Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Structural and mechanistic insight into DNA bending by antitumour calicheamicins

Alberto Mills and Federico Gago

SUPPLEMENTARY INFORMATION

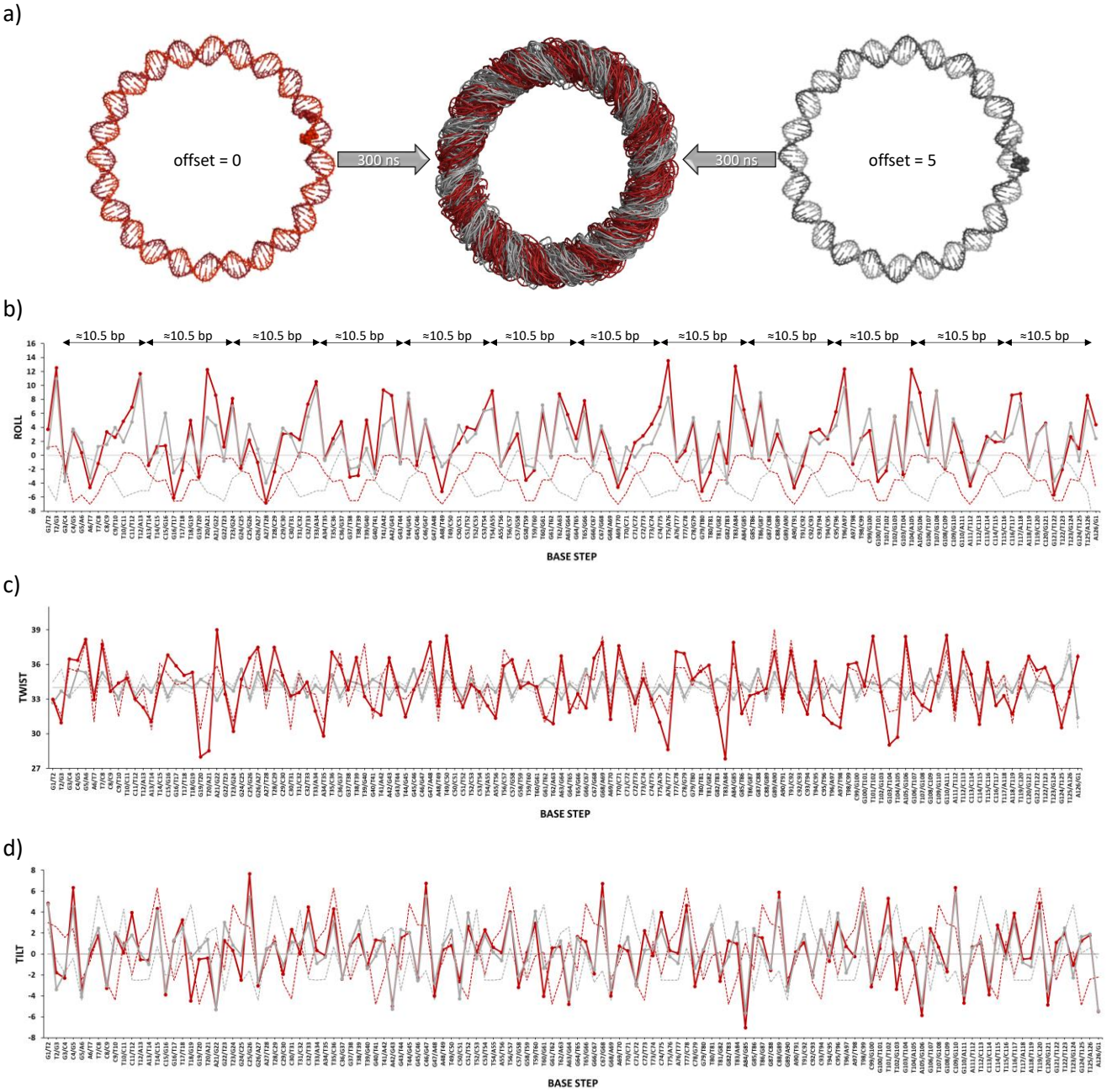

Figure S1. Key structural features of the DNA circles used in the MD simulations. (a) Initial structures of the drug-free CA21×6 DNA circle showing how a given stretch in a DNA strand (spheres) will face opposite directions with respect to the center of the ring (left and right) depending on the definition of the first nucleotide in the input sequence built by the MCDNA server. Convergence of both systems is achieved after the molecular dynamics simulations and shown as a cluster of 30 equilibrated structures (middle). Average roll (b), twist (c), and tilt (d) values obtained from two separate replicas for every base pair step in the drug-free doubly nicked CA21×6 circle (red) and in the same structure containing an offset of 5 bp (gray). Initial opposite values are shown as dashed lines. Note that the peaks of positive roll are in phase with the DNA helical repeat (~10.5 bp).

