

# Assessing the Accuracy and Efficacy of Multiscale Computational Methods in Predicting Reaction Mechanisms and Kinetics of S<sub>N</sub>2 Reactions and Claisen Rearrangement

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## 1. Further details about the ORCA program

The ORCA project originated in the mid-1990s as an internal initiative aimed at understanding specific characteristics in the spectroscopy of open-shell transition metal complexes.<sup>1</sup> Since then, it has matured into a versatile chemistry software suite, widely adopted by an academic user base exceeding 40,000 individuals. Citation metrics underscore ORCA's position as the second most widely used QM program currently available. ORCA distinguishes itself with several notable features, including state-of-the-art performance, a comprehensive theoretical framework, a user-friendly interface, and platform independence. These attributes collectively enable efficient computational studies spanning diverse domains of chemistry.

## 2. A sample ORCA input file for performing QM/MM calculations

```
# ORCA's input file for performing QM/MM calculations.
# This file is generated by a home-made Python program (pdbtoorca) by Mehdi and Maryam.
# The program is for free. However, cite it as follows, if you use it in your project.
# DOI: .....
# The working directory is: /home/zafari/met/test20
# The setup time and date are 18:44:16 and 2023-08-01, respectively.
! RIJCOSX TPSSH def2-SVP def2/J D3BJ TIGHTSCF Opt
!QMMM
%qmmm
ORCAFFFilename "prmtop.ORCAFF.prms"
# Excluding junctions, 34 atoms are included in the QM system, as follows.
QMatoms {0:33 } end
Use_QM_InfoFromPDB false
# The thickness of the active region is 4.0 angstroms (from the QM system). A total of 226 atoms are included in the active
region, as follows.
ActiveAtoms {0:33 112:117 136:141 172:177 196:201 232:237 436:441 466:471 496:501 568:573 640:645 658:663
748:753 838:849 994:999 1036:1041 1270:1275 1462:1467 1498:1503 1516:1521 1594:1599 1606:1611 1618:1623
1636:1641 1738:1749 1798:1803 1810:1815 1834:1839 1846:1851 2062:2067 2170:2175} end
Use_Active_InfoFromPDB false
# An extension shell of 2.5-angstrom thickness will surround the active region.
# There are 2446 atoms in your PDB file, from which 226 atoms are included in the active region and 240 atoms are
included in the extension shell. Hence, 1980 atoms will be ignored in the calculations.
OptRegion_FixedAtoms {52:57 64:69 76:87 94:99 214:219 238:243 274:279 364:369 454:459 520:525 598:603 718:723
790:795 814:819 892:897 1000:1011 1120:1125 1180:1185 1246:1251 1300:1305 1384:1389 1408:1413 1432:1437
1450:1455 1492:1497 1774:1779 1942:1959 2008:2013 2044:2049 2056:2061 2176:2181 2230:2235 2254:2259
2278:2283 2326:2331 2404:2409} end
end
% geom scan
B 0 10 = 4.3, 1.4, 19
end
end
% pal
nprocs
4
end
*pdbfile -1 1 orcapdb.pdb
```

### 3. Geometrical parameters for the S<sub>N</sub>2 reactions from the employed methods

Table S1. Geometrical parameters obtained from the multiscale methods employed in studying the reaction between NH<sub>2</sub>OH and methyl iodide for the Re, TS, and Pr states. Distances are expressed in Å, and the NCI angles are in degrees. The optimization procedure is performed with electrostatic embedding. The row below the QM/MM block represents the thickness of the MM-active region around the QM region (the number before the slash) and the thickness of the MM-fixed region around the MM active region (the number after the slash). The numbers below the QM1/QM2 block represent the thickness of the QM2 region around the QM1 region. For the QM1/QM2/MM calculations, the thicknesses of the QM2, MM active, and MM fixed regions are set at 4.5, 3.0, and 2.5, respectively. All the values for the thickness of the QM2, MM-active, and MM-fixed regions are in Å.

