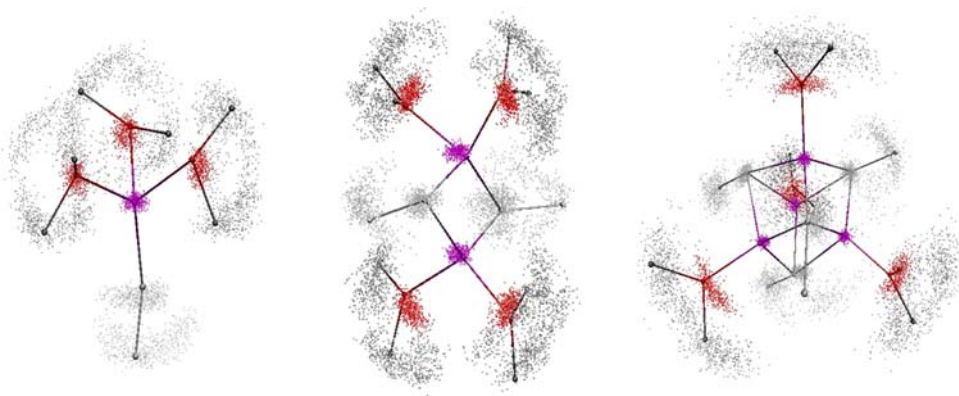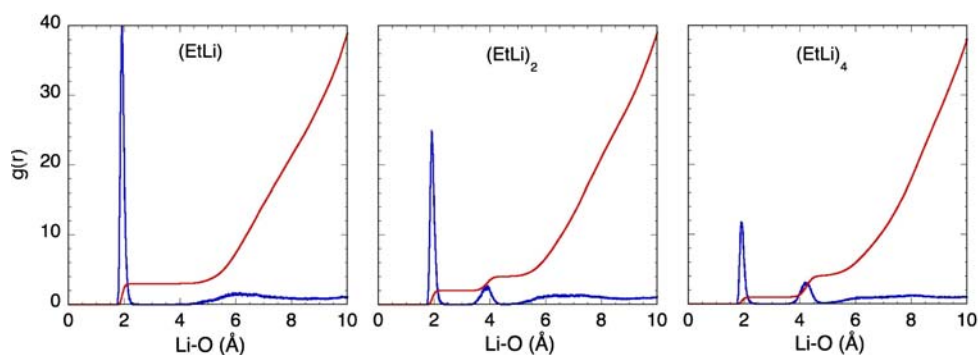

Fig. 2 Li–O radial distribution functions (*blue*) for EtLi aggregates in DME solution and integrated coordination numbers (*red*)

major facts that will be commented and analyzed in more detail below: (1) the dimer and the tetramer adopt cyclic and cubic structures, respectively, and (2) the Li atom is tightly coordinated to solvent molecules so that it always exhibits 4-coordination.

Let us first discuss the interaction of the aggregates with solvent molecules. The Li–O solute–solvent radial distribution functions (RDF) are shown in Fig. 2. Values for the position of RDF maxima and integrated coordination numbers are summarized in Table 1, which also includes Li–O optimized distances in microsolvated systems $(EtLi) \cdot (DME)_3$, $(EtLi)_2 \cdot (DME)_4$ and $(EtLi)_4 \cdot (DME)_4$, for comparison. The RDFs all exhibit a well-defined, very intense peak around 2 Å that corresponds to the interactions of Li atoms with O atoms of DME molecules in the first solvation shell. The integrated number of DME molecules per lithium atom in this shell confirms the values suggested by Fig. 1, i.e. three, two and one for

the monomer, dimer and tetramer, respectively. The height and thickness of the peaks are quite remarkable and reveal strong Li–O interactions in all systems. In fact, DFT/MM calculations in microsolvated systems lead to aggregate—DME interaction energies of -34.7, -37.3, and -31.5 kcal/mol for the monomer, dimer and tetramer, respectively (the values for the dimer and tetramer are consistent with the analysis made by McCarrity and Ogle for nBuLi [7]). The dimer and tetramer RDF curves exhibit another well-defined, though less intense, peak at slightly below and beyond 4 Å, respectively. The analysis of the simulations shows that they correspond to distances of non-bonded Li–O atoms (for symmetry reasons, only one peak of this type is found). The presence of these peaks represents another evidence of the remarkable stability of the first solvation shell. It is worth mentioning that no Li–O dissociation has been observed in our simulations (see details on Li–O bond length fluctuations below).