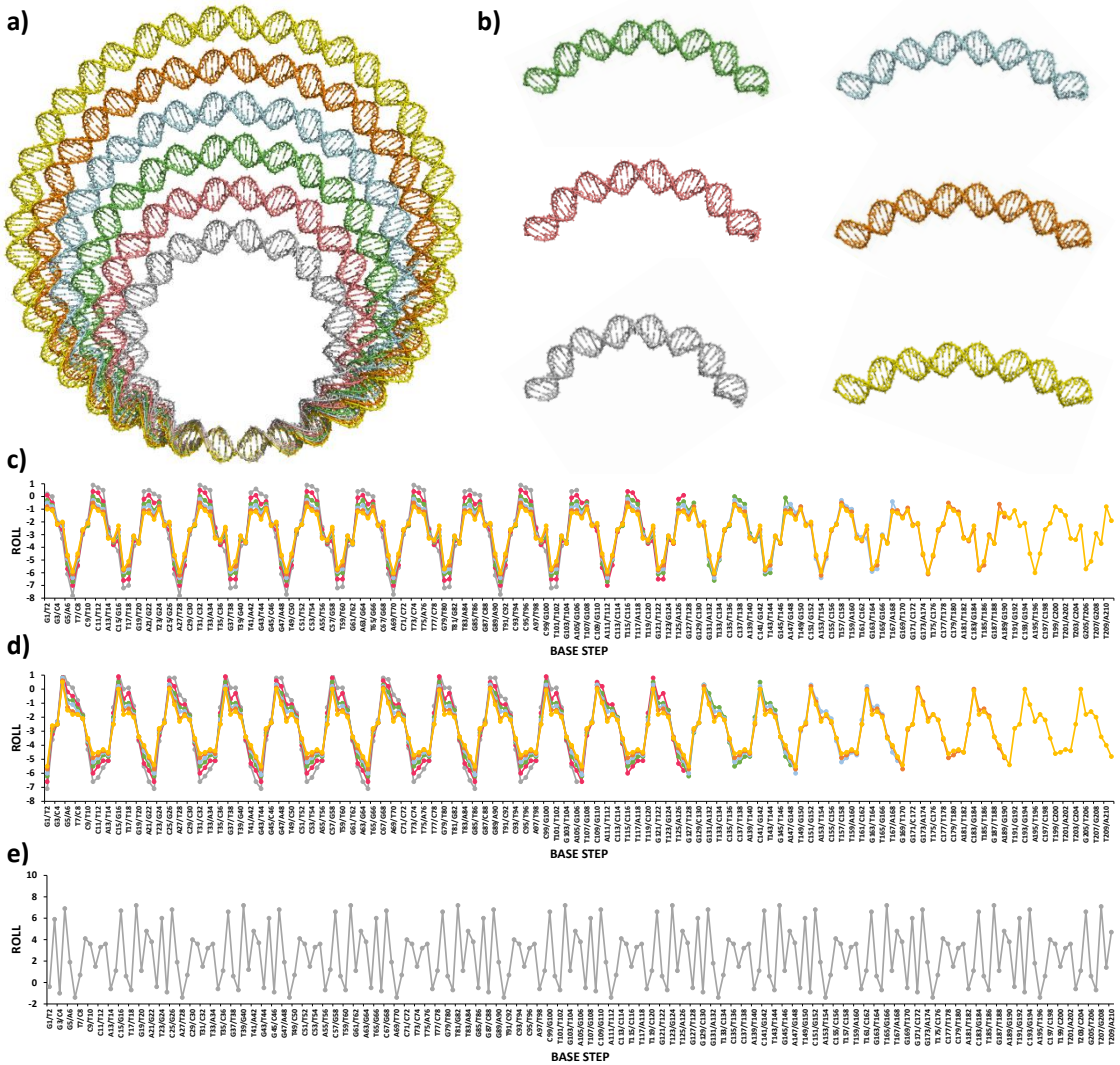

Figure S2. DNA minicircle and linear DNA generation. a) Internally tangent covalently closed DNA circles of increasing lengths (CA21×5–CA21×10), as provided by the MCDNA web server. Note the superposition of the first monomeric unit (bottom) and their identical groove orientations; b) Arcs of varying curvature corresponding to a CA21 dimer extracted from the circles displayed in a); c) Periodic variation in roll measured for the same DNA circles (i.e., no offset) consisting of 105–210 bp; d) Periodic variation in roll measured for the DNA circles but in this case built after making A6 the initial nucleotide (i.e., offset = 5); e) Periodic variation in roll measured for the CA21×10 multimer in linear form, as provided by the same MCDNA web server (https://mmb.irbbarcelona.org/MCDNA/help/method).