|      | QM/MM     |       |      |         |       |      |         |       |      | QM1/QM2 |       |      |      |       |      | QM1/QM2/MM |       |      |
|------|-----------|-------|------|---------|-------|------|---------|-------|------|---------|-------|------|------|-------|------|------------|-------|------|
|      | 10.00/0.0 |       |      | 7.5/2.5 |       |      | 5.0/5.0 |       |      | 4.5     |       |      | 7.5  |       |      |            |       |      |
|      | Re        | TS    | Pr   | Re      | TS    | Pr   | Re      | TS    | Pr   | Re      | TS    | Pr   | Re   | TS    | Pr   | Re         | TS    | Pr   |
| O-N  | 1.43      | 1.44  | 1.40 | 1.43    | 1.46  | 1.40 | 1.43    | 1.47  | 1.41 | 1.43    | 1.48  | 1.42 | 1.44 | 1.45  | 1.40 | 1.42       | 1.42  | 1.40 |
| N-C  |           | 2.11  | 1.47 |         | 2.20  | 1.50 |         | 2.17  | 1.50 |         | 2.10  | 1.50 |      | 2.10  | 1.50 |            | 1.90  | 1.70 |
| C-I  | 2.17      | 2.44  |      | 2.16    | 2.28  |      | 2.16    | 2.29  |      | 2.14    | 2.18  |      | 2.18 | 2.35  |      | 2.14       | 2.82  |      |
| <NCI |           | 167.3 |      |         | 177.8 |      |         | 177.9 |      |         | 154.7 |      |      | 165.7 |      |            | 176.2 |      |

Table S2. Geometrical parameters obtained from the multiscale methods employed in studying the reaction between NH<sub>2</sub>O<sup>-</sup> and methyl iodide for the Re, TS, and Pr states. Distances are expressed in Å, and the NCI angles are in degrees. The optimization procedure is performed with electrostatic embedding. The row below the QM/MM block represents the thickness of the MM active region around the QM region (the number before the slash) and the thickness of the MM fixed region around the MM active region (the number after the slash). The numbers below the QM1/QM2 block represent the thickness of the QM2 region around the QM1 region. For the QM1/QM2/MM calculations, the thicknesses of the QM2, MM active, and MM fixed regions are set at 4.5, 3.0, and 2.5, respectively. All the values for the thickness of the QM2, MM-active, and MM-fixed regions are in Å.

|      | QM/MM     |       |      |         |       |      |         |       |      | QM1/QM2 |       |      |      |       |      | QM1/QM2/MM |       |      |
|------|-----------|-------|------|---------|-------|------|---------|-------|------|---------|-------|------|------|-------|------|------------|-------|------|
|      | 10.00/0.0 |       |      | 7.5/2.5 |       |      | 5.0/5.0 |       |      | 4.5     |       |      | 7.5  |       |      |            |       |      |
|      | Re        | TS    | Pr   | Re      | TS    | Pr   | Re      | TS    | Pr   | Re      | TS    | Pr   | Re   | TS    | Pr   | Re         | TS    | Pr   |
| O-N  | 1.45      | 1.44  | 1.39 | 1.44    | 1.46  | 1.38 | 1.44    | 1.46  | 1.38 | 1.41    | 1.39  | 1.38 | 1.41 | 1.40  | 1.38 | 1.44       | 1.44  | 1.39 |
| N-C  |           | 2.25  | 1.49 |         | 2.22  | 1.49 |         | 2.21  | 1.50 |         | 2.30  | 1.50 |      | 2.50  | 1.50 |            | 2.30  | 1.50 |
| C-I  | 2.16      | 2.35  |      | 2.17    | 2.28  |      | 2.17    | 2.28  |      | 2.17    | 2.27  |      | 2.17 | 2.23  |      | 2.16       | 2.27  |      |
| <NCI |           | 165.3 |      |         | 163.2 |      |         | 163.5 |      |         | 168.7 |      |      | 152.9 |      |            | 167.4 |      |

#### 4. Geometrical parameters for the Claisen rearrangement from the employed methods

Table S3. Key distances (in Å) obtained from QM-only and the QM/MM method with electrostatic embedding used to study the Claisen rearrangement for the Re, TS, and Pr states. The last row represents MAD values with respect to the QM-only structure.

