

# An automated framework for high-throughput predictions of NMR chemical shifts within liquid solutions

**Rasha Atwi**

Stony Brook University

**Ying Chen**

Pacific Northwest National Laboratory

**Kee Sung Han**

Pacific Northwest National Laboratory

**Karl Mueller**

Pacific Northwest National Laboratory

**Vijayakumar Murugesan**

Pacific Northwest National Laboratory

**Nav Nidhi Rajput** (✉ [navnidhi.rajput@stonybrook.edu](mailto:navnidhi.rajput@stonybrook.edu))

Stony Brook University

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## Article

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1 **An automated framework for high-throughput predictions of**  
2 **NMR chemical shifts within liquid solutions**

3 Rasha Atwi<sup>1</sup>, Ying Chen<sup>2</sup>, Kee Sung Han<sup>2</sup>, Karl T. Mueller<sup>2</sup>, Vijaykumar Murugesan<sup>2</sup>, Nav  
4 Nidhi Rajput\*<sup>1</sup>

5 <sup>1</sup>Department of Materials Science and Chemical Engineering, Stony Brook University, Stony  
6 Brook, New York 11794, United States

7 <sup>2</sup>The Joint Center for Energy Storage Research (JCESR), Pacific Northwest National Laboratory,  
8 Richland, WA 99352, USA

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20 \* To whom correspondence should be addressed:

21 Nav Nidhi Rajput; Email: [navnidhi.rajput@stonybrook.edu](mailto:navnidhi.rajput@stonybrook.edu)

## 22 **ABSTRACT**

23 Identifying stable speciation in multicomponent liquid solutions is of fundamental importance to  
24 areas ranging from electrochemistry to organic chemistry and biomolecular systems. However,  
25 elucidating this complex solvation environment is a daunting task even when using advanced  
26 experimental and computational techniques. Here, we introduce a fully automated, high-  
27 throughput computational framework for the accurate and robust prediction of stable species  
28 present in liquid solutions by computing the nuclear magnetic resonance (NMR) chemical shifts  
29 of molecules. The framework automatically extracts and categorizes hundreds of thousands of  
30 atomic clusters from classical molecular dynamics (CMD) simulations to identify the most stable  
31 speciation in the solution and calculate their NMR chemical shifts via DFT calculations.  
32 Additionally, the framework creates an output database of computed chemical shifts for liquid  
33 solutions across a wide chemical and parameter space. This task can be infeasible experimentally  
34 and challenging using conventional computational methods. To demonstrate the capabilities of our  
35 framework, we compare our computational results to experimental measurements for a complex  
36 test case of magnesium bis(trifluoromethanesulfonyl)imide  $\text{Mg}(\text{TFSI})_2$  salt in dimethoxyethane  
37 (DME) solvent, which is a common electrolyte system for Mg-based batteries. Our extensive  
38 benchmarking and analysis of the  $\text{Mg}^{2+}$  solvation structural evolutions reveal critical factors such  
39 as the effect of force field parameters that influence the accuracy of NMR chemical shift  
40 predictions in liquid solutions. Furthermore, we show how the framework reduces the efforts of  
41 performing and managing over 300  $^{13}\text{C}$  and 600  $^1\text{H}$  DFT chemical shift predictions to a single  
42 submission procedure. By enabling more efficient and accurate high-throughput computations of  
43 NMR chemical shifts, our approach can accelerate theory-guided design of liquid solutions for  
44 various applications.

## 45 INTRODUCTION

46 Liquid solutions are critical components of various chemical, materials science, engineering,  
47 and biological applications such as batteries<sup>1-3</sup>, fuel<sup>4</sup>, food industry<sup>5</sup>, and drug discovery<sup>6,7</sup>.  
48 Optimizing the performance of these technologies requires taking into careful account transport  
49 and structural features, along with the thermodynamic stability of chemical compounds comprising  
50 the solution. More specifically, developing a fundamental understanding of the correlations  
51 between functional properties and the underlying atomistic interactions is necessary for advancing  
52 the rational design of liquid solutions. In this regard, nuclear magnetic resonance (NMR)  
53 spectroscopy stands out as a powerful and widespread technique for studying the 3D organization  
54 of matter and associated structural and dynamical properties<sup>8-10</sup>. Over the years, technological  
55 advances in NMR spectroscopy have significantly improved the operational ease and spectral  
56 resolutions obtainable from non-traditional nuclei (such as <sup>17</sup>O, <sup>25</sup>Mg, etc.), leading to a  
57 comprehensive and atomistic view of liquid solutions<sup>11,12</sup>. However, NMR spectroscopy is limited  
58 by the temporal scale and low sensitivity, making it difficult to speciate structural patterns that are  
59 often driven by electrostatic interactions, reactivity, temperature, compositional variance, and  
60 pressure<sup>13-15</sup>.

61 In such complex scenarios, computational NMR studies are necessary to decipher experimental  
62 results and better understand different chemical and physical effects whose interplay determines  
63 the overall spectrum. For example, *ab-initio* molecular dynamics (AIMD) simulations have been  
64 used to capture the structural evolutions and associated chemical shifts<sup>16-18</sup>. However, the  
65 computational cost associated with large systems (>100 atoms) and simulation time scales (~10  
66 ps) imposes severe restrictions for tests of liquid solutions across a wide chemical space. Density  
67 functional theory (DFT) calculations have also provided valuable insights into chemical shift

68 trends<sup>8,19,20</sup>. However, they fail to fingerprint the temporal evolution of solvation structures under  
69 exogenous (temperature and pressure) and endogenous (pH and composition) conditions. In  
70 addition, gaps in knowledge between systems examined *in-situ* or *ex-situ* and those modeled *in*  
71 *silico* still exist. For example, NMR DFT studies are often focused on singular phenomena, e.g.,  
72 magnetic shielding tensor. Recently, an automated framework<sup>21</sup> and a machine learning based  
73 approach<sup>22</sup> were implemented to predict the <sup>13</sup>C/<sup>1</sup>H NMR chemical shift for organic molecules.  
74 However, a generalized approach to identify complexes in multi-component solutions and  
75 accurately predict NMR chemical shift especially for non-traditional nuclei remains a great  
76 challenge. On the other hand, NMR experiments can reveal much more information about the  
77 chemical system, such as details of chemical exchange, correlation times or energetics for  
78 rotational and translational dynamics, etc. Even for the singular focus on chemical shift  
79 calculations, the possible molecular structure(s) are built manually based on chemical intuition,  
80 trial and error, and/or results reported in the literature<sup>20,23,24</sup>. This approach of providing the initial  
81 guesses is fraught with bias, is time-consuming, can be challenging to automate fully, and leaves  
82 behind many persistent metastable configurations of fundamental importance for interpreting  
83 experimental results. To overcome these challenges, we designed an automated computational  
84 framework that allows accurate prediction of NMR chemical shifts even in complex  
85 multicomponent liquid solutions and guide experiments to identify stable speciation in the  
86 solution.

87 The paper is composed of two sections. First, we discuss the details of our high-fidelity and  
88 robust computational tool that seamlessly integrates classical molecular dynamics (CMD)  
89 simulations with DFT calculations through force field generation and information flow between  
90 the two length scales. The tool automates the entire process, starting from sampling hundreds of

91 thousands of possible configurations in solute-solvent systems to identifying the most stable  
92 configurations and predicting and storing their NMR chemical shifts in a database. To the best of  
93 our knowledge, an automatic derivation of NMR chemical shifts with explicit solvation has not  
94 yet been implemented in any software infrastructure. Although the developed tool is general  
95 enough to be applied to any liquid solution, we consider magnesium  
96 bis(trifluoromethanesulfonyl)imide  $\text{Mg}(\text{TFSI})_2$  salt in dimethoxyethane (DME) solvent as an  
97 illustrative example. The chosen electrolyte formulation has received considerable attention in  
98 battery literature but reported findings regarding the speciation and the exact solvation structure  
99 of the Mg cation are under contention. More specifically, experimental work reported the  
100 formation of solvent separated ion pairs (SSIPs), while contact ion pairs (CIPs) were observed in  
101 previous computational results<sup>14,23,25,26</sup>. A comprehensive molecular level understanding of the  
102 speciation present in the solution can allow tuning the chemical structure to control the stability,  
103 solubility, structural, and dynamical properties of liquid solutions. We note that we chose a system  
104 in which complexities in the solvation phenomena arise due to the multivalent nature of the cation,  
105 providing an example to demonstrate that the developed framework can be applied to other simpler  
106 systems. We report a detailed comparison between computed and experimental NMR chemical  
107 shifts for  $^{25}\text{Mg}$ ,  $^{13}\text{C}$ , and  $^1\text{H}$  nuclei in this electrolyte. We also demonstrate the high-throughput  
108 capability of the workflow by accurately predicting more than 300  $^{13}\text{C}$  and 600  $^1\text{H}$  NMR chemical  
109 shifts from a set of 100 organic molecules from the SDBS<sup>27</sup> database and a previous experimental  
110 study<sup>28</sup>. In the second section, we address the fundamental challenge of how to accurately predict  
111 NMR chemical shift of liquid solutions by associating the framework with a benchmarking study.  
112 This study reveals several factors such as the choice of force field parameters that affect the  
113 accuracy of predicted chemical shifts, which can be employed by a number of research

114 communities by increasing the accessibility to DFT-based chemical shifts for a wide variety of  
115 structures and liquid systems.