AMBER PREP FILES FOR CALε

```
    0    0    2

Calicheamicin epsilon fragment 1 (rings R, A and E)
CE1.res
CE1   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  C7    c3    M    3   2   1     1.540   111.208  -180.000 -0.575158
   5  H71   hc    E    4   3   2     1.082   129.002   -14.532  0.194290
   6  H72   hc    E    4   3   2     1.083   104.595   114.634  0.141970
   7  H73   hc    E    4   3   2     1.083    95.670  -134.023  0.156275
   8  C29   c3    M    4   3   2     1.530    20.764     4.334  0.490910
   9  H291  hx    E    8   4   3     1.077   111.623  -102.731  0.056271
  10  H292  hx    E    8   4   3     1.076   111.607   134.028  0.035123
  11  N2    ny    M    8   4   3     1.527   109.423    15.328 -0.644243
  12  HN21  hn    E   11   8   4     1.022   109.164   -61.405  0.413167
  13  HN22  hn    E   11   8   4     1.014   108.771    56.243  0.465282
  14  C25   c3    M   11   8   4     1.518   117.613  -178.499 -0.360946
  15  C27   c3    3   14  11   8     1.526   115.353   -45.401  0.603375
  16  O9    os    E   15  14  11     1.449   105.216  -174.602 -0.649741
  17  H271  h1    E   15  14  11     1.078   112.019   -59.228  0.053554
  18  H272  h1    E   15  14  11     1.077   112.412    66.093 -0.197213
  19  H25   hx    E   14  11   8     1.078   105.175  -165.875  0.205597
  20  C23   c3    M   14  11   8     1.526   108.143    78.645  0.637277
  21  O6    os    S   20  14  11     1.438   104.064    50.025 -0.470014
  22  C8    c3    3   21  20  14     1.448   116.607  -167.208 -0.089934
  23  H81   h1    E   22  21  20     1.080   111.014   -66.362  0.100956
  24  H82   h1    E   22  21  20     1.083   110.550    55.336  0.085115
  25  H83   h1    E   22  21  20     1.078   106.311   174.453  0.125561
  26  H23   h1    E   20  14  11     1.081   110.922   -68.815  0.015701
  27  C21   c3    M   20  14  11     1.530   107.748   171.111 -0.539149
  28  H211  hc    E   27  20  14     1.080   111.055   175.155  0.162205
  29  H212  hc    E   27  20  14     1.082   109.005   -64.365  0.157155
  30  C19   c3    M   27  20  14     1.524   109.382    55.422  0.613432
  31  H19   h2    E   30  27  20     1.070   113.441  -172.486  0.102107
  32  O2    os    M   30  27  20     1.426   106.004    66.074 -0.482751
  33  C2    c3    M   32  30  27     1.441   116.919   178.904 -0.465876
  34  C3    c3    3   33  32  30     1.525   109.877   -85.018  0.588354
  35  C4    c3    3   34  33  32     1.533   111.648  -169.861 -0.174328
  36  C5    c3    3   35  34  33     1.535   110.843    50.068  0.473098
  37  C6    c3    3   36  35  34     1.526   114.196  -169.937 -0.398624
  38  H61   hc    E   37  36  35     1.083   109.886    47.427  0.105899
  39  H62   hc    E   37  36  35     1.080   108.303   165.705  0.142432
  40  H63   hc    E   37  36  35     1.083   111.384   -73.674  0.089676
  41  O5    os    E   36  35  34     1.445   107.686   -52.881 -0.492845
  42  H5    h1    E   36  35  34     1.084   108.600    65.788  0.007449
  43  N4    n7    B   35  34  33     1.485   109.422   167.067 -0.663347
  44  HN41  hn    E   43  35  34     1.010   110.219   169.545  0.482679
  45  O4    os    E   43  35  34     1.469   108.302    57.100 -0.258862
  46  H4    h1    E   35  34  33     1.083   108.206   -70.511  0.141068
  47  O3    oh    S   34  33  32     1.441   106.135    69.597 -0.781787
  48  HO3   ho    E   47  34  33     0.972   107.042   167.130  0.485054
  49  H3    h1    E   34  33  32     1.084   108.697   -49.945  0.067538
  50  H2    h1    E   33  32  30     1.077   110.630    36.376  0.264062
  51  C1    c3    M   33  32  30     1.514   106.735   155.775  0.522118
  52  H1    h2    E   51  33  32     1.079   109.620    58.311  0.026808
  53  O1    os    M   51  33  32     1.405   109.269   -64.020  0.068313