|       |         |      |      | QM/MM |      |      |        |      |      |        |      |      |        |      |      |      |      |      |
|-------|---------|------|------|-------|------|------|--------|------|------|--------|------|------|--------|------|------|------|------|------|
|       | QM-only |      |      | Water |      |      | 25%Met |      |      | 50%Met |      |      | 75%Met |      |      | Met  |      |      |
|       | Re      | TS   | Pr   | Re    | TS   | Pr   | Re     | TS   | Pr   | Re     | TS   | Pr   | Re     | TS   | Pr   | Re   | TS   | Pr   |
| C1-C5 |         | 2.27 | 1.54 |       | 2.35 | 1.55 |        | 2.20 | 1.56 |        | 2.33 | 1.56 |        | 2.33 | 1.54 |      | 2.21 | 1.54 |
| C3-O  | 1.43    | 2.55 |      | 1.45  | 2.45 |      | 1.45   | 2.45 |      | 1.45   | 2.39 |      | 1.45   | 2.46 |      | 1.45 | 2.45 |      |
| C4-C5 | 1.34    | 1.36 | 1.50 | 1.34  | 1.34 | 1.50 | 1.34   | 1.34 | 1.50 | 1.34   | 1.34 | 1.50 | 1.34   | 1.34 | 1.51 | 1.34 | 1.34 | 1.50 |
| C3-C4 | 1.51    | 1.47 | 1.34 | 1.50  | 1.50 | 1.34 | 1.50   | 1.50 | 1.34 | 1.50   | 1.50 | 1.34 | 1.50   | 1.50 | 1.34 | 1.51 | 1.51 | 1.34 |
| C2-O  | 1.35    | 1.33 | 1.21 | 1.37  | 1.37 | 1.22 | 1.36   | 1.36 | 1.22 | 1.36   | 1.36 | 1.22 | 1.36   | 1.35 | 1.22 | 1.36 | 1.36 | 1.21 |
| C1-C2 | 1.34    | 1.35 | 1.51 | 1.34  | 1.34 | 1.50 | 1.34   | 1.34 | 1.51 | 1.34   | 1.34 | 1.50 | 1.34   | 1.35 | 1.50 | 1.34 | 1.34 | 1.51 |
| MAD   | 0.00    | 0.00 | 0.00 | 0.01  | 0.05 | 0.01 | 0.01   | 0.04 | 0.01 | 0.01   | 0.05 | 0.01 | 0.01   | 0.04 | 0.01 | 0.01 | 0.04 | 0.00 |

Table S4. Key distances (in Å) obtained from the QM1/QM2 method with electrostatic embedding used to study the Claisen rearrangement for the Re, TS, and Pr states. The final row indicates MAD relative to the QM-only structure.

|       | QM1/QM2 |      |      |        |      |      |        |      |      |        |      |      |      |      |      |
|-------|---------|------|------|--------|------|------|--------|------|------|--------|------|------|------|------|------|
|       | Water   |      |      | 25%Met |      |      | 50%Met |      |      | 75%Met |      |      | Met  |      |      |
|       | Re      | TS   | Pr   | Re     | TS   | Pr   | Re     | TS   | Pr   | Re     | TS   | Pr   | Re   | TS   | Pr   |
| C1-C5 |         | 2.44 | 1.56 |        | 2.20 | 1.54 |        | 2.33 | 1.56 |        | 2.64 | 1.57 |      | 2.21 | 1.54 |
| C3-O  | 1.46    | 2.54 |      | 1.45   | 2.45 |      | 1.45   | 2.45 |      | 1.46   | 1.50 |      | 1.45 | 2.45 |      |
| C4-C5 | 1.33    | 1.35 | 1.49 | 1.34   | 1.34 | 1.50 | 1.34   | 1.34 | 1.50 | 1.34   | 1.34 | 1.50 | 1.34 | 1.35 | 1.51 |
| C3-C4 | 1.50    | 1.48 | 1.34 | 1.50   | 1.50 | 1.35 | 1.50   | 1.50 | 1.35 | 1.50   | 1.49 | 1.34 | 1.50 | 1.51 | 1.35 |
| C2-O  | 1.37    | 1.37 | 1.22 | 1.35   | 1.35 | 1.22 | 1.36   | 1.36 | 1.22 | 1.34   | 1.35 | 1.22 | 1.35 | 1.35 | 1.22 |
| C1-C2 | 1.34    | 1.34 | 1.49 | 1.34   | 1.34 | 1.50 | 1.34   | 1.34 | 1.50 | 1.35   | 1.34 | 1.49 | 1.35 | 1.35 | 1.51 |
| MAD   | 0.01    | 0.04 | 0.01 | 0.01   | 0.04 | 0.01 | 0.01   | 0.04 | 0.01 | 0.01   | 0.25 | 0.01 | 0.01 | 0.04 | 0.01 |

Table S5. Key distances (in Å) obtained from the QM1/QM2/MM method with electrostatic embedding used to study the Claisen rearrangement for the Re, TS, and Pr states. The final row indicates MAD relative to the QM-only structure.

