Parameter Choice Matters: Validating Probe Parameters for Use in Mixed-Solvent Simulations

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Supporting Information

SI Table S1. Non-bonded parameters for MixMD probes.

| Atom Name | Amber Atom Type | IPASeco | IPAPLS |
|-----------|-----------------|---------|--------|
| C1,C2     | c3              | q       | σ*     | ε*     |
| C1,C3     | CT              | -0.176  | 1.908  | 0.1094 |
| C2        | CT              | 0.309   | 1.908  | 0.1094 |
| O2        | OH              | -0.612  | 1.721  | 0.2104 |
| HO2       | HO              | 0.373   | 0      | 0.418  |
| H11,H12,H13, H131,H32,H33 | HC | 0.049 | 1.487  | 0.0157 |
| H2        | H1              | -0.012  | 1.387  | 0.0157 |

* Note that the change in the typical capital letters for Atom Types was used to uniquely identify the solvent probes from the atom types used for protein atoms.

| Molecule | Atom | Atom Type* | q (e) | σ (Å) | ε (kcal/mol) |
|----------|------|------------|-------|-------|--------------|
| Acetone (ACE) | C1,C2 | c3 | -0.180 | 1.9640 | 0.0660 |
|           | H1-H6 | hc | 0.060 | 1.4031 | 0.0300 |
|           | O     | o  | -0.500 | 1.6612 | 0.2100 |
|           | C     | c  | 0.500 | 2.1050 | 0.1050 |
| N- Methylacetamide (NMA) | C1 | c3 | -0.180 | 1.9643 | 0.0660 |
|           | H1-H6 | h  | 0.060 | 1.4031 | 0.0300 |
|           | C     | c  | 0.500 | 2.1046 | 0.1050 |
|           | O     | o  | -0.500 | 1.6612 | 0.2100 |
|           | N     | n  | -0.500 | 1.8240 | 0.1700 |
|           | HN    | hn | 0.300 | 0.0000 | 0.0000 |
|           | C2    | c3 | 0.020 | 1.9643 | 0.0660 |
### SI Table S1. Continued

| Molecule       | Atom     | Atom Type* | q (e)  | σ (Å)  | ε (kcal/mol) |
|----------------|----------|------------|--------|--------|--------------|
| **Imidazole (IMI)** | N1       | nA/nB      | -0.257 | 1.8240 | 0.1700       |
|                | N2       | nA/nB      | -0.563 | 1.8240 | 0.1700       |
|                | C1       | cW         | -0.286 | 1.9923 | 0.0700       |
|                | C2       | cR         | 0.275  | 1.9923 | 0.0700       |
|                | C3       | cV         | 0.185  | 1.9923 | 0.0700       |
|                | H1       | h          | 0.306  | 0.0000 | 0.0000       |
|                | H2       | hA         | 0.187  | 1.3581 | 0.0300       |
|                | H3       | hA         | 0.078  | 1.3581 | 0.0300       |
|                | H4       | hA         | 0.075  | 1.3581 | 0.0300       |
| **Pyridine (PYR)** | N1       | nC         | -0.678 | 1.8240 | 0.1700       |
|                | C4-C5    | cA         | 0.473  | 1.9923 | 0.0700       |
|                | H4-H5    | hA         | 0.012  | 1.3581 | 0.0300       |
|                | C2-C3    | cA         | -0.447 | 1.9923 | 0.0700       |
|                | H2-H3    | hA         | 0.155  | 1.3581 | 0.0300       |
|                | C1       | cA         | 0.227  | 1.9923 | 0.0700       |
|                | H1       | hA         | 0.065  | 1.3581 | 0.0300       |
| **Pyridazine (1P2)** | N1-N2    | nC         | -0.331 | 1.8240 | 0.1700       |
|                | C3-C4    | cA         | 0.378  | 1.9923 | 0.0700       |
|                | H3-H4    | hA         | -0.009 | 1.3581 | 0.0300       |
|                | C1-C2    | cA         | -0.160 | 1.9923 | 0.0700       |
|                | H1-H2    | hA         | 0.122  | 1.3581 | 0.0300       |
| **Pyrimidine (1P3)** | N1-N2    | nC         | -0.839 | 1.8240 | 0.1700       |
|                | C4       | cQ         | 0.874  | 1.9923 | 0.0700       |
|                | H4       | hA         | -0.032 | 1.3581 | 0.0300       |
|                | C2-C3    | cA         | 0.653  | 1.9923 | 0.0700       |
|                | H2-H3    | hA         | 0.011  | 1.3581 | 0.0300       |
|                | C1       | cA         | -0.689 | 1.9923 | 0.0700       |
|                | H1       | hA         | 0.197  | 1.3581 | 0.0300       |
| **Pyrazine (1P4)** | N1-N2    | nC         | -0.468 | 1.8240 | 0.1700       |
|                | C1-C4    | cA         | 0.192  | 1.9923 | 0.0700       |
|                | H1-H4    | hA         | 0.0420 | 1.3581 | 0.0300       |
| **Benzene (BNZ)** | C1-C6    | cA         | -0.115 | 1.9923 | 0.0700       |
|                | H1-H6    | hA         | 0.115  | 1.3581 | 0.0300       |
| **Phenol (IPH)** | O1       | oH         | -0.585 | 1.7729 | 0.1700       |
|                | H6       | hO         | 0.435  | 0.0000 | 0.0000       |
|                | C1       | cA         | 0.150  | 1.9923 | 0.0700       |
|                | C2-C6    | cA         | -0.115 | 1.9923 | 0.0700       |
|                | H1-H5    | hA         | 0.115  | 1.3581 | 0.0300       |

* Note that the change in the typical capital letters for Atom Types was used to uniquely identify the solvent probes from the atom types used for protein atoms.
SI Figure S1: Two-dimensional representation of probe molecules.

