Supporting Information: Solvent Effect on the Syn/Anti Conformational Stability: A Comparison Between Conformational Bias Monte Carlo and Molecular Dynamics Methods

Henrique Musseli Cezar, Sylvio Canuto, Kaline Coutinho*
Instituto de Física, Universidade de São Paulo, São Paulo, Brazil

*Corresponding address: kaline@if.usp.br

Similar to the Figure 3 of the paper, Figure S1 shows the total rotational energy profile (including the bonded and nonbonded potential terms presented in Equations 7-11) around the C6 − C1=C2 − C3 double bond, showing a stiff potential as discussed in the main text, Section 3.2.

Figures S2 and S3 shows the sampling for the two extra MD simulations performed independently, of 150 ns each one to analyze the conformational changes.

In Tables S1 to S5 the parameters of the force field used to perform the simulations are shown.

Tables S6 and S7 highlight the parameters that were adjusted to obtain the right energy difference for the *syn* and *anti* conformations in gas phase, according to the *ab initio* calculations.

The input files used to perform the simulations in DICE and GROMACS are appended in the end of this Supporting Information.

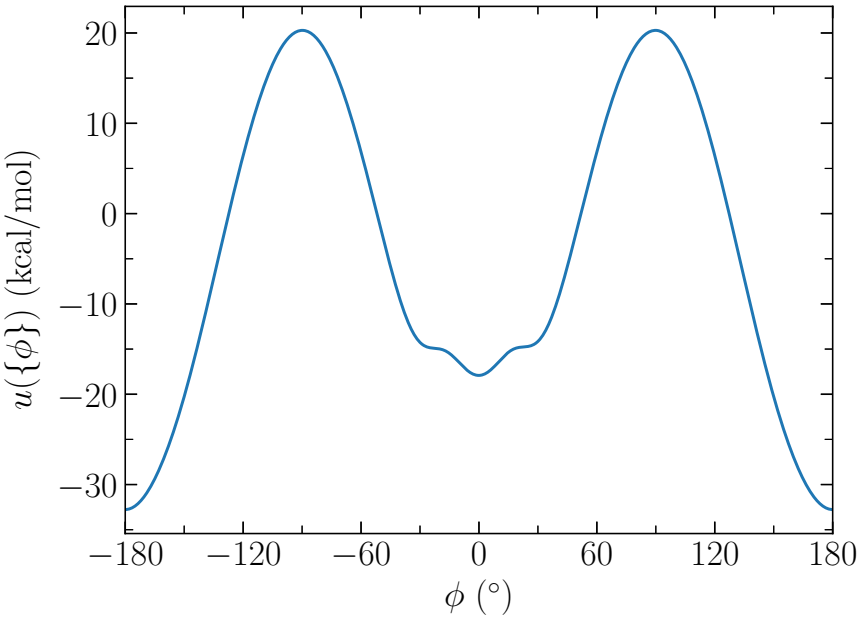

Figure S1: Torsional energy for the rotation of the rigid molecule around the C6−C1=C2−C3 double bond. This energy takes into account all the bonded and nonbonded contributions to the energy.