|       | QM1/QM2/MM |      |      |        |      |      |        |      |      |        |      |      |      |      |      |
|-------|------------|------|------|--------|------|------|--------|------|------|--------|------|------|------|------|------|
|       | Water      |      |      | 25%Met |      |      | 50%Met |      |      | 75%Met |      |      | Met  |      |      |
|       | Re         | TS   | Pr   | Re     | TS   | Pr   | Re     | TS   | Pr   | Re     | TS   | Pr   | Re   | TS   | Pr   |
| C1-C5 |            | 2.20 | 1.54 |        | 2.39 | 1.57 |        | 2.28 | 1.57 |        | 1.81 | 1.54 |      | 2.21 | 1.55 |
| C3-O  | 1.44       | 2.44 |      | 1.45   | 2.45 |      | 1.45   | 2.45 |      | 1.45   | 3.36 |      | 1.45 | 2.45 |      |
| C4-C5 | 1.34       | 1.34 | 1.50 | 1.34   | 1.34 | 1.50 | 1.34   | 1.34 | 1.50 | 1.34   | 1.48 | 1.50 | 1.34 | 1.34 | 1.51 |
| C3-C4 | 1.50       | 1.50 | 1.34 | 1.50   | 1.50 | 1.34 | 1.50   | 1.50 | 1.34 | 1.50   | 1.34 | 1.34 | 1.50 | 1.50 | 1.34 |
| C2-O  | 1.36       | 1.36 | 1.21 | 1.36   | 1.36 | 1.21 | 1.36   | 1.36 | 1.21 | 1.36   | 1.22 | 1.21 | 1.35 | 1.36 | 1.21 |
| C1-C2 | 1.34       | 1.34 | 1.50 | 1.34   | 1.34 | 1.51 | 1.34   | 1.34 | 1.51 | 1.35   | 1.48 | 1.50 | 1.34 | 1.34 | 1.51 |
| MAD   | 0.00       | 0.05 | 0.00 | 0.01   | 0.05 | 0.01 | 0.01   | 0.03 | 0.01 | 0.01   | 0.29 | 0.00 | 0.01 | 0.04 | 0.00 |

Table S6. Key distances (in Å) obtained from QM-only and the QM/MM method with mechanical embedding used to study the Claisen rearrangement for the Re, TS, and Pr states. The final row indicates MAD relative to the QM-only structure.

|       |         |      |      | QM/MM |      |      |        |      |      |        |      |      |        |      |      |      |      |      |
|-------|---------|------|------|-------|------|------|--------|------|------|--------|------|------|--------|------|------|------|------|------|
|       | QM-only |      |      | Water |      |      | 25%Met |      |      | 50%Met |      |      | 75%Met |      |      | Met  |      |      |
|       | Re      | TS   | Pr   | Re    | TS   | Pr   | Re     | TS   | Pr   | Re     | TS   | Pr   | Re     | TS   | Pr   | Re   | TS   | Pr   |
| C1-C5 |         | 2.27 | 1.54 |       | 2.35 | 1.55 |        | 2.19 | 1.55 |        | 2.32 | 1.55 |        | 2.32 | 1.54 |      | 2.20 | 1.53 |
| C3-O  | 1.43    | 2.55 |      | 1.44  | 1.55 |      | 1.44   | 1.60 |      | 1.45   | 1.53 |      | 1.45   | 1.55 |      | 1.45 | 1.61 |      |
| C4-C5 | 1.34    | 1.36 | 1.50 | 1.33  | 1.34 | 1.50 | 1.33   | 1.37 | 1.50 | 1.33   | 1.35 | 1.50 | 1.33   | 1.35 | 1.50 | 1.33 | 1.37 | 1.50 |
| C3-C4 | 1.51    | 1.47 | 1.34 | 1.5   | 1.47 | 1.34 | 1.50   | 1.46 | 1.34 | 1.50   | 1.48 | 1.34 | 1.50   | 1.48 | 1.34 | 1.51 | 1.46 | 1.34 |
| C2-O  | 1.35    | 1.33 | 1.21 | 1.35  | 1.35 | 1.21 | 1.35   | 1.32 | 1.21 | 1.35   | 1.34 | 1.21 | 1.35   | 1.34 | 1.21 | 1.35 | 1.32 | 1.21 |
| C1-C2 | 1.34    | 1.35 | 1.51 | 1.34  | 1.35 | 1.50 | 1.34   | 1.37 | 1.52 | 1.34   | 1.35 | 1.51 | 1.34   | 1.35 | 1.51 | 1.34 | 1.37 | 1.52 |
| MAD   | 0.00    | 0.00 | 0.00 | 0.00  | 0.19 | 0.00 | 0.00   | 0.18 | 0.01 | 0.01   | 0.18 | 0.00 | 0.01   | 0.18 | 0.00 | 0.01 | 0.18 | 0.01 |

Table S7. Key distances (in Å) obtained from the QM1/QM2 method with mechanical embedding used to study the Claisen rearrangement for the Re, TS, and Pr states. The final row indicates MAD relative to the QM-only structure.