Table 1 Position of peak maxima in the radial distribution functions shown in Fig. 2 and integrated number of solvent molecules per Li atom

	1st peak		2nd peak	
	Maximum (Å)	N	Maximum (Å)	N
EtLi	1.915 (1.901, *2.052*)	3.00		
$(EtLi)_2$	1.915 (1.899, *2.067*)	2.00	~3.93	~4.01
$(EtLi)_4$	1.915 (1.899, *2.028*)	1.00	~4.18	~4.02

For comparison, the optimized Li–O bond lengths in microsolvated systems $(EtLi) \cdot (DME)_3$, $(EtLi)_2 \cdot (DME)_4$ and $(EtLi)_4 \cdot (DME)_4$ are given in parenthesis at QM/MM (plain characters) and QM levels (italics)

Table 2 Optimized Li–C distances (in Å) for gas phase and micosolvated (EtLi)$_n$ aggregates vs. average values in DME solution

	Gas phase	Microsolvated		Solution		
		DFT	DFT/MM	Average	Max/Min	SD
EtLi	2.006	2.085	2.101	2.109	2.39/1.90	0.064
(EtLi)$_2$	2.130	2.215	2.201	2.236	2.75/1.90	0.097
(EtLi)$_4$	2.208	2.267	2.254	2.301	3.39/1.91	0.142

Fig. 3 Variation of all Li–C and Li–O bond lengths along the first 25 ps of the DFT/MM MD simulation of (EtLi)$_n$ aggregates in DME solution
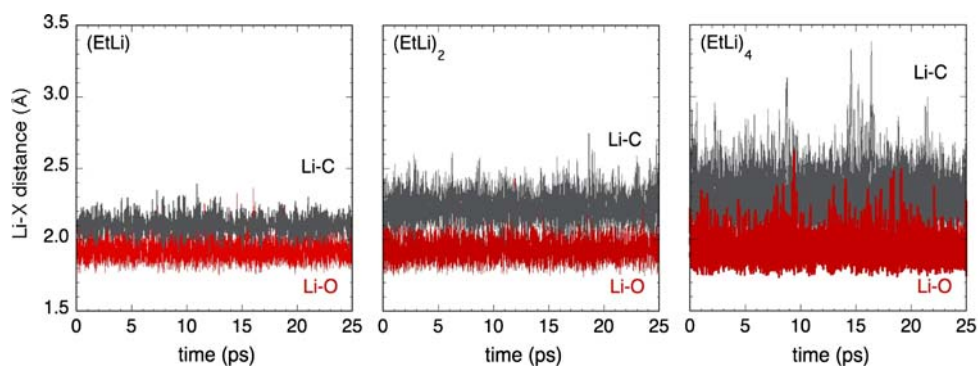
In particular, for the monomer, three DME solvent molecules remain attached to the Li atom along the 80 ps simulation. This contrasts with Car–Parrinello simulations in gas phase for the CH$_3$Li·(DME)$_3$ complex at 300 K in which decoordination of one DME molecule is observed within 4 ps of simulation [15]. In order to check whether formation of aggregates with a lower number of coordinating solvent molecules is plausible or not in solution, we carried out further simulations starting from di-coordinated monomer or dimer. Fast formation (within ∼1 ps) of the trisolvated monomer and tetrasolvated dimer was systematically obtained.

Since the Car–Parrinello simulations in gas phase were carried out at 300 K and our simulations in solution at 200 K, differences in coordination number between the two studies might be due to temperature effects, which are expected to play a noticeable role on this property. For instance, it has been shown [28] that the standard free energy for the association of a third solvent molecule with ethyl-lithium in THF solution is negative at 200 K (−2.8 kcal/mol) and very slightly positive (+0.6 kcal/mol) at 300 K, due to the −$T\Delta S$ term. To further analyze the effect of temperature in our case, we have carried out a QM/MM simulation for the monomer at 300 K (note that these simulation conditions are somewhat artificial as the boiling point of DME at 1 atm is about 250 K). A DME molecule exchange is now observed at about 50 ps of simulation and the coordination number, given by the integrated Li–O RDF, decreases a little (from 3.00 at 200 K to 2.89 at 300 K). However, the system remains mostly tri-coordinated all along the computed trajectory suggesting that differences with respect to Car–

Parrinello dynamics in gas phase can probably be ascribed to medium effects (note incidentally that equilibration in gas phase is necessarily problematic due to the marked trend of the complex to dissociate).

We now focus on solvent effects on the internal structure of the aggregates. Li–C distances for gas phase aggregates, microsolvated systems (EtLi)·(DME)$_3$, (EtLi)$_2$·(DME)$_4$ and (EtLi)$_4$·(DME)$_4$ and aggregates in DME solution (average values in DFT/MM MD simulations) are summarized in Table 2. For comparison, microsolvated system results include both full DFT and DFT/MM calculations. As reported before [12], we found that Li–C distances are sensitive to total Li coordination. On one hand, Li–C distances increase with aggregate size in gas phase (increasing Li–C coordination). On the other hand, Li–C distances also increase when the aggregates coordinate to DME molecules (Li–O coordination), as shown by comparing gas phase results with either microsolvated structure distances of with MD average values in solution. We notice, not surprisingly, that coordination effects due to aggregation are larger than those arising from solvation. Thus, in the solvated aggregates (and similarly for the microsolvated ones), Li–C distances increase from the monomer to the dimer and the tetramer, in spite of the fact that Li atoms exhibit the same total coordination number ($N = 4$) in that case.