## 116 **RESULTS AND DISCUSSION**

### 117 **Overview of the automated framework**

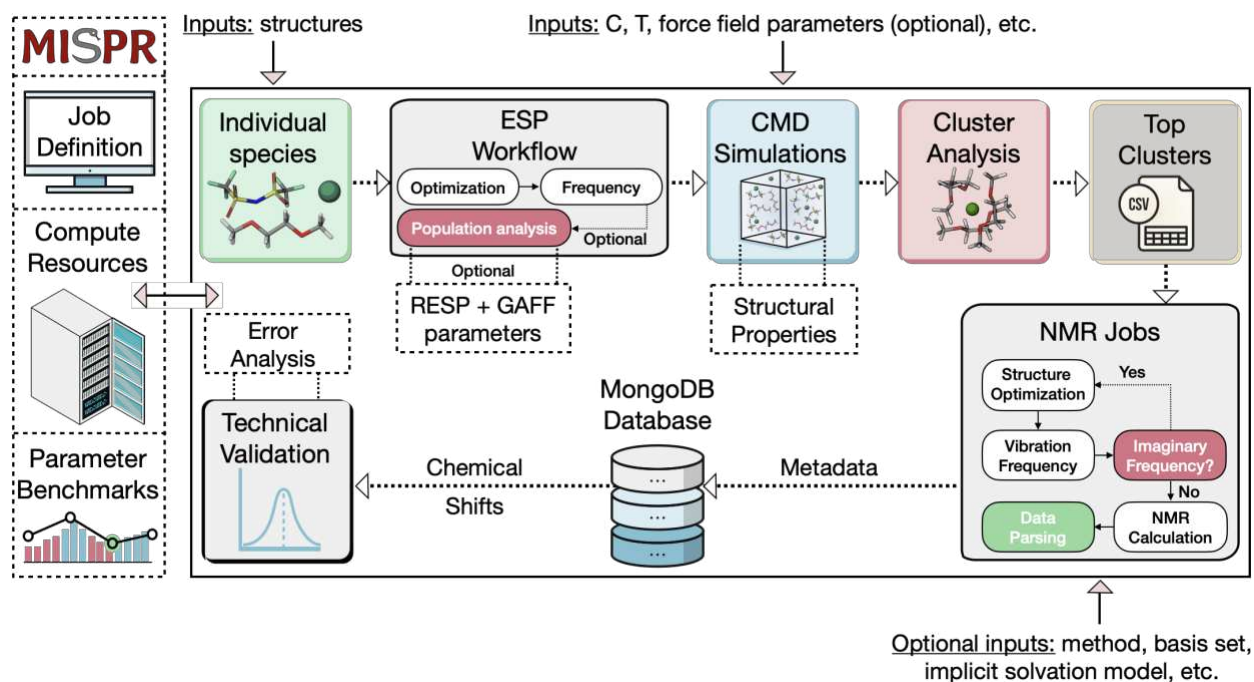
118 We construct an NMR computational framework using MISPR (Molecular Informatics for  
119 Structure-Property-Relationship), our high-throughput and scalable infrastructure that allows  
120 automatic handling of thousands of computational materials science simulations and multiple  
121 systems with a strong focus on data provenance. MISPR automates many computational tasks that  
122 are typically performed manually. Its functionalities span from processing and manipulating  
123 molecular structures, preparing and executing DFT and CMD simulations on supercomputing  
124 resources, parsing and analyzing output data, and creating output databases that organize the  
125 results from individual calculations. To manage the heterogeneous data that DFT and CMD  
126 workflows output and allow for flexible and complex queries, MISPR employs MongoDB<sup>29</sup> for  
127 data storage. MongoDB is a document-oriented NoSQL database that stores data as JSON-  
128 formatted documents with flexible schema. A unique feature of MISPR is that it allows seamless  
129 and automated integration of DFT calculations with CMD simulations to capture structural and  
130 dynamical phenomena that span over wide spatial and temporal scales. It contains multiple preset  
131 DFT and CMD workflow templates that, from the outside, the user only needs to call in a single  
132 Python script with minimal required inputs (e.g., molecular structure, the size and geometry of the  
133 system for CMD simulations, etc.) to generate and run a comprehensive workflow. We built  
134 MISPR on top of base libraries developed by the Materials Project, namely: (1) *pymatgen*<sup>30</sup> for  
135 structure representation and input/output files generation and handling, (2) *FireWorks*<sup>31</sup> for  
136 managing workflows over computing resources, and (3) *custodian*<sup>32</sup> for monitoring inevitable

137 errors during simulations and applying on-the-fly fixes. At the backend, MISPR uses Gaussian<sup>33</sup>  
138 electronic structure software for DFT calculations and LAMMPS<sup>34</sup> (<https://www.lammps.org/>)  
139 open-source code for CMD simulations. Examples of implemented DFT workflows include  
140 calculating binding energy, redox potentials, and bond dissociation energy. CMD workflows in  
141 MISPR allow executing CMD simulations in various ensembles and analyzing collected  
142 trajectories for structural and dynamical properties. Force field parameters and derived properties  
143 are saved in their collections with auxiliary information like molecular metadata (e.g., InChI  
144 representation, chemical formula, etc.) and input parameters, making it easy to reproduce and  
145 query computational results. More details about the MISPR infrastructure will be the subject of a  
146 future publication.

147 The framework designed for automatic NMR chemical shift calculations in liquid solutions is  
148 outlined in Fig 1. The framework takes as input the structures of molecules comprising a liquid  
149 solution of interest. Many molecule formats are supported (e.g., XYZ file, PDB file, pymatgen  
150 molecule object, Gaussian output, etc.) via the OpenBabel<sup>35</sup> and pymatgen libraries. Besides these  
151 formats, the framework can take query criteria to retrieve previously optimized structures from the  
152 database. It can also derive a structure on the fly by either attaching a functional group or linking  
153 two structures at a specific binding site. Next, the framework runs an electrostatic partial charges  
154 (ESP) workflow that first converts the input structure formats to pymatgen molecule objects. The  
155 ESP workflow uses this molecule object to generate a Gaussian input file with input parameters  
156 specified as optional inputs to the workflow. The workflow uses default values if these parameters  
157 are not provided. It then runs three sequential steps: (1) a DFT geometry optimization, (2) a  
158 vibrational frequency calculation to ensure that there are no imaginary frequencies, and (3) a



159 population analysis to assign atomic charges. The framework executes the ESP workflow for each  
 160 component of the liquid solution.



**Fig. 1** Scheme of the computational framework used to calculate NMR chemical shifts in solution as implemented in the MISPR high-throughput infrastructure

161 We note that the framework is general enough to be applied to various complex liquid solutions  
 162 at different conditions (e.g., concentration, temperature, pressure, etc.). It requires, at minimum,  
 163 the concentration of species in the solution and the size and geometry of the system box to prepare  
 164 the multicomponent system for CMD simulations. One of the most challenging aspects of running  
 165 automated CMD simulations is selecting or generating accurate force field parameters. By default,  
 166 the framework uses the output of the ESP workflow to derive the general amber force field  
 167 (GAFF)<sup>36</sup> parameters for each species. The framework also supports other force fields allowing  
 168 the user to test different physical models for a specific application or system. In this case, the user  
 169 may input the force field parameters to the framework in the form of a Python dictionary or retrieve  
 170 them from our in-house database. We note that the user may bypass the ESP workflow if the ESP  
 171 charges have been previously calculated or other force fields are directly provided. The framework

172 then passes the optimized geometries, force field parameters, concentrations, and information  
173 about the geometry of the simulation box (e.g., lengths, shape, etc.) to the next step to build the  
174 system for LAMMPS simulations. Following this, the framework runs a CMD workflow to  
175 generate time trajectories of atomic positions and velocities. Configurations for common CMD  
176 procedures are encoded in a set of protocols that can be used directly or altered to run any series  
177 of LAMMPS calculations according to the user's needs. The default CMD configuration involves  
178 energy minimization, NPT equilibration at the desired temperature and pressure, melting and  
179 quenching, and NVT production runs.

180 The framework then uses the generated LAMMPS trajectory files to compute the radial  
181 distribution function (RDF) between all possible pairs of particle types in the system or specific  
182 pairs specified as inputs. The RDF module is part of a standalone in-house suite of Python tools  
183 that we developed to extract a range of structural and dynamical properties from LAMMPS  
184 trajectory and output files. The RDF defines the probability of finding a particle at a distance  $r$   
185 from another particle. More details about the RDF calculations are provided in the section 1 of the  
186 SI.

187 Sampling solvation structures from the CMD step is a key component of the NMR framework.  
188 Traditional NMR calculations are relatively inefficient at constructing initial guesses for molecular  
189 structures. Building molecular structures by manually placing a number of molecules in the  
190 solvation shell of the particle of interest is extremely time consuming<sup>20,23,24</sup>. In contrast, our  
191 framework passes the computed RDF from the previous step to perform sampling of the first  
192 solvation shell of a particle of interest in a straightforward and automated manner. In the  
193 framework, the first solvation shell is defined by the cutoff distance  $r_{min}$ , corresponding to the  
194 position of the first minimum after the main peak of the RDF between the particle of interest and

195 other coordinating particles in the solution. In the default operation of the framework,  $r_{min}$  is  
196 automatically extracted from the RDF, but the user may override this by providing  $r_{min}$  as an  
197 optional input. Thus, a cluster representing the solvation structure is defined as the group of species  
198 within  $r_{min}$  of the particle. By ensemble averaging hundreds of thousands of clusters, we obtain a  
199 distribution of clusters corresponding to all the possible chemical environments surrounding the  
200 particle of interest in the solution.