  54  C20   c3    M   53  51  33     1.455   121.175   162.883 -0.619755
  55  C22   ca    S   54  53  51     1.525   114.209     2.772  0.216903
  56  C24   ca    B   55  54  53     1.389   118.840   -83.924 -0.195436
  57  C26   ca    B   56  55  54     1.381   120.988   177.769 -0.176109
  58  C28   ca    B   57  56  55     1.385   119.490     0.264 -0.133238
  59  C30   ca    B   58  57  56     1.382   119.925     0.810 -0.203530
  60  C31   ca    S   59  58  57     1.387   120.764    -0.264 -0.020947
  61  C32   c3    3   60  59  58     1.529   118.303   176.879  0.631388
  62  C9    c3    3   61  60  59     1.562   110.931   -77.491 -0.507272
  63  C10   c     B   62  61  60     1.517   112.955   -89.862  0.715855
  64  C11   c3    B   63  62  61     1.511   113.822    34.716  0.137953
  65  N11   ns    B   64  63  62     1.443   110.890   174.315 -0.822505
  66  C17   c     B   65  64  63     1.344   124.333  -141.499  1.133175
  67  O71   o     E   66  65  64     1.220   125.496   179.570 -0.743550
  68  O72   os    S   66  65  64     1.349   111.834    -1.043 -0.384627
  69  C18   c3    3   68  66  65     1.459   118.465   174.054 -0.115862
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  70  H181  h1    E   69  68  66     1.077   110.290    63.557  0.099382
  71  H182  h1    E   69  68  66     1.076   104.984  -176.985  0.133469
  72  H183  h1    E   69  68  66     1.078   109.986   -57.645  0.115196
  73  HN11  hn    E   65  64  63     0.999   117.689    33.379  0.400176
  74  H11   h1    E   64  63  62     1.077   107.458    56.464  0.107779
  75  O10   o     E   63  62  61     1.211   123.520  -146.069 -0.570501
  76  H91   hc    E   62  61  60     1.083   108.794   151.302  0.146354
  77  H92   hc    E   62  61  60     1.085   110.870    32.546  0.161428
  78  C13   c2    S   61  60  59     1.492   109.710   166.777 -0.067169
  79  C14   c2    B   78  61  60     1.307   130.609  -128.931 -0.293220
  80  C15   c3    B   79  78  61     1.513   115.522   179.657  0.245620
  81  H151  h1    E   80  79  78     1.081   112.578   131.687  0.056656
  82  H152  h1    E   80  79  78     1.079   110.113  -105.578  0.006962
  83  H14   ha    E   79  78  61     1.070   124.131     3.156  0.178797
  84  O8    oh    S   61  60  59     1.435   106.548    41.974 -0.758952
  85  HO8   ho    E   84  61  60     0.968   111.245  -172.670  0.484071
  86  H30   ha    E   59  58  57     1.070   120.224  -179.912  0.177257
  87  H28   ha    E   58  57  56     1.072   120.247  -179.430  0.161366
  88  H26   ha    E   57  56  55     1.072   120.124  -179.786  0.167888
  89  H24   ha    E   56  55  54     1.073   119.199    -1.870  0.182626
  90  H07   h1    E   54  53  51     1.078   106.754  -117.655  0.304768
  91  C12   c3    M   54  53  51     1.538   108.572   124.373 -0.169158
  92  S1    ss    M   91  54  53     1.821   114.786    46.010 -0.218291


LOOP
  C19   O9
   C1   O5
  C31  C22
  C12  C11
  C12  C13
   S1  C15

IMPROPER
  C20  C24  C22  C31
  C22  C26  C24  H24
  C24  C28  C26  H26
  C26  C30  C28  H28
  C28  C31  C30  H30
  C32  C22  C31  C30
   C9  C11  C10  O10
  C11  C17  N11 HN11
  N11  O71  C17  O72
  C14  C32  C13  C12
  C13  C15  C14  H14

DONE
STOP
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Calicheamicin epsilon fragment 2 (rings B, C and D)
CE2.res
CE2   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  CA1   c3    M    3   2   1     1.540   111.208  -180.000  0.476239
   5  OA5   os    S    4   3   2     1.440   129.965   -50.773 -0.522638
   6  CA5   c3    B    5   4   3     1.447   112.047   156.253  0.386429
   7  CA6   c3    3    6   5   4     1.529   106.315  -172.737 -0.347973
   8  HA61  hc    E    7   6   5     1.098   109.136    59.658  0.089521
   9  HA62  hc    E    7   6   5     1.097   110.928  -179.909  0.075036