Another interesting point is the large range of variation of Li–C bonds in the MD simulations, especially in the tetramer. Actually, in the latter case, the maximum distance along the simulation is as large as 3.39 Å meaning that some structures cannot formally be described by a cubic aggregate (at least one Li–C bond has been broken). The lifetime
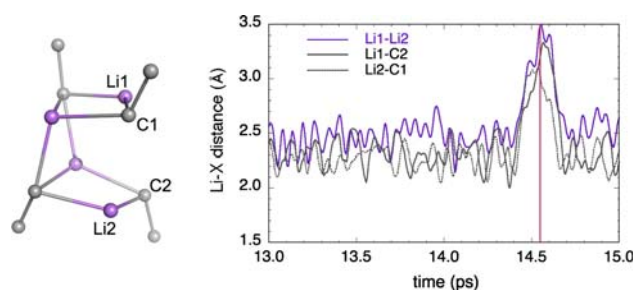
Fig. 4 Variation of selected Li–C and Li–Li bond lengths in the range 13–15 ps for the DFT/MM MD simulation of the (EtLi)$_4$ aggregate in DME solution. The vertical line (in *red*) indicates the time at which the opened structure in the *left* part of the figure has been formed

of these "open" structures is an important question because of their possible participation in the measured spectroscopic properties, especially NMR, or their involvement in reaction mechanisms. To investigate this point further we report in Fig. 3 the variation of Li–C bond lengths in the simulations. Fluctuations of the Li–O bond are also reported in this figure. To simplify the comparison, we have chosen to show an equivalent simulation time for the three systems (25 ps).

As shown, the increase of the Li–C bond lengths from the monomer to the dimer and the tetramer is accompanied by an enlargement of the amplitude of their fluctuations. The latter effect is also observed for the Li–O bonds though the average distance in this case does not change much with aggregate (in consistency with the results shown above for the first maxima of RDF curves). The figure for the tetramer highlights the presence, at more or less regular intervals, of some very large Li–C fluctuations. Figure 4 zooms on variations in the 13–15 ps region for two specific Li–C bonds (those being broken) and for the associated Li–Li distance.

At about 14.4 ps, the two Li–C distances (and the Li–Li one as well) begin to increase reaching a maximum at about 14.5–14.6 ps. They then decrease to attain their average value at approximately 14.7 ps. The whole process may be represented by a fast opening/closing of the cubic tetrameric configuration going through a structure of the type presented in Fig. 4. The movement takes around 0.3 ps and therefore the opened structure cannot be considered as a stable conformation nor it can be expected to be directly observed in conventional experiments. Nonetheless, strictly speaking, its formation is not a rare event. From the simulations here we estimate that, at 200 K, the probability to observe a tetramer exhibiting at least one Li–C bondlength greater than 2.9 Å is 3.6% (1.5% if one considers 3 Å). On average, structures of this type have been observed each 3–4 ps in our simulation.

In summary, these simulations provide definite conclusions concerning the coordination number of lithium atoms in simple alkyllithium systems in ethereal solvents at 200 K. They confirm that the coordination number of the Li atom is always 4 and that the coordinated solvent molecules display

a substantial lifetime. Indeed, no decoordination has been observed at the level of our simulation times (as large as 80 ps for the monomer). The tetramer, which is expected to be the major species in ethereal solvents [29], has been described as a cubic structure that presents large fluctuations of Li–C distances and may lead to short-lived open configurations. The role that open conformations may have on aggregate reactivity is potentially important and will deserve further investigation.