201 Next, the framework categorizes the extracted clusters into unique configurations based on the  
202 type and number of species surrounding the particle and their mode of coordination. Then, it  
203 calculates the probability of each configuration as the ratio of the number of clusters that belong  
204 to a specific configuration to the total number of extracted clusters. Configurations with the highest  
205 probability of occurrence correspond to persistent metastable solvation structures in the solution.  
206 By default, the framework selects the top configurations whose probabilities sum to more than  
207 90% of the total number of extracted clusters, but the user may also select the configurations as  
208 needed. The selection of the configurations is done to reduce the number of required DFT  
209 calculations and their associated computational cost. It is also important to select a representative  
210 cluster from each configuration since it is common that thousands of clusters with subtle  
211 geometrical differences (e.g., bond lengths, orientation, etc.) belong to the same configuration. To  
212 this end, the framework performs a local minimization procedure on all the clusters from the  
213 selected top configurations using the MMFF94s force field<sup>37</sup> as implemented in the RDKit  
214 library<sup>38</sup>. The framework then feeds the lowest-energy conformer of each configuration to an NMR  
215 DFT workflow. We note that it would be infeasible to manually generate and categorize this large  
216 number of structural files and account for all the possible solvation structures using conventional

217 methods that rely on chemical intuition. This task is especially challenging for chemical systems  
218 that have not been previously explored in detail.

219 The NMR workflow relaxes the CMD clusters selected from the previous step, performs a  
220 vibrational frequency analysis, and calculates the magnetic shielding tensor on each atom if a true  
221 potential energy surface (PES) minimum is reached. The framework by default uses the  
222  $\omega$ B97X<sup>39</sup>/def2-TZVP level of theory for performing these three sequential DFT steps. Switching  
223 the functional, basis set, and other Gaussian input parameters (e.g., solvation model, numerical  
224 and algorithmic parameters, etc.) is straightforward and requires the user to input them in the form  
225 of a Python dictionary to the framework. The framework then performs an analysis step that stores  
226 the calculation results in an NMR collection in the database or a local JSON file with all the  
227 necessary metadata for future reference. Creating a local file allows the user to check outputs  
228 quickly, retrieve data without accessing the database, and exchange data with other parties. An  
229 example of the structure of an NMR document is shown in Fig S1. Finally, results from the  
230 computational framework are compared to experimental NMR spectra to elucidate the solvation  
231 structures.

232 In the NMR workflow, a series of convergence checks are performed to ensure the results are  
233 as reliable as possible. For example, we implemented checks for normal termination of DFT  
234 calculations and automatic inspection of the 3D structure resulting from optimization to confirm  
235 connectivity matches the input structure. Once each step of the NMR workflow has terminated,  
236 the output file is parsed for errors. An automatic error correction process is employed through  
237 well-defined rules via the custodian package if an error is detected. If possible, the error handler  
238 applies the appropriate remedy, generally by modifying the input parameters, writing a new  
239 Gaussian input file, and restarting the calculation. If no remedy has been implemented for a

240 particular error or the error handler cannot interpret the encountered error, the calculation is  
241 allowed to fail. The error handler improves the success rate of the calculations without relying on  
242 human intervention, which would be impossible for handling large computational investigations.  
243 Examples of the errors addressed are SCF failure, geometry optimization convergence, error in  
244 internal coordinates, and exceeded wall time limit.

245 The framework takes solvent effects into account by two approaches. It uses an explicit  
246 approach where several solvent molecules surrounding the species are correctly placed in its first  
247 solvation shell since the geometries are extracted directly from CMD simulations. Second, it  
248 approximates bulk solvent effects using a dielectric continuum model. This approach allows  
249 incorporating a thermodynamically stable and realistic chemical environment of species compared  
250 to the traditional approach, which relies on either implicit solvent models or manual prediction of  
251 the possible solvation structures. Since multiple configurations are considered, collected data result  
252 in various chemical shifts corresponding to different chemical environments experienced by the  
253 nucleus of interest. Therefore, predictions from this approach can be compared and fitted to the  
254 entire experimental NMR peak rather than just matching the peak center, especially when peak  
255 broadening occurs due to distribution of chemical shifts or intermediate exchange dynamics in  
256 solutions.

257 Components of the NMR framework presented in Fig 1 can be decoupled according to the  
258 needs of the user. For example, we used the NMR workflow as a standalone code to compute the  
259  $^{13}\text{C}$  and  $^1\text{H}$  chemical shifts for a set of 100 organic molecules. Detailed information about the  
260 library is provided in Table S1. The calculations were performed in a chloroform solvent at the  
261  $\omega\text{B97X}/\text{def2-TZVP}$  level of theory and referenced to tetramethylsilane (TMS). The code snippet  
262 in Fig S2 demonstrates how to submit these calculations starting from structures defined in the

263 XYZ file format. Upon submitting the script, the calculations were added to a *FireWorks* database  
264 and subsequently executed over computing resources. The workflow generated and managed over  
265 600 input and output files and inserted more than 300  $^{13}\text{C}$  and 600  $^1\text{H}$  chemical shifts into the  
266 database via a simple one-shot script. We compared our predictions to experimental data from the  
267 SDBS<sup>27</sup> database and a previous study<sup>28</sup>. Fig S3 and Fig S4 show parity plots of the computed  
268 chemical shifts and their associated error distribution, respectively. A good correlation is observed  
269 between the workflow output and the experimental data with only minor deviations from the fitted  
270 line. This example demonstrates how our high-throughput approach may be adapted for the  
271 determination of accurate NMR chemical shifts.

### 272 **Factors affecting the accuracy of NMR chemical shifts**

273 Reliably differentiating among different extracted solvation structures requires high accuracy  
274 NMR chemical shift predictions. The successful implementation of our framework necessitates  
275 adequate consideration of several important factors. First, a key question for the CMD component  
276 is the quality of the interatomic potentials since significant deviations in system properties have  
277 often been observed compared to experimental data<sup>40</sup>. Second, the DFT level of theory comprising  
278 the density functional and basis set is critical for achieving well-converged chemical shieldings.  
279 Achieving this convergence for small molecules is relatively straightforward by combining DFT  
280 or even coupled cluster calculations with large basis sets. However, this is much more challenging  
281 with complexes consisting of multiple species. Therefore, there is a need to balance the cluster size  
282 with the quality of the DFT level of theory. In addition, the choice of the implicit solvent model is  
283 crucial for approximating the bulk solvent effect. A remarkable number of benchmarking studies  
284 have been done on quantum mechanical methods for predicting properties in complex  
285 multicomponent battery electrolytes similar to the test case here<sup>41-43</sup>. However, parallel studies for

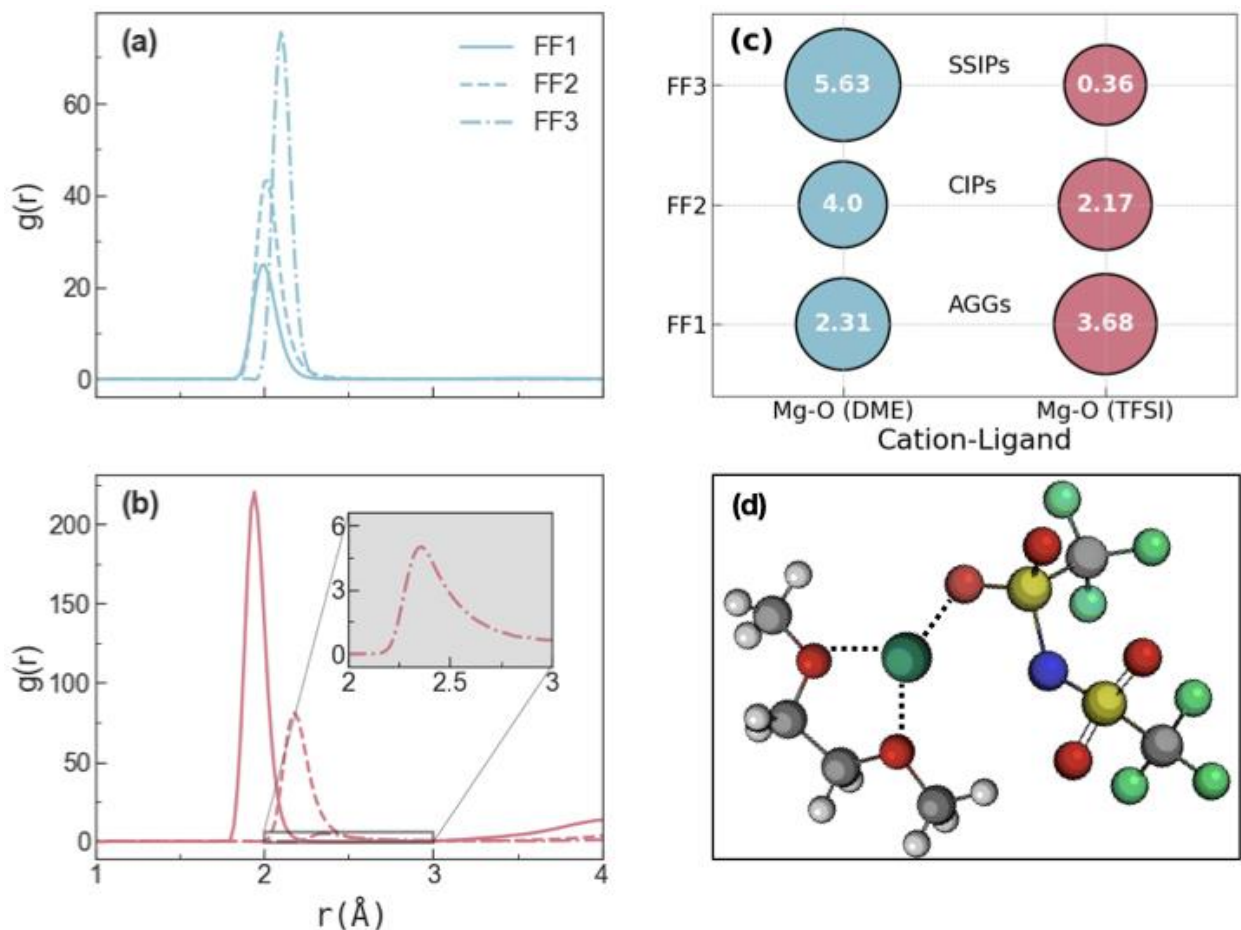
286 NMR calculations for these types of systems are still in their infancy. Other factors include  
287 selecting an appropriate number of molecules in the chemical reference to account for  
288 intermolecular interactions and a representative conformer from each solvation environment. In  
289 the following sections, we report the role of each of these factors using results obtained by the  
290 framework for the Mg(TFSI)<sub>2</sub>/DME test case system.