|       | QM1/QM2 |      |      |        |      |      |        |      |      |        |      |      |      |      |      |
|-------|---------|------|------|--------|------|------|--------|------|------|--------|------|------|------|------|------|
|       | Water   |      |      | 25%Met |      |      | 50%Met |      |      | 75%Met |      |      | Met  |      |      |
|       | Re      | TS   | Pr   | Re     | TS   | Pr   | Re     | TS   | Pr   | Re     | TS   | Pr   | Re   | TS   | Pr   |
| C1-C5 |         | 2.26 | 1.56 |        | 2.36 | 1.54 |        | 2.32 | 1.56 |        | 2.32 | 1.56 |      | 2.36 | 1.53 |
| C3-O  | 1.46    | 2.49 |      | 1.45   | 1.55 |      | 1.45   | 1.57 |      | 1.45   | 1.58 |      | 1.45 | 1.54 |      |
| C4-C5 | 1.33    | 1.41 | 1.49 | 1.33   | 1.34 | 1.50 | 1.33   | 1.35 | 1.50 | 1.33   | 1.35 | 1.49 | 1.33 | 1.35 | 1.50 |
| C3-C4 | 1.50    | 1.37 | 1.34 | 1.50   | 1.47 | 1.34 | 1.50   | 1.47 | 1.34 | 1.50   | 1.47 | 1.34 | 1.50 | 1.48 | 1.34 |
| C2-O  | 1.37    | 1.26 | 1.22 | 1.36   | 1.35 | 1.21 | 1.36   | 1.34 | 1.21 | 1.35   | 1.35 | 1.21 | 1.36 | 1.34 | 1.21 |
| C1-C2 | 1.34    | 1.41 | 1.48 | 1.34   | 1.35 | 1.50 | 1.34   | 1.35 | 1.49 | 1.35   | 1.35 | 1.49 | 1.34 | 1.35 | 1.51 |
| MAD   | 0.01    | 0.06 | 0.01 | 0.01   | 0.19 | 0.00 | 0.01   | 0.18 | 0.01 | 0.01   | 0.18 | 0.01 | 0.01 | 0.19 | 0.00 |

Table S8. Key distances (in Å) obtained from the QM1/QM2/MM method with mechanical embedding used to study the Claisen rearrangement for the Re, TS, and Pr states. The final row indicates MAD relative to the QM-only structure.

|       | QM1/QM2/MM |      |      |        |      |      |        |      |      |        |      |      |      |      |      |
|-------|------------|------|------|--------|------|------|--------|------|------|--------|------|------|------|------|------|
|       | Water      |      |      | 25%Met |      |      | 50%Met |      |      | 75%Met |      |      | Met  |      |      |
|       | Re         | TS   | Pr   | Re     | TS   | Pr   | Re     | TS   | Pr   | Re     | TS   | Pr   | Re   | TS   | Pr   |
| C1-C5 |            | 2.26 | 1.54 |        | 2.38 | 1.56 |        | 2.27 | 1.56 |        | 2.22 | 1.54 |      | 2.20 | 1.54 |
| C3-O  | 1.44       | 1.56 |      | 1.44   | 1.53 |      | 1.44   | 1.57 |      | 1.45   | 1.63 |      | 1.44 | 1.64 |      |
| C4-C5 | 1.33       | 1.35 | 1.49 | 1.33   | 1.35 | 1.50 | 1.33   | 1.36 | 1.50 | 1.33   | 1.36 | 1.50 | 1.33 | 1.36 | 1.50 |
| C3-C4 | 1.50       | 1.47 | 1.34 | 1.50   | 1.48 | 1.34 | 1.50   | 1.47 | 1.34 | 1.50   | 1.46 | 1.34 | 1.50 | 1.45 | 1.34 |
| C2-O  | 1.35       | 1.33 | 1.20 | 1.36   | 1.35 | 1.20 | 1.36   | 1.34 | 1.20 | 1.36   | 1.32 | 1.21 | 1.35 | 1.31 | 1.20 |
| C1-C2 | 1.34       | 1.35 | 1.50 | 1.34   | 1.35 | 1.51 | 1.34   | 1.36 | 1.51 | 1.34   | 1.36 | 1.50 | 1.34 | 1.37 | 1.51 |
| MAD   | 0.00       | 0.17 | 0.01 | 0.01   | 0.20 | 0.01 | 0.01   | 0.17 | 0.01 | 0.01   | 0.17 | 0.00 | 0.00 | 0.17 | 0.00 |

## 5. Graphs of experimental dielectric constants and densities of methanol/water mixture versus the mass percentage of methanol