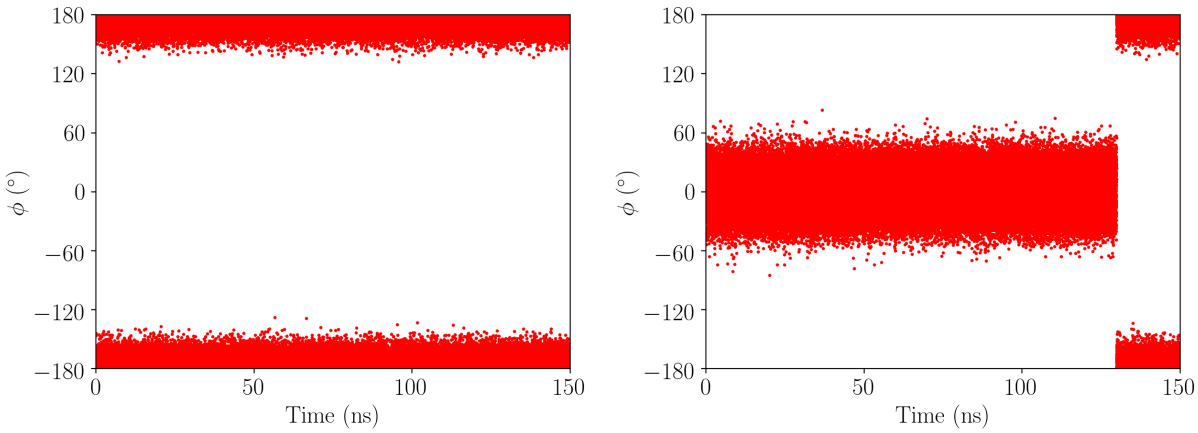

Figure S2: Evolution of the C=C−C=O dihedral for an independent MD simulations (started with different velocities) of MOx in water, starting from the *anti* (left) and *syn* (right) configurations.

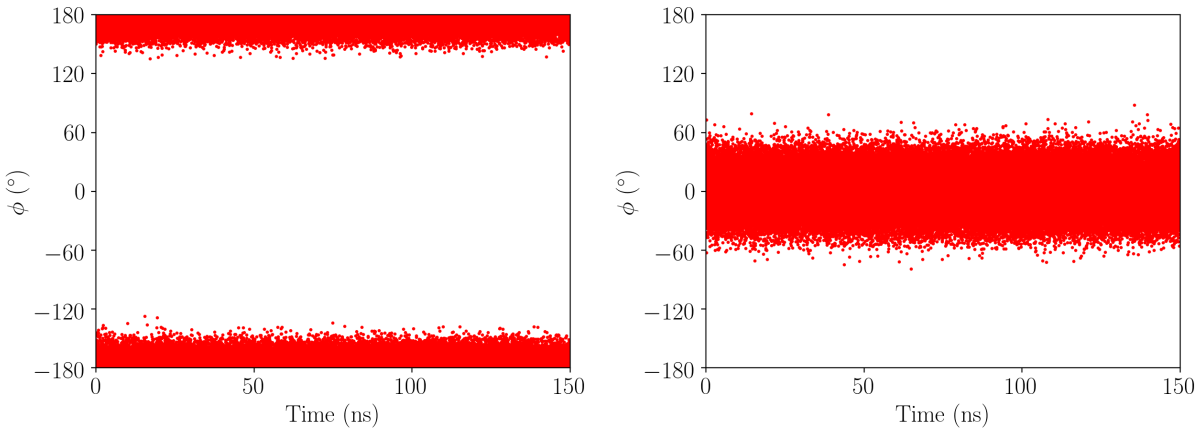

Figure S3: Evolution of the C=C−C=O dihedral for an independent MD simulations (started with different velocities) of MOx in water, starting from the *anti* (left) and *syn* (right) configurations.

Table S1: Nonbonded parameters

atom	q (e)	ϵ (kcal/mol)	σ (Å)
C1	0.40	0.076	3.55
C2	−0.60	0.076	3.55
C3	0.77	0.105	3.75
O4	−0.75	0.210	2.96
C5	−0.30	0.066	3.50
C6	−0.30	0.066	3.50
C7	−0.30	0.066	3.50
H8	0.18	0.030	2.42
H9	0.10	0.015	2.42
H10	0.10	0.015	2.42
H11	0.10	0.015	2.42
H12	0.10	0.030	2.50
H13	0.10	0.030	2.50
H14	0.10	0.030	2.50
H15	0.10	0.030	2.50
H16	0.10	0.030	2.50
H17	0.10	0.030	2.50

Table S2: Bond parameters

bond	K_{r}(kcal/mol)	r_{eq} (Å)
C1−C7	317.0	1.5080
C1−C6	317.0	1.5120
C1=C2	549.0	1.3535
C2−H8	340.0	1.0889
C2−C3	410.0	1.4857
C3−C5	317.0	1.5202
C3=O4	570.0	1.2291
C5−H11	340.0	1.0923
C5−H10	340.0	1.0963
C5−H9	340.0	1.0963
C6−H14	340.0	1.0990
C6−H13	340.0	1.0990
C6−H12	340.0	1.0936
C7−H17	340.0	1.0989
C7−H16	340.0	1.0875
C7−H15	340.0	1.0990