### 291 Role of the force field

292 The choice of the force field parameters used in CMD simulations can significantly influence  
293 the speciation observed in solution, and thus the NMR chemical shift predictions. Therefore, we  
294 benchmark the most commonly used and reliable force fields for liquid solutions, including GAFF  
295 (FF1), non-polarizable OPLS<sup>44</sup> (FF2), and polarizable OPLS (FF3) force fields to compare their  
296 performance in terms of the solution properties. FF1 and FF2 are computationally less expensive  
297 due to their non-polarizable nature and have been used extensively in the battery literature showing  
298 satisfactory agreement with experimental findings. FF3, built on top of FF2, allows for a  
299 polarizable response of molecules to an electric field using the Drude oscillator model<sup>45</sup>. In this  
300 model, particles are added to each polarizable atom to mimic physical dipoles and model the  
301 corresponding distortion of electron density.

302 The simulation density ( $\rho$ ) using the three force fields, shown in Table S2, agrees well with  
303 the experimental value. The lowest average error (1.2 %) is achieved with FF3. The RDFs between  
304 the cation and oxygen atoms of DME and TFSI<sup>-</sup> are shown in Fig 2a and 2b, respectively. FF1  
305 results in the weakest cation-solvent [Mg<sup>2+</sup>-DME] interaction and the most vital cation-anion  
306 [Mg<sup>2+</sup>- TFSI<sup>-</sup>] interaction, as evident from the sharp RDF peak between the cation and oxygen  
307 atoms of the anion. On the other hand, with FF3, little coordination occurs with the anion (inset of  
308 Fig 2b), indicating that solvent molecules dominate the first solvation shell of the cation. Fig 2c

309 shows  $\text{Mg}^{2+}$  - O (DME) and  $\text{Mg}^{2+}$  - O (TFSI<sup>-</sup>) coordination numbers, calculated by integrating the  
 310 corresponding RDF curves for the first solvation shell. FF3 results indicate that  $\text{Mg}(\text{TFSI})_2$  tends  
 311 to form SSIPs in DME, while FF2 shows that the salt participates in forming CIPs. On the other  
 312 extreme, FF1 results in the formation of aggregate solvates (AGGs), in which two or more anions  
 313 coordinate with the cation. An example of the type of coordination represented by the RDFs is  
 314 displayed in Fig 2d. The tested force fields also result in different percentages of DME and TFSI<sup>-</sup>  
 315 that coordinate to  $\text{Mg}^{2+}$  with two oxygen atoms, *i.e.*, in bidentate configuration, as shown in Fig  
 316 S5.



**Fig. 2** Structural properties of  $\text{Mg}(\text{TFSI})_2$  in DME at 298.15 K using FF1 (GAFF), FF2 (non-polarizable OPLS), and FF3 (polarizable OPLS). RDF of (a)  $\text{Mg}^{2+}$  - O (DME) and (b)  $\text{Mg}^{2+}$  - O (TFSI), (c) coordination numbers with  $\text{Mg}^{2+}$  with the corresponding type of structure: solvent separated ion pairs (SSIPs), contact ion pairs (CIPs), and aggregates (AGGs), and (d) corresponding types of coordination with oxygen atoms of DME and TFSI<sup>-</sup>



317 The top  $\text{Mg}^{2+}$  configurations identified by the framework are provided in Fig S6 and Fig S7.  
318 Overall, we find significant differences in the type and distribution of these structures among the  
319 tested force fields. For example, the most probable solvation structure predicted with FF1 involves  
320 one DME molecule in bidentate configuration and four TFSI<sup>-</sup> anions in monodentate configuration.  
321 In addition, rather than forming a single stable solvate like in the case of FF3, the distribution of  
322 coordination environments for the cation with FF1 is much more heterogeneous and involves  
323 configurations dominated by the anion. With FF2, the electrostatic interaction with the anion is  
324 slightly suppressed, and the most probable solvation shell is composed of two DME solvents and  
325 TFSI<sup>-</sup> anions participating in bidentate and monodentate configurations, respectively. FF3 results  
326 in an  $\text{Mg}^{2+}$  solvation shell dominated by three DME molecules participating in bidentate  
327 configuration, with only minor structures containing an anion. This configuration has been  
328 previously suggested based on experimental measurements of diffusion and Raman and NMR  
329 spectroscopy<sup>23,26</sup>, and computationally by Kubisiak and Eilmes<sup>46</sup> for a concentration range of 0.1-  
330 1 M.

331 Variations in the structural properties between the tested force fields are translated to the  
332 dynamical behavior of the electrolyte. The distribution of diffusion coefficients (Fig S8) from FF3  
333 indicates 2.58 slow DME molecules per  $\text{Mg}^{2+}$  cation. This result is in close agreement with the  
334 experimentally measured value of 3.0<sup>23</sup> and is consistent with the computed structural properties.  
335 FF1 and FF2 predict 1.17 and 1.86 slow DME molecules per  $\text{Mg}^{2+}$ , respectively. The calculated  
336 ionic diffusion coefficients with FF3 are also in better agreement with experimental results (mean  
337 absolute error of 20%), whereas those from FF1 and FF2 are underestimated by approximately  
338 90% and 30%, respectively (Fig S9).

339 The discrepancies in the predicted properties are not particularly a problem of a specific force  
340 field or the Mg(TFSI)<sub>2</sub>/DME system, but rather due to a lack of accounting for the critical  
341 interactions in the non-polarizable simulations. The predicted properties using FF3 are the most  
342 consistent with previous experimental<sup>23,26</sup> and computational<sup>46</sup> studies among the tested force  
343 fields. However, the better performance of FF3 comes at the expense of its 2-3 fold higher  
344 computational time compared to FF1 and FF2. To summarize, the computational results for the  
345 cation-anion motifs and the propensity of the salt to form ion aggregation in the solution are  
346 strongly dependent on the type of the force field. Therefore, evaluating the quality of the force  
347 field used in the sampling process is a necessary primary step to obtain reliable structures for NMR  
348 computations. Here, we proceed with the FF3-predicted solvation structures to report results from  
349 the DFT component of the NMR framework.

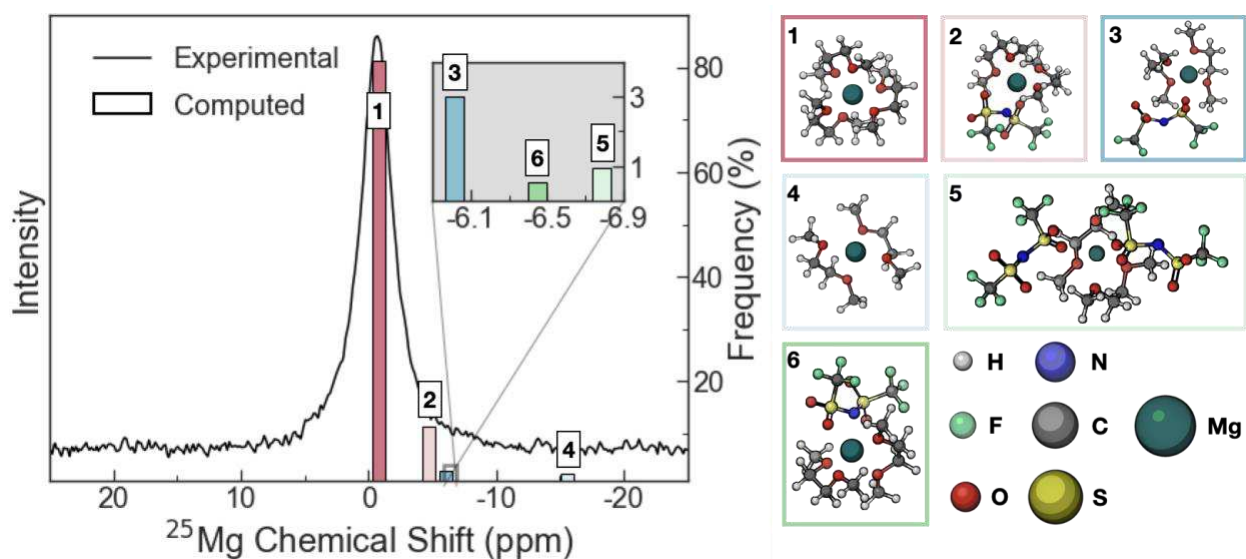
#### 350 Role of the DFT level of theory