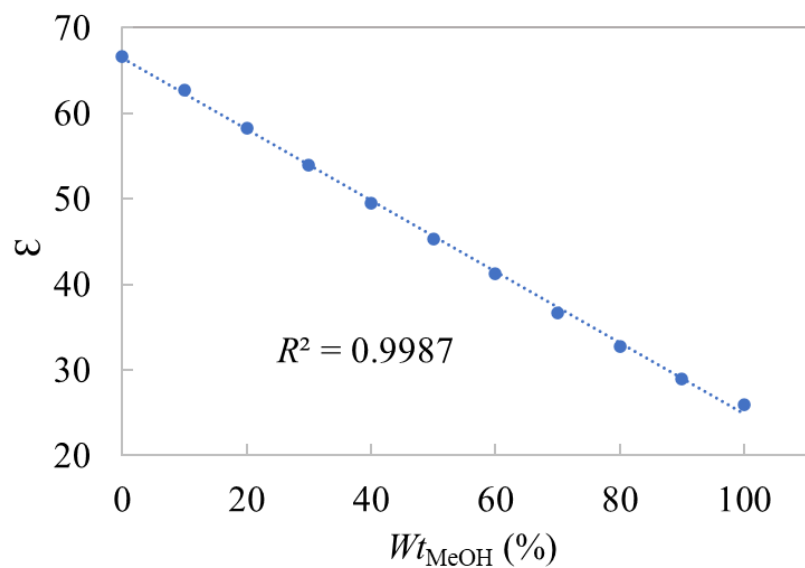


Figure S1. Dielectric constants ( $\epsilon$ ) versus methanol mass percentage for methanol/water mixtures. The experimental data were obtained from the work of Gösta Åkerlöf at 60 °C.<sup>2</sup>

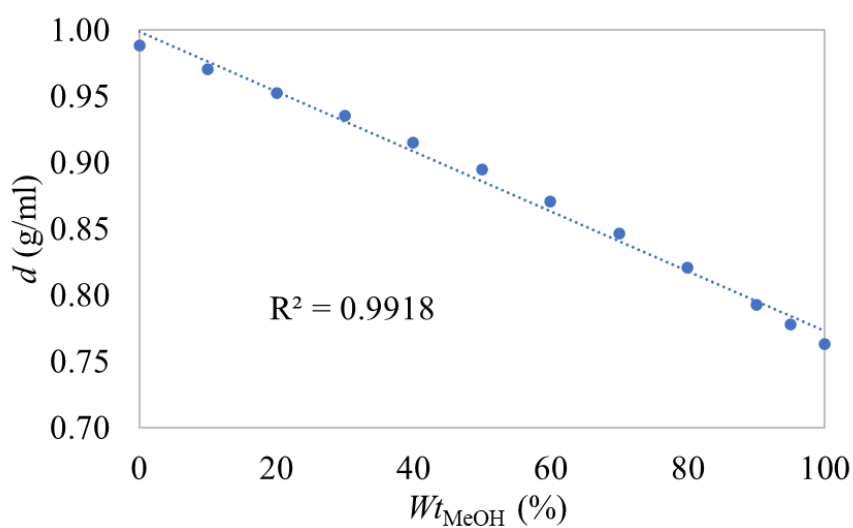


Figure S2. Density versus methanol mass percentage for methanol/water mixtures. The experimental data were obtained from the work of S. Z. Mikhail and W. R. Kimel.<sup>3</sup>

## 6. Detailed GAFF parameters of the reactants

### 6.1 GAFF parameters for hydroxylamine (NH<sub>2</sub>OH)

This is a remark line

molecule.res

HAM INT 0

CORRECT OMIT DU BEG

0.0000

|   |      |    |   |   |    |    |       |         |          |           |
|---|------|----|---|---|----|----|-------|---------|----------|-----------|
| 1 | DUMM | DU | M | 0 | -1 | -2 | 0.000 | .0      | .0       | .00000    |
| 2 | DUMM | DU | M | 1 | 0  | -1 | 1.449 | .0      | .0       | .00000    |
| 3 | DUMM | DU | M | 2 | 1  | 0  | 1.523 | 111.21  | .0       | .00000    |
| 4 | N1   | n3 | M | 3 | 2  | 1  | 1.540 | 111.208 | -180.000 | -0.765002 |
| 5 | H1   | hn | E | 4 | 3  | 2  | 1.022 | 109.845 | -32.599  | 0.401944  |
| 6 | H2   | hn | E | 4 | 3  | 2  | 1.022 | 109.839 | -147.483 | 0.401944  |
| 7 | O1   | oh | M | 4 | 3  | 2  | 1.448 | 11.876  | -90.000  | -0.495460 |
| 8 | H3   | ho | E | 7 | 4  | 3  | 0.970 | 101.834 | 0.060    | 0.456574  |

