SUPPORTING INFORMATION

Beyond Static Structures: Putting Forth REMD as a Tool to Solve Problems in Computational Organic Chemistry

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Table S1. Temperatures used in the replica exchange molecular dynamics simulations.

Replica Number	Temperature for Diathiacyclophane and Cope rearrangment	Temperature for molecular rotor and Cinchona alkaloid
1	300.00	300.00
2	333.98	310.45
3	371.81	321.27
4	413.93	332.46
5	460.81	344.04
6	513.01	356.03
7	571.12	368.43
8	635.81	381.27
9	707.83	394.55
10	788.01	408.30
11	877.26	422.52
12	976.63	437.24
13	1087.26	452.47
14	1210.41	468.24
15	1347.51	484.55
16	1500.15	501.43
17	NA	518.90
18	NA	536.98
19	NA	555.68
20	NA	575.04
21	NA	595.08
22	NA	615.81
23	NA	637.26
24	NA	659.46
25	NA	682.44
26	NA	706.21
27	NA	730.82
28	NA	756.28
29	NA	782.63
30	NA	809.89
31	NA	838.11
32	NA	867.31
33	NA	897.52
34	NA	928.79
35	NA	961.15
36	NA	994.63
37	NA	1029.28
38	NA	1065.14
39	NA	1102.25
40	NA	1140.65
41	NA	1180.39
42	NA	1221.51
43	NA	1264.07
44	NA	1308.11
45	NA	1353.68
46	NA	1400.84
47	NA	1449.65
48	NA	1500.15

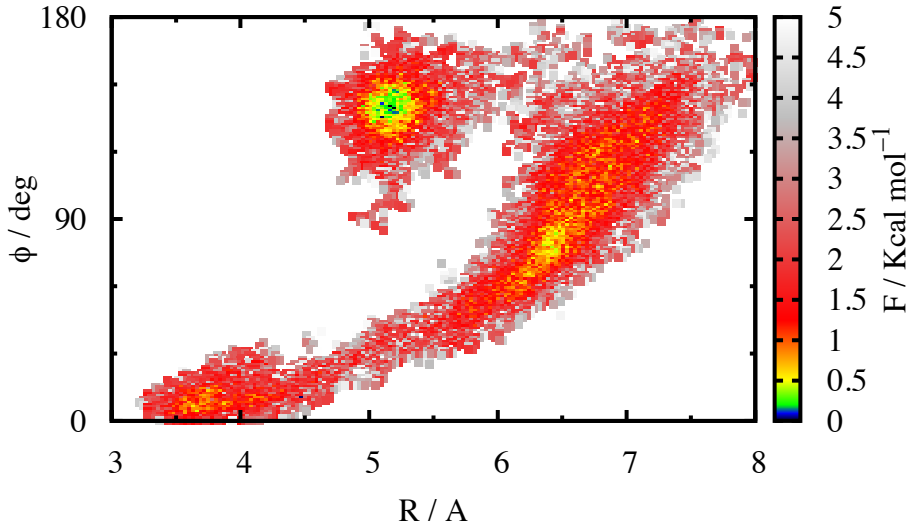

Figure S1. Zoom-in of the free energy landscape for dithiacyclophane.

Table S2. Relative electronic or free energies (in kcal/mol) of dithiacyclophane conformers determined from static computations or REMD simulations. Static values are taken from the DFTB3/3OB-UFF//M06-2X/def2-TZVP, M06-2X/def2-TZVP and PBE0-dDsC/def2-TZVP//M06-2X/def2-TZVP levels respectively. Free energy contributions are given at 300 K.

	DFTB3/3OB-UFF		**M06-2X**		**PBE0-dDsC**	
	Electronic Energy	REMD Free Energy[a]	Electronic Energy	Static Free Energy[b]	Electronic Energy	Static Free Energy[b]
1. Closed	1.96	0.68	2.19	2.77	3.75	4.34
2. Open	1.61	0.19	1.77	1.00	2.38	1.61
3. Disarticulated	0.00	0.00	0.00	0.00	0.00	0.00

[a]The free energy of a basin *i* is computed evaluating the following integral:

$$F_i = k_B T \log \int_{N_i} e^{-F(x)/k_B T}\, dx$$

where each of the non-overlapping integration regions (N_i) covers a neighborhood of the local free-energy minima. The equation makes it possible to account for the thermal fluctuations that distort in a different manner the geometry of the various configurations.