351 We evaluate the performance of selected DFT functionals and basis sets in predicting chemical  
352 shifts of <sup>25</sup>Mg, <sup>13</sup>C, and <sup>1</sup>H of the top configurations and the chemical shifts of <sup>13</sup>C and <sup>1</sup>H  
353 resonances in the bulk solution. All calculations presented in this section are performed using the  
354 polarizable continuum model (PCM)<sup>47-49</sup>. The NMR workflow (Fig 1) is designed to be used in  
355 high-throughput mode to study speciation evolution in liquid solutions at variable conditions, *e.g.*,  
356 concentration and temperature. Therefore, the comparison is made not only based on accuracy but  
357 also on factors that are particularly important for high-throughput simulations (*e.g.*, computational  
358 cost and tendency to fail). Predictions from combinations of four commonly utilized DFT  
359 functionals (B3LYP<sup>50</sup>, M06-2X<sup>51</sup>, PBE1PBE<sup>52</sup>, and ωB97X<sup>39</sup>) and three Gaussian basis sets (6-  
360 31+G\*, 6-311++G\*\*, and def2-TZVP) are compared with experimental NMR data.

361 During the benchmark study, the most common failures encountered include failure to  
362 converge the geometry to a PES minimum in a finite number of optimization steps, difficulties in  
363 converging SCF calculations, and errors in internal coordinate transformations. Around 78% of  
364 the total performed calculations were completed without error correction procedures. Levels of  
365 theory primarily involved in the failed calculations include B3LYP/6-31+G\* and PBE1PBE  
366 hybrid functional coupled with each of the 6-31+G\* and 6-311++G\*\* basis sets. Given that one  
367 of our primary goals is to find a level of theory that is not likely to fail with complex  
368 multicomponent clusters, these levels of theory are not considered the most appropriate for the  
369 required task.

370 The  $^{25}\text{Mg}$  NMR results from the top-performing level of theory ( $\omega\text{B97X}/\text{def2-TZVP}$ ) are  
371 shown in Fig 3 along with the corresponding structure of the predicted species. A single broad  
372 peak is observed, indicating either a single solvation structure or a convolution of multiple  
373 structures with a rapid exchange. The predicted  $^{25}\text{Mg}$  chemical shift in the most probable  
374 configuration is -0.809 ppm, which is highly consistent with the experimental peak center located  
375 at -0.71 ppm. Given the broad line width of the  $^{25}\text{Mg}$  peak, *i.e.*, the half peak height at 0.83 and -  
376 2.13 ppm, the chemical shift of  $^{25}\text{Mg}$  in configuration 2 (Table 1) is also deemed to be in  
377 satisfactory agreement with experimental data. Therefore, multiple  $\text{Mg}^{2+}$  structures that are  
378 entirely dissociated from the anion are possible in the solution. Excluding configuration 4, the  
379 increase in the ion-dipole interaction between  $\text{Mg}^{2+}$  and  $\text{TFSI}^-$  in the following order: configuration  
380 1 < configuration 2 < configuration 3 < configuration 6 < configuration 5 leads to the observed  
381 monotonic upfield shift in the corresponding  $^{25}\text{Mg}$  chemical shift. The presence of loosely packed  
382 clusters of  $[\text{Mg}(\text{DME})_n]$  ( $n \leq 2$ ), *i.e.*, configuration 4, is attributed to the high degree of freedom  
383 and structural flexibility of DME. This type of configuration has been reported to be favorable at

384 lower concentrations due to lower electrostriction (reduced solvent volume in the  $\text{Mg}^{2+}$  solvation  
 385 shell relative to the bulk) and diminished entropy loss<sup>23</sup>. On the contrary, higher concentrations  
 386 (0.51 M) such as the one used in this study lead to closer distances between  $\text{Mg}^{2+}$  ions, resulting  
 387 in stronger electrostatic interactions and dampened DME motion, thus favoring fully solvated  
 388 clusters ( $n = 3$ , configuration 1). This behavior is consistent with the low probability of  
 389 configuration 4 and the predicted  $^{25}\text{Mg}$  chemical shift of this configuration, which is far from the  
 390 experimental peak center (Fig 3).



**Fig. 3** Predicted  $^{25}\text{Mg}$  NMR chemical shifts using the NMR computational protocol and the experimental NMR spectrum along with the corresponding predicted solvation structures of 1:18  $\text{Mg}(\text{TFSI})_2$  in DME solution. DFT calculations are performed at the  $\omega\text{B97X}/\text{def2-TZVP}$  level of theory using the PCM solvation model

**Table 1** DFT predicted chemical shifts for 1:18 Mg(TFSI)<sub>2</sub> in DME solution along with deviations from experimental data

Molecule <sup>a</sup>	$\delta$ <sup>25</sup> Mg (ppm)		$\delta$ <sup>13</sup> C (ppm)		$\delta$ <sup>1</sup> H (ppm)	
	PCM <sup>b,c</sup>	SMD <sup>b,c</sup>	Shift <sup>c,d</sup>	Deviation <sup>e</sup>	Shift <sup>d,f</sup>	Deviation <sup>e</sup>
Bulk DME			CH <sub>2</sub> : 72.32	CH <sub>2</sub> : 0.83	CH <sub>2</sub> : 3.74	CH <sub>2</sub> : 0.06
			CH <sub>3</sub> : 59.16	CH <sub>3</sub> : 0.27	CH <sub>3</sub> : 3.64	CH <sub>3</sub> : -0.01
Configuration 1	-0.809	0.283	CH <sub>2</sub> : 72.62	CH <sub>2</sub> : -0.26	CH <sub>2</sub> : 4.24	CH <sub>2</sub> : 0.16
[Mg(DME) <sub>3</sub> ] <sup>2+</sup>			CH <sub>3</sub> : 62.70	CH <sub>3</sub> : -0.09	CH <sub>3</sub> : 4.07	CH <sub>3</sub> : 0.29
Configuration 2	-4.741	-4.649	CH <sub>2</sub> : 72.50	CH <sub>2</sub> : -0.14	CH <sub>2</sub> : 4.20	CH <sub>2</sub> : 0.20
Mg(DME) <sub>2</sub> (TFSI) <sup>+</sup>			CH <sub>3</sub> : 62.18	CH <sub>3</sub> : 0.43	CH <sub>3</sub> : 4.11	CH <sub>3</sub> : -0.01
Configuration 3	-6.016	2.784	CH <sub>2</sub> : 72.16	CH <sub>2</sub> : 0.20	CH <sub>2</sub> : 4.27	CH <sub>2</sub> : 0.13
Mg(DME) <sub>2</sub> (TFSI) <sup>+</sup>			CH <sub>3</sub> : 61.64	CH <sub>3</sub> : 0.97	CH <sub>3</sub> : 4.15	CH <sub>3</sub> : -0.05
Configuration 4	-15.559	-3.982	CH <sub>2</sub> : 73.37	CH <sub>2</sub> : -1.01	CH <sub>2</sub> : 4.32	CH <sub>2</sub> : 0.08
[Mg(DME) <sub>2</sub> ] <sup>2+</sup>			CH <sub>3</sub> : 62.73	CH <sub>3</sub> : -0.12	CH <sub>3</sub> : 4.14	CH <sub>3</sub> : -0.04
Configuration 5	-6.785	-6.196	CH <sub>2</sub> : 71.85	CH <sub>2</sub> : 0.51	CH <sub>2</sub> : 4.10	CH <sub>2</sub> : 0.30
[Mg(DME) <sub>2</sub> (TFSI) <sub>2</sub> ]			CH <sub>3</sub> : 62.57	CH <sub>3</sub> : 0.04	CH <sub>3</sub> : 4.14	CH <sub>3</sub> : -0.04
Configuration 6	-6.450	-5.815	CH <sub>2</sub> : 72.68	CH <sub>2</sub> : -0.32	CH <sub>2</sub> : 4.29	CH <sub>2</sub> : 0.11
[Mg(DME) <sub>2</sub> (TFSI) <sup>+</sup>			CH <sub>3</sub> : 62.52	CH <sub>3</sub> : 0.09	CH <sub>3</sub> : 4.13	CH <sub>3</sub> : -0.03

<sup>a</sup> For the difference between configurations 2, 3, and 6, refer to Fig S3,