LOOP

IMPROPER

DONE

STOP

### 6.2 GAFF parameters for methyl iodide (MEI)

This is a remark line

molecule.res

MEI INT 0

CORRECT OMIT DU BEG

0.0000

|   |      |    |   |   |    |    |       |         |          |           |
|---|------|----|---|---|----|----|-------|---------|----------|-----------|
| 1 | DUMM | DU | M | 0 | -1 | -2 | 0.000 | .0      | .0       | .00000    |
| 2 | DUMM | DU | M | 1 | 0  | -1 | 1.449 | .0      | .0       | .00000    |
| 3 | DUMM | DU | M | 2 | 1  | 0  | 1.523 | 111.21  | .0       | .00000    |
| 4 | C1   | c3 | M | 3 | 2  | 1  | 1.540 | 111.208 | -180.000 | -0.606799 |
| 5 | H1   | h1 | E | 4 | 3  | 2  | 1.088 | 107.320 | 124.134  | 0.237272  |
| 6 | H2   | h1 | E | 4 | 3  | 2  | 1.087 | 107.334 | -115.874 | 0.237272  |
| 7 | H3   | h1 | E | 4 | 3  | 2  | 1.088 | 107.324 | 4.141    | 0.237272  |
| 8 | I1   | i  | M | 4 | 3  | 2  | 2.187 | 0.000   | -90.000  | -0.105016 |

LOOP

IMPROPER

DONE

STOP



### 6.3 GAFF parameters for amine oxide anion ( $\text{NH}_2\text{O}^-$ )

This is a remark line

molecule.res

AMO INT 0

CORRECT OMIT DU BEG

0.0000

|   |      |    |   |   |    |    |       |         |          |           |
|---|------|----|---|---|----|----|-------|---------|----------|-----------|
| 1 | DUMM | DU | M | 0 | -1 | -2 | 0.000 | .0      | .0       | .00000    |
| 2 | DUMM | DU | M | 1 | 0  | -1 | 1.449 | .0      | .0       | .00000    |
| 3 | DUMM | DU | M | 2 | 1  | 0  | 1.523 | 111.21  | .0       | .00000    |
| 4 | N1   | n3 | M | 3 | 2  | 1  | 1.540 | 111.208 | -180.000 | -0.712723 |
| 5 | H1   | hn | E | 4 | 3  | 2  | 1.066 | 113.197 | -35.490  | 0.208064  |
| 6 | H2   | hn | E | 4 | 3  | 2  | 1.066 | 113.197 | -144.510 | 0.208064  |
| 7 | O1   | o  | M | 4 | 3  | 2  | 1.409 | 7.544   | -90.000  | -0.703406 |