Table S3: Angle parameters

angle	K_θ(kcal/mol)	θ_{eq} (°)
C1−C7−H17	35.0	109.7417
C1−C7−H16	35.0	114.7257
C1−C7−H15	35.0	109.7393
C1−C6−H14	35.0	110.6340
C1−C6−H13	35.0	110.6379
C1−C6−H12	35.0	112.2333
C1−C2−H8	35.0	117.0643
C1=C2−C3	85.0	133.0941
C2=C1−C7	70.0	128.0244
C2=C1−C6	70.0	118.8519
C2−C3−C5	70.0	123.5601
C2−C3=O4	80.0	117.4863
C3−C2−H8	35.0	109.8416
C3−C5−H11	35.0	108.1687
C3−C5−H10	35.0	111.3490
C3−C5−H9	35.0	111.3430
O4=C3−C5	80.0	118.9536
C6−C1−C7	70.0	113.1237
H9−C5−H11	33.0	109.0341
H9−C5−H10	33.0	107.8594
H10−C5−H11	33.0	109.0430
H12−C6−H14	33.0	108.3238
H12−C6−H13	33.0	108.3248
H13−C6−H14	33.0	106.4772
H15−C7−H17	33.0	106.1862
H15−C7−H16	33.0	108.0421
H16−C7−H17	33.0	108.0437

Table S4: Dihedral parameters

dihedral	V_1(kcal/mol)	V_2(kcal/mol)	V_3(kcal/mol)	f_1 (rad)	f_2 (rad)	f_3 (rad)
C6−C1−C7−H17	0.0	0.0	0.3	0.0	0.0	0.0
C2=C1−C7−H17	0.0	0.0	−0.372	0.0	0.0	0.0
C6−C1−C7−H16	0.0	0.0	0.3	0.0	0.0	0.0
C2=C1−C7−H16	0.0	0.0	−0.372	0.0	0.0	0.0
C6−C1−C7−H15	0.0	0.0	0.3	0.0	0.0	0.0
C2=C1−C7−H15	0.0	0.0	−0.372	0.0	0.0	0.0
C7−C1−C6−H14	0.0	0.0	0.3	0.0	0.0	0.0
C2=C1−C6−H14	0.0	0.0	−0.372	0.0	0.0	0.0
C7−C1−C6−H13	0.0	0.0	0.3	0.0	0.0	0.0
C2=C1−C6−H13	0.0	0.0	−0.372	0.0	0.0	0.0
C7−C1−C6−H12	0.0	0.0	0.3	0.0	0.0	0.0
C2=C1−C6−H12	0.0	0.0	−0.372	0.0	0.0	0.0
C7−C1=C2−H8	0.0	14.0	0.0	0.0	0.0	0.0
C6−C1=C2−H8	0.0	14.0	0.0	0.0	0.0	0.0
C7−C1=C2−C3	0.0	14.0	0.0	0.0	0.0	0.0
C6−C1=C2−C3	0.0	14.0	0.0	0.0	0.0	0.0
C1=C2−C3−C5	1.4	5.2	−4.7	0.0	0.0	0.0
H8−C2−C3−C5	0.0	0.0	0.7	0.0	0.0	0.0
C1=C2−C3=O4	−1.8	4.3	−1.9	0.0	0.0	0.0
H8−C2−C3=O4	0.0	0.0	0.0	0.0	0.0	0.0
C2−C3−C5−H11	0.0	0.0	0.366	0.0	0.0	0.0
O4=C3−C5−H11	0.0	0.0	0.0	0.0	0.0	0.0
C2−C3−C5−H10	0.0	0.0	0.366	0.0	0.0	0.0
O4=C3−C5−H10	0.0	0.0	0.0	0.0	0.0	0.0
C2−C3−C5−H9	0.0	0.0	0.366	0.0	0.0	0.0
O4=C3−C5−H9	0.0	0.0	0.0	0.0	0.0	0.0