<sup>b</sup> Compared to experimental peak center at -0.71 ppm,

<sup>c</sup> Using  $\omega$ B97X/def2-TZVP,

<sup>d</sup> Using PCM model,

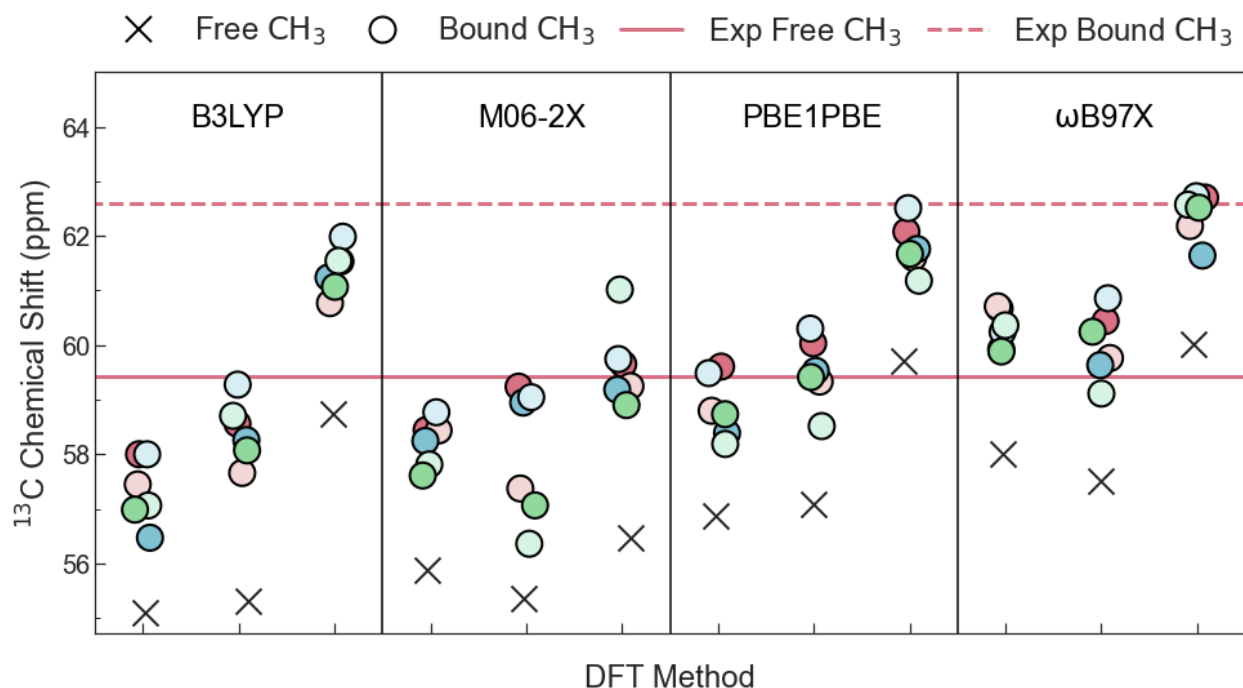
<sup>e</sup> Deviation =  $\delta_{exp} - \delta_{DFT}$ ,

<sup>f</sup> Using M06-2X/def2-TZVP.

391 The benchmarking results for  $^{25}\text{Mg}$  chemical shift calculations are displayed in Fig S10. On  
392 average, going from left to right, *i.e.*, increasing the number of basis functions, moves most of the  
393 predicted chemical shifts corresponding to different electronic environments surrounding the  $^{25}\text{Mg}$   
394 nucleus within the bounds of the observed NMR spectrum. From top to bottom, significant  
395 variations are observed in the predicted chemical shifts using the four functionals with 6-31+G\*,  
396 while this difference is less clear with def2-TZVP. In addition, we find that different levels of  
397 theory can lead to contradictory conclusions regarding the dominant species in solution. For  
398 example, the structure is predicted to be  $[\text{Mg}(\text{DME})_2(\text{TFSI})]^+$  using PBE1PBE/6-31+G\* while the  
399 fully solvated  $[\text{Mg}(\text{DME})_3]^{2+}$  is found with PBE1PBE/def2-TZVP.

400 Fig 4 shows  $^{13}\text{C}$  NMR shifts assigned to  $\text{CH}_3$  of DME existing in the bulk solution (labeled  
401 'free  $\text{CH}_3$ ') and DME coordinated to  $\text{Mg}^{2+}$  (labeled 'bound  $\text{CH}_3$ ') from DFT predictions and  
402 experimental measurements. Similar plots for  $^{13}\text{C}$  shifts assigned to  $\text{CH}_2$  and  $^1\text{H}$  shifts assigned to  
403  $\text{CH}_3$  and  $\text{CH}_2$  of both types of DME molecules are shown in Figs S11-S13, respectively. While  
404 free and bound DME molecules are distinguishable from experimental and predicted  $^{13}\text{C}$  and  $^1\text{H}$   
405 NMR chemical shifts, it is impossible to differentiate between bound DME at different  
406 configurations identified in this work. The spectroscopic differences between the structures may  
407 be subtle (see, for example, Table 1 for  $^{13}\text{C}$  and  $^1\text{H}$  chemical shifts in different configurations). On  
408 the contrary,  $^{25}\text{Mg}$  chemical shifts can be utilized for this purpose, whereby changes in charge  
409 density localization on different  $\text{Mg}^{2+}$  complexes directly alter the screening effects experienced  
410 by the  $^{25}\text{Mg}$  nucleus, thus giving rise to different NMR responses. As displayed in Fig 4 and Fig  
411 S11, the highest deviation from experimental  $^{13}\text{C}$  shifts are obtained with the 6-31+G\* and 6-  
412 311++G\*\* basis sets combined with any tested density functional. The basis set from the 'def2'  
413 family of Alrichs and coworkers<sup>53</sup>, particularly in combination with  $\omega\text{B97X}$ , leads to  $^{13}\text{C}$  NMR

414 chemical shift error that approaches the underlying uncertainty in experimental measurements  
 415 (Table 1). Fig S12 and S13 indicate that for  $^1\text{H}$  chemical shifts, M06-2X/def2-TZVP outperforms  
 416 the other tested levels of theory with absolute errors between 0.01 and 0.3 ppm (Table 1).



**Fig. 4** Strip plot of the computed and experimental  $^{13}\text{C}$  NMR chemical shifts assigned to  $\text{CH}_3$  of DME coordinated to  $\text{Mg}^{2+}$  (labeled Bound  $\text{CH}_3$ ) and  $\text{CH}_3$  of free DME (labeled Free  $\text{CH}_3$ ). For color code of 'Bound  $\text{CH}_3$ ', please refer to Fig 3. Results from each DFT functional are shown with the basis sets in the following order: 6-31+G\*, 6-311++G\*\*, and def2-TZVP

417 We conclude that the choice of the basis set has the highest impact on the accuracy of NMR  
 418 chemical shift predictions. The 6-31+G\* basis set is ruled out as a suitable basis set for NMR  
 419 calculations of complexes similar to those studied herein due to its degraded accuracy compared  
 420 to other basis sets, despite its lower computational cost (see Fig S14 for timings). For  $^{25}\text{Mg}$  and  
 421  $^{13}\text{C}$  chemical shifts, the  $\omega\text{B97X}/\text{def2-TZVP}$  level of theory is recommended if computational  
 422 resources are available as its remarkable accuracy and the applicability of def2-TZVP to broader  
 423 chemical systems make it well worth the additional cost. If computational resources are limited,  
 424 M06-2X/6-311++G\*\* is recommended for  $^{25}\text{Mg}$  shifts as its cost is not prohibitive while still

425 predicting the correct  $\text{Mg}^{2+}$  solvation structure. Finally, M06-2X with def2-TZVP or 6-311++G\*\*  
426 are recommended for  $^1\text{H}$  chemical shift predictions.

#### 427 Effect of geometry optimization

428 To examine the possibility of making DFT calculations more affordable, we calculated the  
429  $^{25}\text{Mg}$  chemical shift of 33 pre-relaxed clusters extracted from CMD simulations. We then compare  
430 their deviation from calculations utilizing optimized geometries at the same level of theory (Fig  
431 S15). We find a mean absolute deviation of  $\sim 37.6$  ppm between the two types of calculations,  
432 with a systematic downfield shift from calculations utilizing fully optimized structures. This result  
433 is not surprising due to the sensitivity of the  $^{25}\text{Mg}$  nucleus to subtle differences in the local structure  
434 and coordination environment. Therefore, relaxing the structures ensures that 'reasonable  
435 geometries' are used, and therefore is a prerequisite for obtaining accurate NMR chemical shifts  
436 that are comparable to experimental measurements.

#### 437 Choice of the chemical reference

438 Because water is selected as the  $^1\text{H}$  chemical shift reference, another consideration is the  
439 accurate computational representation of the effect of strong hydrogen bonding among water  
440 molecules. To this end, calculations on clusters of  $(\text{H}_2\text{O})_n$  ( $n = 1 - 4, 6, 8, 10, 12$ ) are performed.  
441 At the M06-2X/def2-TZVP level of theory, the isotropic shielding constant of  $^1\text{H}$  moves upfield  
442 when the number of water molecules increases and tends to converge at  $\sim 27.6$  ppm for eight water  
443 molecules. In addition, multiple clusters for non-hydrogen-bonding dimethylsulfoxide  $(\text{DMSO})_n$   
444 ( $n = 1 - 4, 6$ ), used as a reference in  $^{13}\text{C}$  chemical shift calculations, are considered. The use of a  
445 DMSO dimer is found to be sufficient, whereby the  $^{13}\text{C}$  isotropic shielding constant converges at  
446  $\sim 150$  ppm at the  $\omega\text{B97X}/\text{def2-TZVP}$  level of theory. Finally, since intermolecular interactions  
447 inevitably exist in DME solution, calculations on  $(\text{DME})_n$  ( $n = 1 - 4$ ) are carried out for predicting



448 the  $^{13}\text{C}$  and  $^1\text{H}$  chemical shifts of DME molecules in the bulk solution, and  $(\text{DME})_2$  is found to  
449 result in bulk  $\text{CH}_3$  and  $\text{CH}_2$  chemical shifts that reproduce the experimental data. All calculated  
450 isotropic shielding constants for  $\text{H}_2\text{O}$ , DMSO, and DME clusters are included in the dataset  
451 associated with this work.