  10  HA63  hc    E    7   6   5     1.098   109.744   -59.480  0.109188
  11  HA5   h1    E    6   5   4     1.102   110.484   -52.256 -0.020574
  12  HA1   h2    E    4   3   2     1.102    83.747    59.853  0.017973
  13  CA2   c3    M    4   3   2     1.532   108.929   170.908 -0.249539
  14  HA21  hc    E   13   4   3     1.096   110.287   -34.202  0.077447
  15  HA22  hc    E   13   4   3     1.098   107.968    85.130  0.067176
  16  CA3   c3    M   13   4   3     1.538   109.695  -154.671  0.268196
  17  OA3   oh    S   16  13   4     1.444   105.520    65.480 -0.558754
  18  HOA3  ho    E   17  16  13     0.992   105.513   173.592  0.376013
  19  HA3   h1    E   16  13   4     1.100   110.482  -174.030  0.005285
  20  CA4   c3    M   16  13   4     1.548   109.701   -53.199  0.018558
  21  HA4   h1    E   20  16  13     1.096   111.531   -68.945  0.075932
  22  S4    ss    M   20  16  13     1.846   108.636   175.522 -0.353059
  23  CB7   c     M   22  20  16     1.815    99.475   139.932  0.489805
  24  OB7   o     E   23  22  20     1.220   122.519    -9.144 -0.379671
  25  CB5   ca    M   23  22  20     1.500   112.717   173.259 -0.496682
  26  CB6   ca    B   25  23  22     1.407   121.411   115.392  0.510147
  27  CB1   ca    S   26  25  23     1.399   117.844  -178.286 -0.637039
  28  IB1   i     E   27  26  25     2.129   120.672   176.562  0.076836
  29  CB8   c3    3   26  25  23     1.514   120.683     0.362 -0.420920
  30  HB81  hc    E   29  26  25     1.092   110.831    15.214  0.145676
  31  HB82  hc    E   29  26  25     1.098   110.583   135.146  0.105627
  32  HB83  hc    E   29  26  25     1.102   110.929  -105.995  0.109143
  33  CB4   ca    M   25  23  22     1.399   117.867   -65.567  0.467116
  34  OB4   os    S   33  25  23     1.390   118.382    -3.462 -0.268276
  35  CBX   c3    3   34  33  25     1.469   113.842   119.353 -0.131904
  36  HBX1  h1    E   35  34  33     1.093   110.331    55.482  0.093304
  37  HBX2  h1    E   35  34  33     1.094   104.866   174.832  0.117166
  38  HBX3  h1    E   35  34  33     1.097   109.388   -67.393  0.115284
  39  CB3   ca    M   33  25  23     1.404   120.932  -178.968 -0.341090
  40  OB3   os    S   39  33  25     1.390   119.756   179.804 -0.166252
  41  CB9   c3    3   40  39  33     1.474   112.338   -70.308 -0.201255
  42  HB91  h1    E   41  40  39     1.095   108.832   -66.129  0.128638
  43  HB92  h1    E   41  40  39     1.095   110.046    56.696  0.110118
  44  HB93  h1    E   41  40  39     1.095   104.988   175.498  0.135559
  45  CB2   ca    M   39  33  25     1.409   119.128    -2.441  0.753228
  46  OC1   os    M   45  39  33     1.377   124.900  -174.774 -0.518270
  47  CC1   c3    M   46  45  39     1.460   119.747   -35.969  0.381405
  48  CC2   c3    3   47  46  45     1.548   104.673   178.981  0.031686
  49  CC3   c3    3   48  47  46     1.535   109.442    71.725  0.102991
  50  CC4   c3    B   49  48  47     1.533   109.372    53.291 -0.115560
  51  OC4   oh    S   50  49  48     1.433   108.853  -178.328 -0.539419
  52  HOC4  ho    E   51  50  49     0.997   101.388   -41.541  0.362319
  53  HC4   h1    E   50  49  48     1.101   107.958    59.438  0.096071
  54  OC3   os    S   49  48  47     1.438   113.739   169.442 -0.258024
  55  CC7   c3    3   54  49  48     1.442   112.634    79.938 -0.166732
  56  HC71  h1    E   55  54  49     1.102   111.926   -66.533  0.095418
  57  HC72  h1    E   55  54  49     1.104   111.459    55.687  0.100030
  58  HC73  h1    E   55  54  49     1.097   106.098   174.669  0.116837
  59  HC3   h1    E   49  48  47     1.100   110.002   -66.065  0.071622
  60  OC2   oh    S   48  47  46     1.434   108.879  -172.917 -0.533065
  61  HOC2  ho    E   60  48  47     0.992   105.999    66.741  0.381122