Table S5: Improper dihedral parameters

improper dihedral	K_ϕ(kcal/mol)	ϕ_{eq} (°)
C7−C6−C1=C2	15.0	180.0
C1−H8−C2−C3	15.0	180.0
C2−C5−C3=O4	10.5	180.0

Table S6: MOx Fourier dihedral parameters for the set of dihedrals around the rotatable bond C=C−C=O, adjusted to obtain the gas energy difference. The expression for the torsional energy is given in the paper. All the parameters are in kcal/mol.

	V_1	V_2	V_3	f_1	f_2	f_3
C1=C2−C3−C5	1.4	5.2	−4.7	0.0	0.0	0.0
H8−C2−C3−C5	0.0	0.0	0.7	0.0	0.0	0.0
C1=C2−C3=O4	−1.8	4.3	−1.9	0.0	0.0	0.0
H8−C2−C3=O4	0.0	0.0	0.0	0.0	0.0	0.0

Table S7: MOx Ryckaert-Bellemans dihedral parameters for the set of dihedrals around the rotatable bond C=C−C=O, adjusted to obtain the gas energy difference. The corresponding function type in GROMACS is type 3. The type of each atom in MOx is shown in the `mox.itp` file below. These values were added to the ffbonded.itp file of the OPLS-AA force field. All the parameters are in kJ/mol.

	C_0	C_1	C_2	C_3	C_4	C_5
CM−CM−C_2−CT	14.853 20	−32.426 00	−21.756 80	39.329 60	0.000 00	0.000 00
CT−C_2−CM−HC	1.464 40	4.393 20	0.000 00	−5.857 60	0.000 00	0.000 00
CM−CM−C_2−O_2	10.250 80	−8.158 80	−17.991 20	15.899 20	0.000 00	0.000 00
HC−CM−C_2−O_2	0.000 00	0.000 00	0.000 00	0.000 00	0.000 00	0.000 00
CM−C_2−CT−HC	0.765 67	2.297 01	0.000 00	−3.062 69	0.000 00	0.000 00