#### 452 Role of the implicit solvation model

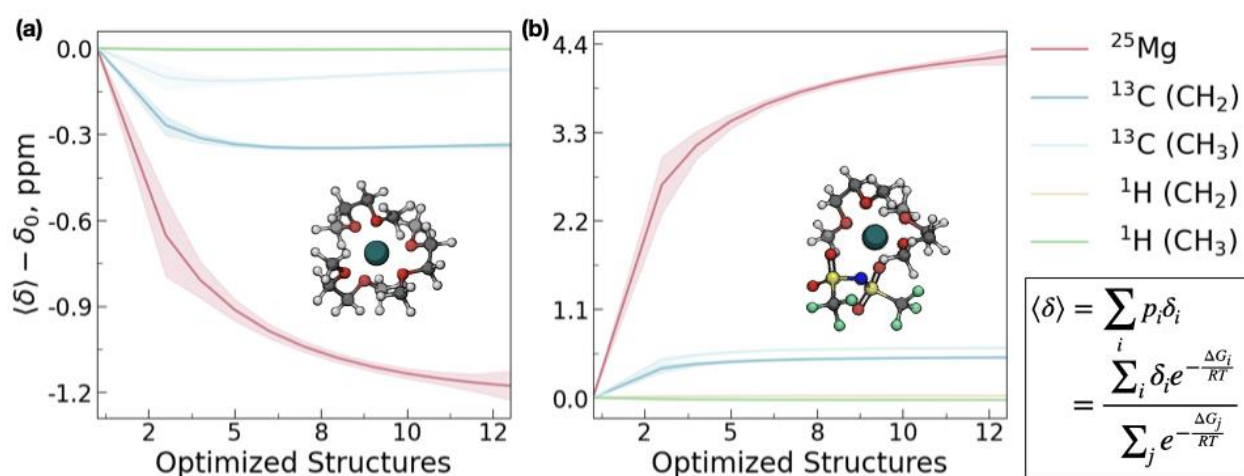
453 In addition to the explicit solvent molecules modeled in the  $\text{Mg}^{2+}$  first solvation shell, an  
454 implicit model is used to incorporate long-range electrostatic effects. Implicit solvent models have  
455 the advantage of reducing the number of degrees of freedom of the environment (solvent), thereby  
456 decreasing the computational cost to describe the dielectric continuum outside the solute cavity.  
457 SMD is reliable in many applications<sup>54</sup> and therefore is compared to the PCM results in this work.  
458 As evident from the data in Table 1, both methods lead to similar interpretations of experimental  
459 results in terms of the most probable solvation structure. However, the PCM method predicts more  
460 accurately the chemical shift of the top configuration. The only significant differences between the  
461 two methods are for configurations 3 and 4. Similarly, more minor errors associated with  $^{13}\text{C}$  and  
462  $^1\text{H}$  chemical shifts are achieved with PCM than the SMD model using the  $\omega\text{B97X}/\text{def2-TZVP}$  and  
463  $\text{M06-2X}/\text{def2-TZVP}$  levels of theory, respectively (Fig S16).

#### 464 Role of conformer

465 Another consideration in the NMR framework is that it utilizes the lowest-energy conformer  
466 from each configuration to initialize the NMR DFT calculations. Previous NMR DFT studies have  
467 also reported findings on possible solvation structures based on a single conformer<sup>20,24,55</sup>.  
468 However, the measured shift is the weighted average of chemical shifts of all possible conformers  
469 in solution during the NMR acquisition time. Therefore, we assess the sensitivity of DFT chemical  
470 shifts to conformer sampling by starting from the MMFF94 energies of a total of  $\sim 270,000$

471 conformers of configuration 1 and ~ 4,000 conformers of configuration 2 extracted from CMD  
472 simulations. From each configuration, 15 conformers spanning the entire energy range are selected  
473 to initialize full NMR calculations that include geometry optimization, frequency, and chemical  
474 shift estimation at the  $\omega$ B97X/def2-TZVP level of theory using the PCM solvation model.  
475 Boltzmann averaging is done according to the equation shown in Fig 5 to calculate the ensemble  
476 NMR chemical shift. Because optimization at the higher level of theory leads to the reordering of  
477 conformational energies, the results are reported relative to the MM global minimum energy  
478 conformer. The plots in Fig 5 show the mean difference (including the 95% confidence interval)  
479 between the Boltzmann average NMR chemical shift for the entire ensemble,  $\langle\delta\rangle$ , and our initial  
480 chemical shift estimation,  $\delta_0$ , as a function of the number of optimizations performed. We note  
481 that for each number of optimized structures ( $N_{opt}$ ) shown on the x-axis of Fig 5, the calculated  
482  $\langle\delta\rangle$  is the result of averaging over all possible combinations of  $N_{opt}$  from a pool of 15 structures,  
483 with a restriction that the MM global minimum energy conformer is included in these  
484 combinations. To maintain statistical significance, only  $N_{opt}$  resulting in more than 30 possible  
485 combinations are used, thus  $N_{opt} = 2, 13, 14, 15$  are excluded from the analysis. Variable degrees  
486 of errors are obtained with each nucleus type, with the highest difference in the  $^{25}\text{Mg}$  chemical  
487 shift. In this electrolyte system, a maximum unsigned error of 1.2 ppm in the  $^{25}\text{Mg}$  chemical shift  
488 of configuration 1 upon excluding conformational sampling does not alter the interpretation of  
489 experimental findings in terms of the most probable solvation structure while saving 15 $\times$  the  
490 computational resources. Nevertheless, conformational sampling has a more pronounced impact  
491 on other less probable solvation structures like configuration 2, for which an error of 4.4 ppm is  
492 incurred if only the MM global minimum is considered for calculations at the higher level of  
493 theory. Significantly lower errors are obtained for  $^{13}\text{C}$  chemical shifts of  $\text{CH}_2$  and  $\text{CH}_3$  groups,

494 while  $^1\text{H}$  chemical shifts are insensitive to conformer sampling regardless of the type of  
 495 configuration to which the proton belongs. Therefore, an evaluation of the impact of  
 496 conformational sampling on DFT predictions for a nucleus of interest should be done whenever  
 497 possible to boost the confidence in correlations established between experiments and the results of  
 498 the computational framework described in this work. Such a process would determine whether the  
 499 conformer issue is critical in the examined case study to possibly avoid instances of multiple  
 500 conformers that would need to be considered.



**Fig. 5** Effect of multiple conformers for (a) configuration 1 and (b) configuration 2 on  $^{25}\text{Mg}$ ,  $^{13}\text{C}$ , and  $^1\text{H}$  NMR chemical shifts. In the equation of the Boltzmann weighted average of the chemical shift  $\langle \delta \rangle$ ,  $p_i$  and  $\Delta G_i$  are the Boltzmann weight and the formation energy of structure  $i$  relative to the most stable configuration predicted by DFT, respectively

## 501 CONCLUSIONS

502 In conclusion, we have developed and tested a computational framework that couples first-  
 503 principle calculations with CMD simulations to robustly and efficiently calculate, analyze, and  
 504 store NMR chemical shifts from a variety of molecules in liquid solutions. The framework  
 505 overcomes limitations in current NMR computational studies such as the Edisonian approach in  
 506 selecting possible solvation structures and the significant time required for manual file  
 507 management, data collection, and error handling. By overcoming these limitations, we were able

508 to accurately identify multiple stable species present in the solution that contribute to the overall  
509 NMR spectral shape. Minimal inputs comprising structures of species in solution and their force  
510 field parameters are required to obtain accurate shifts, but the calculation procedure can be tuned  
511 by overriding default inputs like the level of theory and solvation model. Factors such as the choice  
512 of the force field used to identify the type of speciation in solution, DFT level of theory, implicit  
513 solvation model, and conformer sampling are critical in determining the accuracy of predictions  
514 made by the framework. We have successfully applied the framework to calculate chemical shifts  
515 in a complex multicomponent  $\text{Mg}(\text{TFSI})_2/\text{DME}$  solution and resolved the discrepancy in the  
516 literature regarding the  $\text{Mg}^{2+}$  solvation structure in this solution. Our results show formation of  
517 solvent separated ion pairs in this electrolyte which is consistent with the experimental NMR  
518 results reported in this work and the previously reported SCXRD results<sup>26</sup>. The benchmark test  
519 case shows that our procedure can generate reliable results that can facilitate NMR deconvolution  
520 assignments to determine ionic association interactions within liquid solutions similar to those  
521 reported in this work. An extension of this framework is under development and will be  
522 successfully added to the existing one. Features that will be supported include the ability to explore  
523 the role of the second solvation shell and coupling this strategy with a more detailed analysis of  
524 the exchange dynamics in the solution. In addition, support for performing automated polarizable  
525 CMD simulations using the thermalized Drude dipole method as implemented in LAMMPS will  
526 be added. The current and extended framework will be used to study other monovalent and  
527 multivalent electrolytes whose structure is not intuitive or when the chemical and parameter spaces  
528 are too large for human search using conventional non-automated methods. Data collected from  
529 the framework is expected to provide fingerprints to guide future experimental investigations of  
530 liquid solutions with optimal properties.