LOOP

IMPROPER

DONE

STOP

## 6.4 GAFF parameters for 8-(vinylloxy)dec-9-enoate

This is a remark line

molecule.res

AEN INT 0

CORRECT OMIT DU BEG

0.0000

|    |      |    |   |    |    |    |       |         |          |           |
|----|------|----|---|----|----|----|-------|---------|----------|-----------|
| 1  | DUMM | DU | M | 0  | -1 | -2 | 0.000 | .0      | .0       | .00000    |
| 2  | DUMM | DU | M | 1  | 0  | -1 | 1.449 | .0      | .0       | .00000    |
| 3  | DUMM | DU | M | 2  | 1  | 0  | 1.523 | 111.21  | .0       | .00000    |
| 4  | C1   | c2 | M | 3  | 2  | 1  | 1.540 | 111.208 | -180.000 | -0.635805 |
| 5  | H1   | ha | E | 4  | 3  | 2  | 1.084 | 139.375 | -49.020  | 0.220665  |
| 6  | H2   | ha | E | 4  | 3  | 2  | 1.084 | 94.286  | 165.424  | 0.220665  |
| 7  | C2   | c2 | M | 4  | 3  | 2  | 1.335 | 35.044  | 25.830   | 0.088235  |
| 8  | H3   | h4 | E | 7  | 4  | 3  | 1.091 | 121.911 | 47.157   | 0.140018  |
| 9  | O1   | os | M | 7  | 4  | 3  | 1.358 | 122.851 | -134.488 | -0.269663 |
| 10 | C3   | c3 | M | 9  | 7  | 4  | 1.439 | 116.613 | 168.301  | 0.329102  |
| 11 | H4   | h1 | E | 10 | 9  | 7  | 1.103 | 108.326 | 37.055   | 0.030768  |
| 12 | C4   | c2 | B | 10 | 9  | 7  | 1.505 | 108.403 | 154.432  | -0.217616 |
| 13 | H5   | ha | E | 12 | 10 | 9  | 1.089 | 114.243 | -178.520 | 0.146086  |
| 14 | C5   | c2 | B | 12 | 10 | 9  | 1.332 | 125.735 | 1.615    | -0.390546 |
| 15 | H6   | ha | E | 14 | 12 | 10 | 1.087 | 121.049 | 179.624  | 0.168788  |
| 16 | H7   | ha | E | 14 | 12 | 10 | 1.085 | 121.507 | -0.435   | 0.168788  |
| 17 | C6   | c3 | M | 10 | 9  | 7  | 1.541 | 110.096 | -81.148  | -0.269856 |
| 18 | H8   | hc | E | 17 | 10 | 9  | 1.098 | 108.204 | -62.055  | 0.086083  |
| 19 | H9   | hc | E | 17 | 10 | 9  | 1.099 | 107.350 | 52.659   | 0.086083  |
| 20 | C7   | c3 | M | 17 | 10 | 9  | 1.535 | 114.558 | 173.912  | 0.005898  |
| 21 | H10  | hc | E | 20 | 17 | 10 | 1.100 | 110.040 | 65.219   | 0.046396  |
| 22 | H11  | hc | E | 20 | 17 | 10 | 1.097 | 109.644 | -51.165  | 0.046396  |
| 23 | C8   | c3 | M | 20 | 17 | 10 | 1.536 | 112.890 | -173.186 | -0.081685 |
| 24 | H12  | hc | E | 23 | 20 | 17 | 1.101 | 108.879 | 58.730   | 0.016615  |
| 25 | H13  | hc | E | 23 | 20 | 17 | 1.102 | 108.703 | -56.390  | 0.016615  |
| 26 | C9   | c3 | M | 23 | 20 | 17 | 1.539 | 113.955 | -179.208 | -0.088914 |
| 27 | H14  | hc | E | 26 | 23 | 20 | 1.101 | 108.992 | 58.620   | 0.010237  |
| 28 | H15  | hc | E | 26 | 23 | 20 | 1.101 | 108.274 | 173.101  | 0.010237  |
| 29 | C10  | c3 | M | 26 | 23 | 20 | 1.536 | 114.756 | -64.424  | 0.159787  |
| 30 | H16  | hc | E | 29 | 26 | 23 | 1.096 | 111.724 | 60.706   | -0.027162 |
| 31 | H17  | hc | E | 29 | 26 | 23 | 1.102 | 108.831 | -55.576  | -0.027162 |
| 32 | C11  | c3 | M | 29 | 26 | 23 | 1.529 | 114.950 | -178.662 | -0.214286 |
| 33 | H18  | hc | E | 32 | 29 | 26 | 1.104 | 108.988 | -48.481  | 0.010802  |
| 34 | H19  | hc | E | 32 | 29 | 26 | 1.099 | 111.646 | 68.444   | 0.010802  |
| 35 | C12  | c  | M | 32 | 29 | 26 | 1.581 | 113.343 | -167.880 | 0.841445  |
| 36 | O3   | o  | E | 35 | 32 | 29 | 1.259 | 115.172 | 28.700   | -0.818909 |
| 37 | O2   | o  | M | 35 | 32 | 29 | 1.254 | 115.023 | -152.995 | -0.818909 |

LOOP

IMPROPER

C2 H1 C1 H2

C1 H3 C2 O1

C5 C3 C4 H5

C4 H6 C5 H7

C11 O3 C12 O2

DONE

STOP

## 7. An input file of (*packmol.inp*) water/methanol solvent with weight percentages of 50/50% for the Packmol package

```
# This determines the minimum distance between molecules. The default value is 2 angstroms.
tolerance 2.0
# Specify the file format (PDB).
filetype pdb
# Output file name
output r1-Methanol.pdb
# Assign the solute file.
structure AEN.pdb
# Assign a number to the solute molecule (1 in this instance).
number 1
# Place the solution's center of mass in the center of the box.
# These values relate to the -x, -y, -z, x, y, and z values of the center of mass.
# Alternatively, you may change them.
fixed 15. 15. 15. 0. 0. 0.
centerofmass
end structure
# add first type of solvent molecules
structure MET.pdb
number 224
inside cube 0. 0. 0. 30
end structure

# add second type of solvent molecules
structure WAT.pdb
number 402
inside cube 0. 0. 0. 30
end structure# Identify the cubic box's coordinates (-x, -y, -z, x, y, and z values).
inside box -15. -15. -15. 15. 15. 15.
end structure
```

## 8. References

- (1) Neese, F. *Electronic Structure and Spectroscopy of Novel Copper Chromophores in Biology*; UFO, Atelier für Gestaltung und Verlag, 1997.
- (2) Åkerlöf, G. Dielectric Constants of Some Organic Solvent-Water Mixtures at Various Temperatures. *J. Am. Chem. Soc.* **1932**, 54 (11), 4125–4139. <https://doi.org/10.1021/ja01350a001>.
- (3) Mikhail, S. Z.; Kimel, W. R. Densities and Viscosities of Methanol-Water Mixtures. *J. Chem. Eng. Data* **1961**, 6 (4), 533–537. <https://doi.org/10.1021/je60011a015>.