GROMACS input: mox.itp

```
[ moleculetype ]
; Name            nrexcl
MSO             3

[ atoms ]
;   nr       type  resnr residue  atom   cgnr  charge    mass
        1  opls_141   1   LIG      C1    1      0.4     12.011   ; CM
        2  opls_142   1   LIG      C2    2     -0.6     12.011   ; CM
        3  opls_280   1   LIG      C3    3      0.77    12.011   ; C_2
        4  opls_281   1   LIG      O1    3     -0.75    15.9994  ; O_2
        5  opls_135   1   LIG      C4    4     -0.3     12.011   ; CT
        6  opls_135   1   LIG      C5    5     -0.3     12.011   ; CT
        7  opls_135   1   LIG      C6    6     -0.3     12.011   ; CT
        8  opls_144   1   LIG      H1    2      0.18    1.008    ; HC
        9  opls_282   1   LIG      H2    4      0.1     1.008    ; HC
       10  opls_282   1   LIG      H3    4      0.1     1.008    ; HC
       11  opls_282   1   LIG      H4    4      0.1     1.008    ; HC
       12  opls_140   1   LIG      H5    5      0.1     1.008    ; HC
       13  opls_140   1   LIG      H6    5      0.1     1.008    ; HC
       14  opls_140   1   LIG      H7    5      0.1     1.008    ; HC
       15  opls_140   1   LIG      H8    6      0.1     1.008    ; HC
       16  opls_140   1   LIG      H9    6      0.1     1.008    ; HC
       17  opls_140   1   LIG      H10   6      0.1     1.008    ; HC


[ bonds ]
1 7 1   0.1508   265265.6
1 6 1   0.1512   265265.6
1 2 1   0.13535  459403.2
2 8 1   0.10889  284512.0
2 3 1   0.14857  343088.0
3 5 1   0.15202  265265.6
3 4 1   0.12291  476976.0
5 11 1   0.10923  284512.0
5 10 1   0.10963  284512.0
5 9 1   0.10963  284512.0
6 14 1   0.10990  284512.0
6 13 1   0.10990  284512.0
6 12 1   0.10936  284512.0
7 17 1   0.10989  284512.0
7 16 1   0.10875  284512.0
7 15 1   0.10990  284512.0


[ angles ]
1 7 17 1  109.7415  292.880
1 7 16 1  114.7257  292.880
1 7 15 1  109.6430  292.880
1 6 14 1  110.6340  292.880
1 6 13 1  110.6379  292.880
1 6 12 1  112.2333  292.880
1 2 8 1  117.0643  292.880
1 2 3 1  133.0941  711.280
2 1 7 1  128.0244  585.760
2 1 6 1  118.8519  585.760
2 3 5 1  123.5601  585.760
2 3 4 1  117.4863  669.440
3 2 8 1  109.8416  292.880
3 5 11 1  108.1687  292.880
3 5 10 1  111.3490  292.880
3 5 9 1  111.3490  292.880
4 3 5 1  118.9536  669.440
6 1 7 1  113.1237  585.760
9 5 11 1  109.0341  276.144
9 5 10 1  109.8594  276.144
10 5 11 1  109.0430  276.144
12 6 14 1  108.3238  276.144
12 6 13 1  108.3248  276.144
13 6 14 1  106.4772  276.144
15 7 17 1  106.1862  276.144
15 7 16 1  108.0421  276.144
16 7 17 1  108.0437  276.144


[ dihedrals ]
6 1 7 17 3
2 1 7 17 3
6 1 7 16 3
2 1 7 16 3
6 1 7 15 3
2 1 7 15 3
7 1 6 14 3
2 1 6 14 3
7 1 6 13 3
2 1 6 13 3
```

```
7 1 6 12 3
2 1 6 12 3
7 1 2 8 3
6 1 2 8 3
7 1 2 3 3
6 1 2 3 3
1 2 3 5 3
8 2 3 5 3
1 2 3 4 3
8 2 3 4 3
2 3 5 11 3
4 3 5 11 3
2 3 5 10 3
4 3 5 10 3
2 3 5 9 3
4 3 5 9 3


[ dihedrals ]
7 6 1 2 1   improper_Z_CM_X_Y
1 8 2 3 1   improper_Z_CM_X_Y
2 5 3 4 1    improper_O_C_X_Y


[ pairs ]
17 6 1
17 2 1
16 6 1
16 2 1
15 6 1
15 2 1
14 7 1
14 2 1
13 7 1
13 2 1
12 7 1
12 2 1
8 7 1
8 6 1
3 7 1
3 6 1
5 1 1
5 8 1
4 1 1
4 8 1
11 2 1
11 4 1
10 2 1
10 4 1
9 2 1
9 4 1
```

GROMACS input: npt.mdp

```
integrator = md
tinit = 0.0
dt = 0.002
nsteps = 125000000
nstcomm = 5
comm-grps = System

nstxout = 1000
nstvout = 1000
nstfout = 0
nstlog = 1000
nstenergy = 1000
nstxtcout = 1000
xtc_precision = 100
xtc-grps =

energygrps = System
nstlist = 15
ns_type = grid
pbc = xyz
cutoff-scheme = Verlet
rlist = 1.5
coulombtype = reaction-field
epsilon-rf = 80.0
rcoulomb = 1.5
vdw_type = cut-off
rvdw = 1.5
DispCorr = No
tcoupl = v-rescale
tc-grps = System
tau_t = 0.1
ref_t = 300.0
Pcoupl = berendsen
Pcoupltype = isotropic
tau_p = 0.5
compressibility = 4.5e-5
ref_p = 1.0
gen-vel = no

continuation = no
constraints = h-bonds
constraint_algorithm=lincs
lincs_iter                  = 1             ; accuracy of LINCS
lincs_order                 = 4             ; also related to accuracy
```