Isopropanol (IPA)

Acetone (ACE)

Acetonitrile (ACN)

N-Methylacetamide (NMA)

Imidazole (IMI)
Pure-Solvent Simulations

Agreement of our probe parameters with experimental results (MSDS and CRC) was assessed by comparing the computational and experimental densities. The computational density was obtained from the simulation output for the average density over the 5-ns production run as generated by *sander*. All of the pure liquid simulations correctly reproduced the experimental density values within an accuracy of approximately 4% for all solvents except ACN, IMI, and 1P3 (SI SI Table S1). An error of 5.2% for ACN was expected since Grabuleda *et al.* obtained a calculated density of 0.736 g/mL (error of 5.2%) in their parameter development. The error of 7.3% for imidazole is misleading since the experimental density was obtained at a temperature of 374K, however the value is relevant as an illustration of the adequate reproduction of the fundamental behavior of the solvent. The computational densities for the same probe (ACE, IPA, or NMA) simulated from different parameters (AMBER or OPLS) demonstrated that the AMBER parameters reproduced experimental densities for pure solvent more closely. However, as we found with our studies of IPA+H2O, replication of the correct density in a pure solvent simulation was not an adequate justification for the use of a parameter set. As a result, RDF calculations of the distribution of probe density became the key metric for appropriate behavior of a solvent probe within a mixed-solvent setting.
**SI Table S1.** Comparison of density from MD simulation to experimental results.

| Probe                        | Calculated Density (g/mL) | Experimental Density$^a$ (g/mL) (CRC) | Error (%) |
|------------------------------|----------------------------|---------------------------------------|-----------|
| Isopropanol (IPA$^{OPLS}$)  | 0.8001±0.0051             | 0.7809                                | 2.5       |
| Isopropanol (IPA$^{Seco}$)  | 0.7809±0.0536             | 0.7809                                | 0         |
| Acetonitrile (ACN)           | 0.7359±0.0060             | 0.777$^b$                             | 5.3       |
| Acetone (ACE)*               | 0.8137±0.0041             | 0.7845                                | 3.7       |
| Acetone (ACE)$^†$            | 0.7795±0.0246             | 0.7845                                | 0.64      |
| N-Methylacetamide (NMA)*     | 0.9517±0.0043             | 0.9371                                | 1.6       |
| N-Methylacetamide (NMA)$^†$  | 0.9366±0.0068             | 0.9371                                | 0.053     |
| Imidazole (IMI)*             | 1.1053±0.0056             | 1.0303$^{374K}$                       | 7.3       |
| Pyridine (PYR)*              | 0.9647±0.0061             | 0.9819$^{293K}$                       | 1.8       |
| Pyridazine (1P2)*            | 1.0589±0.0040             | 1.1035$^{295K}$                       | 4.0       |
| Pyrimidine (1P3)*            | 1.0928±0.0059             | 1.0160                                | 7.6       |
| Pyrazine (1P4)*              | 1.0447±0.0046             | 1.0311$^{334K}$                       | 1.3       |
| Benzene (BNZ)*               | 0.8625±0.0066             | 0.8765$^{293K}$                       | 1.6       |
| Phenol (IPH)*                | 1.0368±0.0058             | 1.0545$^{318K}$                       | 1.7       |

$^a$ at 298K unless otherwise noted in superscript  
$^b$ compared to density used by Grabuleda et al.  
*OPLS parameters. †AMBER parameters.

**SI Table S3.** Composition of mixed-solvent boxes to achieve 50% w/w probe concentration.

| Solvent Box | No. of Probe Molecules | No. of Water Molecules |
|-------------|------------------------|------------------------|
| IPA/H$_2$O  | 828                    | 2779                   |
| ACE/H$_2$O  | 960                    | 3061                   |
| NMA/H$_2$O  | 640                    | 2567                   |
| IMI/H$_2$O  | 727                    | 2743                   |
| PYR/H$_2$O  | 641                    | 2804                   |
| 1P2/H$_2$O  | 620                    | 2726                   |
| 1P3/H$_2$O  | 626                    | 2797                   |
| 1P4/H$_2$O  | 633                    | 2827                   |
| BNZ/H$_2$O  | 602                    | 2688                   |
| IPH/H$_2$O  | 506                    | 2655                   |
SI Figure S2. (A) N-N radial distribution function for ACN probe and (B) O-O radial distribution function for water in a mixed-solvent environment, both of which show that appropriate convergence to unity was observed for ACN+H₂O.

SI Figure S3. (A) O-O radial distribution function for ACE probe, (B) N-N radial distribution function for ACN probe, and (C) O-O radial distribution function for water in a mixed-solvent environment composed of ACE+ACN+H₂O. Convergence to unity was seen for all three solvent probe types.