  62  HC2   h1    E   48  47  46     1.100   108.431   -50.108  0.086571
  63  HC1   h2    E   47  46  45     1.088   109.767    59.361  0.072787
  64  OC5   os    M   47  46  45     1.413   111.993   -57.298 -0.529153
  65  CC5   c3    M   64  47  46     1.463   114.913   -64.159  0.652269
  66  HC5   h1    E   65  64  47     1.099   110.310    61.173 -0.088999
  67  CC6   c3    M   65  64  47     1.526   106.425  -179.001 -0.423119
  68  HC61  hc    E   67  65  64     1.100   109.770    57.140  0.104654
  69  HC62  hc    E   67  65  64     1.098   109.137   176.761  0.111458
  70  HC63  hc    E   67  65  64     1.097   110.514   -63.078  0.100087
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LOOP
  CA4  CA5
  CB2  CB1
  CC5  CC4

IMPROPER
  CB5  OB7  CB7   S4
  CB7  CB6  CB5  CB4
  CB8  CB5  CB6  CB1
  CB6  CB2  CB1  IB1
  CB5  CB3  CB4  OB4
  CB4  CB2  CB3  OB3
  CB1  CB3  CB2  OC1

DONE
STOP
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Additions to the *gaff* force field for non-standard residues CE1 and CE2

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Extra AMBER parameters for calicheamicin epsilon
MASS

BOND
c3-ny  222.58   1.511
hn-ny  482.87   1.030
c3-n7  261.19   1.465
hn-n7  511.28   1.019
n7-os  160.59   1.441
c3-ns  263.77   1.462
c -ns  356.21   1.379
hn-ns  527.31   1.013

ANGLE
c3-c3-ny   80.976     114.210
c3-ny-hn   46.193     110.110
c3-ny-c3   64.460     109.660
hx-c3-ny   60.076     108.010
hn-ny-hn   40.020     108.300
c3-c3-n7   83.305     111.040
c3-n7-hn   47.782     109.290
c3-n7-os   85.469     105.800
h1-c3-n7   61.163     109.880
hn-n7-os   62.667     102.750
c -c3-ns   84.540     109.060
c -ns-c3   65.252     120.690
c3-ns-hn   46.147     117.680
h1-c3-ns   61.544     108.880
c3-c3-ns   83.161     111.610
ns-c -o   113.811     123.050
ns-c -os  115.486     109.220
c -ns-hn   48.691     117.550
c3-os-n7   83.747     109.830

DIHE
hn-n7-os-c3   1    1.800         0.000          2.000
c3-n7-os-c3   1    0.840         0.000          2.000
c3-c3-ny-hn   9    1.400         0.000          3.000
c3-c3-ny-c3   1    0.156         0.000          3.000
hx-c3-ny-c3   9    1.400         0.000          3.000
hx-c3-ny-hn   1    0.109         0.000          3.000
c3-c3-c3-ny   1    0.210         0.000          3.000
c3-c3-c3-n7   1    0.210         0.000          3.000
c3-c3-n7-hn   1    0.217         0.000          3.000
c3-c3-n7-os   6    1.800         0.000          3.000
h1-c3-n7-hn   6    1.800         0.000          3.000
h1-c3-n7-os   6    1.800         0.000          3.000
c3-c3-c3-ns   1    0.100         0.000          3.000
c -c3-ns-c    1    0.390       180.000         -2.000
c -c3-ns-c    1    0.640         0.000          1.000
c -c3-ns-hn   6    0.000         0.000          2.000
o -c -ns-c3   4   10.000       180.000          2.000
os-c -ns-c3   4   10.000       180.000          2.000
h1-c3-ns-c    1    0.000       180.000          2.000
c3-c3-ns-c    1    0.100       180.000         -4.000
c3-c3-ns-c    1    0.170         0.000         -3.000
c3-c3-ns-c    1    1.020       180.000          1.000
o -c -ns-hn   1    2.500       180.000         -2.000
o -c -ns-hn   1    2.000         0.000          1.000
os-c -ns-hn   4   10.000       180.000          2.000
h1-c3-ns-hn   6    0.000         0.000          2.000
c3-c3-ns-hn   6    0.000         0.000          2.000

IMPROPER
ca-ca-ca-ha         1.1          180.0         2.0
c3-c3-c -o         10.5          180.0         2.0
c -c3-ns-hn         1.1          180.0         2.0
ns-o -c -os         1.1          180.0         2.0
c2-c3-c2-c3         1.1          180.0         2.0
c2-c3-c2-ha         1.1          180.0         2.0
ca-o -c -ss         1.1          180.0         2.0
c -ca-ca-ca         1.1          180.0         2.0
ca-ca-ca-os         1.1          180.0         2.0
```