DICE input: mesityloxide.txt

```
2
17          mox generated with gromacs2dice
 1  6           1.186200   -0.066353   -0.000104          0.4            0.0760           3.5500
 1  6           0.004992   -0.727124    0.000127          -0.6            0.0760           3.5500
 1  6          -1.410503   -0.275840   -0.000048          0.77            0.1050           3.7500
 2  8          -2.282194   -1.142390   -0.000485          -0.75          0.2100           2.9600
 1  6          -1.826392    1.186385    0.000542          -0.3            0.0660           3.5000
 1  6           2.469464   -0.865902    0.000301          -0.3            0.0660           3.5000
 1  6           1.416942    1.423868   -0.000512          -0.3            0.0660           3.5000
 3  1           0.046002   -1.815223    0.000450          0.18            0.0300           2.4200
 3  1          -1.448515    1.709058   -0.886015          0.1             0.0150           2.4200
 3  1          -1.446606    1.708995    0.886311          0.1             0.0150           2.4200
 3  1          -2.917863    1.230065    0.001621          0.1             0.0150           2.4200
 3  1           2.285361   -1.943856    0.001739          0.1             0.0300           2.5000
 3  1           3.079794   -0.618417    0.880163          0.1             0.0300           2.5000
 3  1           3.078888   -0.620630   -0.880808          0.1             0.0300           2.5000
 3  1           2.009933    1.707875    0.880054          0.1             0.0300           2.5000
 3  1           0.510345    2.024556   -0.004095          0.1             0.0300           2.5000
 3  1           2.015986    1.706490   -0.877381          0.1             0.0300           2.5000
3 SPC/E JCP,91,6269 1987
1 8 0.0000  0.0000 0.0000 -0.8476 0.155 3.165
2 1 0.5774  0.8165 0.0000  0.4238 0.000 0.000
2 1 0.5774 -0.8165 0.0000  0.4238 0.000 0.000
$end
```