## 531 METHODS

### 532 Computational

533 CMD simulations are performed using the LAMMPS simulation package<sup>34</sup> version 3Mar2020  
534 (<http://lammps.sandia.gov>). Initial configurations of ions in the solvent are first obtained by  
535 randomly packing the molecules in a cubic box of size  $5 \times 5 \times 5 \text{ nm}^3$  with periodicity in XYZ  
536 directions using the PACKMOL package<sup>56</sup>. We consider MgTFSI<sub>2</sub> in DME at a salt-to-solvent  
537 ratio of 1:18. In FF1, *i.e.*, GAFF<sup>36</sup> parameterization, TFSI<sup>-</sup> and DME parameters are obtained by  
538 first generating the electrostatic potential of single molecules in Gaussian 16<sup>33</sup> at the B3LYP/6-  
539 31+G\* level of theory and fitting the electrostatic potential surface of the optimized structures  
540 using the RESP method in Antechamber<sup>57</sup>. AMBER force field parameters by Aqvist are used for  
541 Mg cations<sup>58</sup>. FF2, corresponding to the OPLS<sup>36</sup> force field, uses TFSI bonded parameters by  
542 Lopes/Pádua<sup>59</sup> and nonbonded parameters by Köddermann<sup>60</sup>. DME parameters are taken from the  
543 work of Anderson and Wilson<sup>61</sup> except for the parameters of C-C-O-C and O-C-C-O dihedrals,  
544 which are based on GAFF parameterization<sup>36</sup>. Lastly, based on FF2, we build FF3  
545 parameterization that includes polarization effects via the classical Drude oscillators model<sup>45,62</sup>.  
546 Drude particles are attached to all atoms, excluding hydrogen and Mg<sup>2+</sup> due to their relatively small  
547 polarizabilities. Atomic polarizabilities and charges for TFSI are based on the APPLE&P force  
548 field<sup>63</sup>, whereas those for DME are taken from work on poly(ethylene oxide)<sup>64</sup>. Nonbonded  
549 parameters for Mg<sup>2+</sup> cations are adapted from AMOEBA-PRO-13-FF<sup>65</sup>. Force field parameters  
550 used in this work are listed in Tables S3-S7.

551 Lennard Jones interactions are truncated at a cutoff distance of 1.2 nm, and the particle-particle  
552 particle-mesh (PPPM)<sup>66</sup> method is used to handle long-range electrostatic interactions. With FF3,  
553 a Thole damping factor<sup>67</sup> of 1.0 is used to smear the neighboring induced dipoles located on the

554 same molecule and prevent the 'polarization catastrophe'<sup>68</sup>. Initial structures are subjected to a two-  
555 step energy minimization, first using the steepest descent algorithm employing convergence  
556 criteria of 1,000 kcal/mol Å and then using a conjugated-gradient minimization scheme with an  
557 energy convergence criteria of 10 kcal/mol Å. The two-step minimization allows for the release of  
558 strained contacts in the initial configuration. Isothermal-isobaric simulations (NPT) are performed  
559 to obtain the correct density on the minimized system using a Nosé/Hoover temperature thermostat  
560 and pressure barostat to maintain the temperature at 298.15 K and the pressure at 1 atm for 2 ns.  
561 With FF3, Drude particles are thermalized at a lower temperature relative to Drude cores to avoid  
562 fast vibrations of the small reduced masses, thus allowing the use of a reasonable time step. The  
563 system is then melted to 500.15 K for 2 ns and subsequently quenched to 298.15 K for 3 ns.  
564 Following that, canonical ensemble (NVT) simulations are performed for 50 ns using a time step  
565 of 0.001 ps at 298.15 K to equilibrate the system. Molecular trajectories are sampled every 5 ps,  
566 resulting in 10,000 snapshots, from which properties of interest are calculated.

567 All DFT calculations are performed using Gaussian 16<sup>33</sup>. Magnetic shieldings are calculated  
568 for the extracted Mg<sup>2+</sup> clusters, ranging in size from 33 to 78 atoms. The benchmark study is  
569 performed with twelve combinations of functionals and basis sets (Fig 4) chosen due to their broad  
570 application in the NMR literature. An ultrafine integration grid is employed, and van der Waals  
571 interactions are treated using Grimme dispersion correction (D3)<sup>69</sup> with the B3LYP, M06-2X, and  
572 PBE1PBE functionals. Besides the explicit solvent model used in this work, bulk solvent effects  
573 are described using a continuum model, particularly PCM<sup>47-49</sup> or SMD<sup>54</sup>. Following the  
574 optimization and frequency steps, magnetic response calculations are performed using the gauge-  
575 independent atomic orbital (GIAO)<sup>70,71</sup> method at the same level of theory. Chemical shifts are  
576 converted to the experimentally observed scale using  $\delta_{cluster} = \sigma_{ref} - \sigma_{cluster}$ , where  $\delta_{cluster}$

577 and  $\sigma_{cluster}$  are the chemical shift and the isotropic shielding constant of the nucleus of interest in  
578 a given cluster, respectively, and  $\sigma_{ref}$  is the calculated isotropic shielding constant of the same  
579 nucleus in a suitable reference compound. We use an  $Mg^{2+}$  ion coordinated octahedrally by six  
580 water molecules, dimethyl sulfoxide, and water, as the chemical references for  $^{25}Mg$ ,  $^{13}C$ , and  $^1H$ ,  
581 respectively. To reduce systematic errors, we use secondary references (TMS) by adding 39.5 and  
582 4.7 ppm to the calculated chemical shifts of carbon and proton, respectively. These values  
583 correspond to the experimental chemical shifts of the secondary references relative to the primary  
584 standards. We again stress that all the steps described here are automated within our computational  
585 framework except for the polarizable CMD simulations.

## 586 **Experimental**

587  $Mg(TFSI)_2$  (99.5%, Solvionic) were dried for 48 hours under vacuum at 180 °C, and the DME  
588 solvent (Battery-grade, Gotion) was further dried over activated 3 Å molecular sieves in a  
589 glovebox until its water content was determined to be below 10 ppm using a Karl-Fisher Titrator  
590 (Metrohm).  $Mg(TFSI)_2/DME$  solutions were prepared inside a glovebox filled with nitrogen right  
591 before NMR measurements.  $^1H$  and  $^{13}C$  NMR measurements were performed on a Varian DDPS  
592 spectrometer with a 17.6 T magnet using a broad-band (BBO) probe with  $^1H$  and  $^{13}C$  Larmor  
593 frequencies of 748.1 and 188.1 MHz, respectively. The 90° pulse widths were 16  $\mu s$  for  $^1H$  and 16  
594  $\mu s$  for  $^{13}C$ .  $^1H$  spectra were collected using 30° pulses with a transition number of 16 and a recycle  
595 delay of 20 s with a coaxial tube holding  $Mg(TFSI)_2/DME$  solution and an outer NMR tube holding  
596  $D_2O$  (99.9%, from Sigma Aldrich) as an external reference at 4.77 ppm.  $^{13}C$  spectra were collected  
597 using 30° pulses with averaging of 1024 transients and a recycle delay of 12 s using a thin-wall 5  
598 mm NMR tube.  $^{25}Mg$  NMR spectra were collected at a 14.1 T magnet (Varian DDR spectrometer)  
599 with a  $^{25}Mg$  Larmor frequency of 36.7 MHz and a 90° pulse width of 20  $\mu s$ . A small tip angle of

600 15° with a recycle delay of 0.1 s was used and 128,000 transients were acquired. In order to  
601 minimize the spectrometer drift effect on chemical shift, DMSO-d<sub>6</sub> and 5 M MgCl<sub>2</sub> were used to  
602 reference <sup>13</sup>C (39.52 ppm) and <sup>25</sup>Mg (0 ppm), respectively, right before each NMR measurement.

### 603 **DATA AVAILABILITY**

604 The dataset used to generate the results in this work along with the optimized 3D structures in  
605 XYZ format are available in the repository at <https://github.com/rashatwi/nmr-dataset>.

### 606 **CODE AVAILABILITY**

607 The open-source LAMMPS-code is used in the CMD simulations while the proprietary Gaussian-  
608 code is primarily used in the DFT calculations. The framework shown in Fig 1 is implemented  
609 using the MISPR infrastructure, which defines, executes, manages, and stores DFT and CMD  
610 workflows. The codes used in this work will be made publicly available with the future release of  
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622 **AUTHOR CONTRIBUTIONS**

623 RA developed the automated NMR framework and the underlying Python-based codes, performed  
624 all the necessary calculations, and had primary writing responsibilities. YC and KSH carried the  
625 NMR experiments. VM and KTM guided the experimental aspect of the project. NNR guided and  
626 led all the computational aspects of the project. All authors contributed to writing and reviewing  
627 the manuscript.

628 **COMPETING INTERESTS**

629 The authors declare no competing interests.

630 **ADDITIONAL INFORMATION**

631 **Supplementary information:**

632 **Correspondence:**

633 Correspondence to Nav Nidhi Rajput.

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