MD simulations of a periodic box containing 75 iodobenzene molecules

COMPOUND	DENSITY (g/cm³)	COMPRESSIBILITIES[1] (at 298K and 0,1 MPa)
BZN	0.876	0.966 Pa^{-1}
FBZ	1.025	0.942 Pa^{-1}
CBZ	1.11	0.771 Pa^{-1}
BBZ	1.5	0.668 Pa^{-1}
IBZ	1.83	0.582 Pa^{-1}

$\Delta H_{vap}(T)=E_{inter}(T)+RT$; R= 0.00192 kcal/mol K

$vdW - vdW_{intra} = vdW_{inter}$; $Ele - Ele_{intra} = Ele_{inter}$; $vdW_{inter} + Ele_{inter} = E_{total}$; $\Delta H_{vap} = RT - E_{total}$ / # molecules

Iodobenzene (**IBZ**):

- vdW_{intra}= -0.2971 → -0.2971 x 75 = **-22.2825**
- Ele_{intra}= 3.0380 → 3.0380 x 75 = **227.85**

From MD for box of IBZ: **Density** = 1.8 g cm^{-3}

- vdW= -801.745 → **vdW_{inter} =** -801.745 - (-22.2825) = **-779.463**
- Ele= 182.5467 → **Ele_{inter}** = 182.5467 - 227.85 = **-45.3033**
    - **E_{total}** = -779.463 + (-45.3033) **= -824.766**
        - ***ΔH_{vap}*** = 0,00192 x 298 – (-824.766 / 75) = **11.569 kcal mol^{-1}**

Experimental values:

http://www.chemspider.com/Chemical-Structure.11087.html

Density = 1.823-1.826 g cm^{-3}

Enthalpy of vaporization (ΔH_{vap} = 9.82-12.3 kcal mol^{-1})

https://webbook.nist.gov/cgi/cbook.cgi?ID=C591504&Units=CAL&Mask=187F

References for Supporting Information

1. Y. Marcus and G. T. Hefter, *Journal of Molecular Liquids*, 1997, **73-74**, 61-74.