DICE input: mox.dfr

```
$atoms fragments
1        1        7        6        2        3        8        F
2        3        5        2        4        M
3        5        3        11        10        9        F
4        6        1        13        12        14        F
5        7        1        16        15        17        F
$end atoms fragments

$fragment connection
1        4
1        5
1        2
2        3
$end fragment connection

$bond
1 7             317.0        1.5080
1 6             317.0        1.5120
1 2             549.0        1.3535
2 8             340.0        1.0889
2 3             410.0        1.4857
3 5             317.0        1.5202
3 4             570.0        1.2291
5 11             340.0        1.0923
5 10             340.0        1.0963
5 9             340.0        1.0963
6 14             340.0        1.0990
6 13             340.0        1.0990
6 12             340.0        1.0936
7 17             340.0        1.0989
7 16             340.0        1.0875
7 15             340.0        1.0990
$end bond

$angle
1 7 17           harmonic        35.0        109.7417
1 7 16           harmonic        35.0        114.7257
1 7 15           harmonic        35.0        109.7393
1 6 14           harmonic        35.0        110.6340
1 6 13           harmonic        35.0        110.6379
1 6 12           harmonic        35.0        112.2333
1 2 8           harmonic        35.0        117.0643
1 2 3           harmonic        85.0        133.0941
2 1 7           harmonic        70.0        128.0244
2 1 6           harmonic        70.0        118.8519
2 3 5           harmonic        70.0        123.5601
2 3 4           harmonic        80.0        117.4863
3 2 8           harmonic        35.0        109.8416
3 5 11           harmonic        35.0        108.1687
3 5 10           harmonic        35.0        111.3490
3 5 9           harmonic        35.0        111.3430
4 3 5           harmonic        80.0        118.9536
6 1 7           harmonic        70.0        113.1237
9 5 11           harmonic        33.0        109.0341
9 5 10           harmonic        33.0        107.8594
10 5 11           harmonic        33.0        109.0430
12 6 14           harmonic        33.0        108.3238
12 6 13           harmonic        33.0        108.3248
13 6 14           harmonic        33.0        106.4772
15 7 17           harmonic        33.0        106.1862
15 7 16           harmonic        33.0        108.0421
16 7 17           harmonic        33.0        108.0437
$end angle

$dihedral
6 1 7 17          OPLS        -0.0        -0.0         0.3        0.0        0.0        0.0
2 1 7 17          OPLS         0.0        -0.0        -0.372        0.0        0.0        0.0
6 1 7 16          OPLS        -0.0        -0.0         0.3        0.0        0.0        0.0
2 1 7 16          OPLS         0.0        -0.0        -0.372        0.0        0.0        0.0
6 1 7 15          OPLS        -0.0        -0.0         0.3        0.0        0.0        0.0
2 1 7 15          OPLS         0.0        -0.0        -0.372        0.0        0.0        0.0
7 1 6 14          OPLS        -0.0        -0.0         0.3        0.0        0.0        0.0
2 1 6 14          OPLS         0.0        -0.0        -0.372        0.0        0.0        0.0
7 1 6 13          OPLS        -0.0        -0.0         0.3        0.0        0.0        0.0
2 1 6 13          OPLS         0.0        -0.0        -0.372        0.0        0.0        0.0
7 1 6 12          OPLS        -0.0        -0.0         0.3        0.0        0.0        0.0
2 1 6 12          OPLS         0.0        -0.0        -0.372        0.0        0.0        0.0
7 1 2 8          OPLS        -0.0        14.0        -0.0        0.0        0.0        0.0
6 1 2 8          OPLS        -0.0        14.0        -0.0        0.0        0.0        0.0
7 1 2 3          OPLS        -0.0        14.0        -0.0        0.0        0.0        0.0
6 1 2 3          OPLS        -0.0        14.0        -0.0        0.0        0.0        0.0
1 2 3 5          OPLS         1.4         5.2        -4.7        0.0        0.0        0.0
8 2 3 5          OPLS        -0.0        -0.0         0.7        0.0        0.0        0.0
1 2 3 4          OPLS        -1.8         4.3        -1.9        0.0        0.0        0.0
8 2 3 4          OPLS        -0.0        -0.0        -0.0        0.0        0.0        0.0
```

```
2 3 5 11           OPLS        -0.0        -0.0         0.366        0.0        0.0        0.0
4 3 5 11           OPLS        -0.0        -0.0        -0.0         0.0        0.0        0.0
2 3 5 10           OPLS        -0.0        -0.0         0.366        0.0        0.0        0.0
4 3 5 10           OPLS        -0.0        -0.0        -0.0         0.0        0.0        0.0
2 3 5 9           OPLS        -0.0        -0.0         0.366        0.0        0.0        0.0
4 3 5 9           OPLS        -0.0        -0.0        -0.0         0.0        0.0        0.0
$end dihedral

$improper dihedral
7 6 1 2           15.0        180.0
1 8 2 3           15.0        180.0
2 5 3 4           10.5        180.0
$end improper dihedral
```

DICE input: npt.ter

```
title =  mesityloxide_wat_therm
ljname = mesityloxide.txt
outname = outmox
ncores = 8
init = yes
coolstep = 150
nmol = 1 1200
dens = 1.0
temp = 300.0
press = 1.0
upbuf = 4
accum = no
vstep = 62500
nstep = 4
iprint = 1
isave = 5000
irdf = 0
iratio = 10
vratio = 10
seed = 609956
```

DICE input: npt.in

```
title =  mesityloxide_wat
ljname = mesityloxide.txt
outname = outmox
ncores = 8
init = no
nmol = 1 1200
dens = 1.0
temp = 300.0
press = 1.0
upbuf = 4
accum = no
vstep = 250000
nstep = 4
iprint = 1
isave = 50
irdf = 5
iratio = 10
vratio = 10
seed = 366045

sampling = 2

flex = mox
equiphi = yes
ntrialphi = 32
fudgelj = 0.5
fudgeclb = 0.5
pcbmc = 0.8
nsf = 10000
sfint = 1000
```