References

1. Clayden J (2002) Organolithiums: selectivity for synthesis. Pergamon, Oxford
2. Gros P, Fort Y (2002) nBuLi/lithium aminoalkoxide aggregates: new and promising lithiating agents for pyridine derivatives. Eur J Org Chem: 3375–3383
3. Hodgson DM (2003) Organolithiums in enantioselective synthesis. Springer, New York
4. Chinchilla R, Nájera C, Yus M (2005) Functionalized organolithium compounds in total synthesis. Tetrahedron 61:3139–3176
5. Margerison D, Newport JP (1963) Degree of association of *n*-butyl lithium in hydrocarbon media. Trans Faraday Soc 59:2058–2063
6. Lewis HL, Brown TL (1970) Association of alkyllithium compounds in hydrocarbon media. Alkyllithium-base interactions. J Am Chem Soc 92:4664–4670
7. McCarrity JF, Ogle CA (1985) High-field H NMR study of the aggregation and complexation of *n*-butyllithium in tetrahydrofuran. J Am Chem Soc 107:1805–1810. doi:10.1021/ja00293a001
8. Schleyer PvR (1984) Remarkable structures of lithium compounds. Pure Appl Chem 56:151–162
9. Jemmis ED, Gopakumar G (2004) Theoretical studies in organolithium chemistry. Wiley, New York
10. Streitwieser A (2006) Ion pair aggregates and reactions: experiment and theory. J Mol Model 12:673–680. doi:10.1007/s00894-005-0045-3
11. Yoshida T, Sakakibara K, Asami M et al (2003) Molecular mechanics (MM3) calculations on lithium amide compounds. J Comput Chem 24:319–327. doi:10.1002/jcc.10161
12. Gérard H, De la Lande A, Maddaluno J et al (2006) Revisiting the Structure of (LiCH3)$_n$ Aggregates using Car–Parrinello molecular dynamics. J Phys Chem A 110:4787–4794. doi:10.1021/jp056326h
13. Röethlisberger U, Klein ML (1995) Ab initio molecular dynamics investigation of singlet $C_2H_2Li_2$: determination of the ground state structure and observation of LiH intermediates. J Am Chem Soc 117:42–48
14. Röthlisberger U, Sprik M, Klein ML (1998) Living polymers Abinitio molecular dynamics study of the initiation step in the polymerization of isoprene induced by ethyl lithium. J Chem Soc, Faraday Trans 94:501–508. doi:10.1039/a707860i
15. De la Lande A, Fressigné C, Gérard H, et al (2007) First-principles molecular dynamics evaluation of thermal effects on the NMR $^1J_{Li,C}$ spin–spin coupling. Chem Eur J 13:3459–3469. doi:10.1002/chem.200601108
16. Jorgensen WL, Maxwell DS, Tirado-Rives J (1996) Development and testing of the opls all-atom force field on conformational energetics and properties of organic liquids. J Am Chem Soc 118:11225–11236. doi:10.1021/ja9621760

17. Tuñón I, Martins-Costa MTC, Millot C et al (1995) A hybrid density functional–classical molecular dynamics simulation of a water molecule in liquid water. J Mol Struct (Theochem) 1: 196–201

18. Tuñón I, Martins-Costa MTC, Millot C et al (1996) A coupled density functional-molecular mechanics Monte Carlo simulation method: the water molecule in liquid water. J Comput Chem 17:19–29

19. Tuñón I, Martins-Costa MTC, Millot C et al (1997) Molecular dynamics simulations of elementary chemical processes in liquid water using Density Functional and Molecular Mechanics potentials. I. Proton transfer in strongly H-bonded complexes. J Chem Phys 106:3633–3642

20. Strnad M, Martins-Costa MTC, Millot C et al (1997) Molecular dynamics simulations of elementary chemical processes in liquid water using Density Functional and Molecular Mechanics potentials. II. Charge separation processes. J Chem Phys 106:3643–3657

21. Chalmet S, Ruiz-López MF (1999) Molecular dynamics simulation of formamide in water using Density Functional theory and classical potentials. J Chem Phys 111:1117–1125

22. Martins-Costa MTC (2006) A Gaussian 03/Tinker 4.2 interface for hybrid QM/MM applications, University of Nancy I-CNRS

23. Martins-Costa MTC, Ruiz-López MF (2007) Molecular dynamics of hydrogen peroxide in liquid water using a combined quantum/classical force field. Chem Phys 332:341–347. doi:10.1016/j.chemphys.2006.12.018

24. Frisch MJ, Trucks GW, Schlegel HB et al (2004) Gaussian 03. Gaussian, Inc., Wallingford, CT

25. Ponder JW (2004) TINKER: software tools for molecular design. Washington University School of Medicine, Saint Louis, MO

26. Chandrasekhar J, Spellmeyer DC, Jorgensen WL (1984) Energy component analysis for dilute aqueous solutions of lithium(1+), sodium(1+), fluoride(1−), and chloride(1−) ions. J Am Chem Soc 106:903–910. doi:10.1021/ja00316a012

27. Verstraete P, Deffieux A, Fritsch A et al (2003) Theoretical study of a series of alkyllithium clusters. J Mol Struct Theochem 631:53–66. doi:10.1016/S0166-1280(03)00133-7

28. Pratt LM, Truhlar DG, Cramer CJ et al (2007) Aggregation of alkyllithiums in tetrahydrofuran. J Org Chem 72:2962–2966. doi:10.1021/jo062557o

29. Seitz LM, Brown TL (1966) Organometallic exchange reactions. I. Lithium-7 and proton nuclear magnetic resonance spectra of methyllithium and ethyllithium in ether. J Am Chem Soc 88:2174–2178. doi:10.1021/ja00962a019