[b]The estimation of the static free energy is based on the harmonic approximation as provided by most quantum chemistry codes although not by DFBT+.

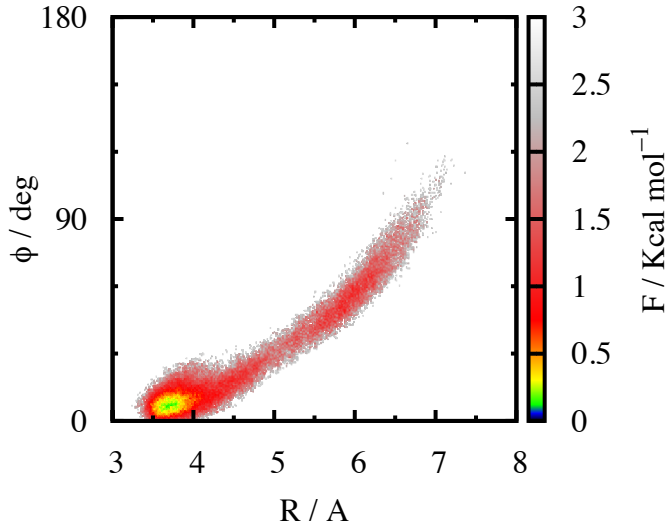

Figure S2. Free energy map for a standard MD simulation of dithiaparacylophane. Note that the region associated with the "disarticulated" structure has not been found.

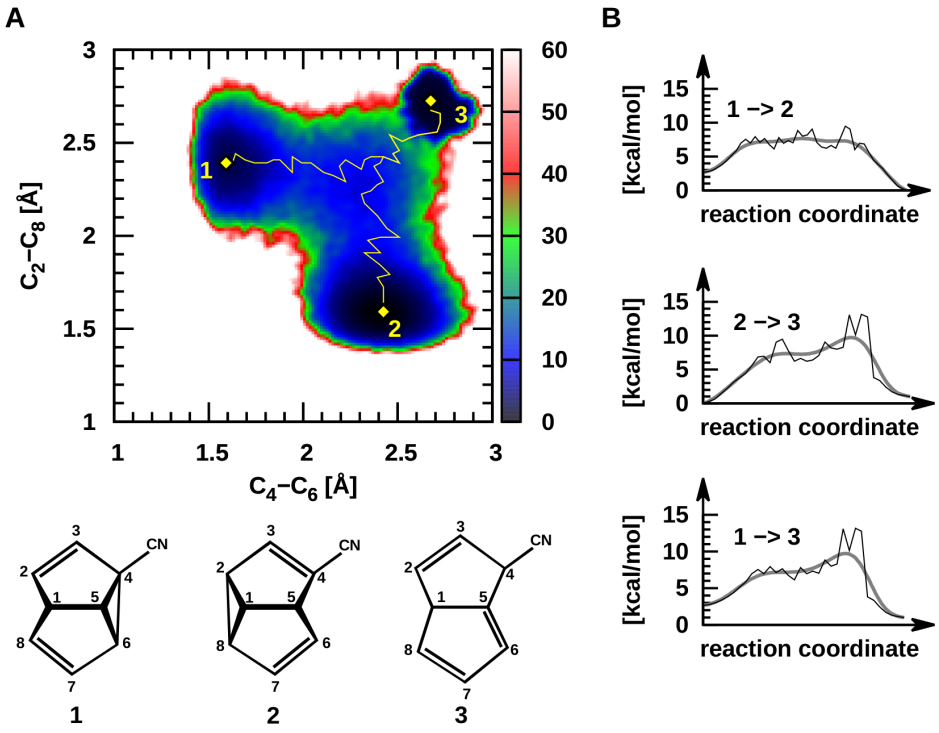

Figure S3. Cope rearrangement for CN substituted (C4) semibullvalene. **A:** Free energy map obtained from REMD@DFTB3 simulations indicating the expected Cope rearrangement (minimum energy pathway, **1**↔**2**, given in yellow) as well as an unexpected region corresponding to opening of the semibullvalenes structure to give dihydropentalene (**1**↔**3**, **2**↔**3**). **B:** Minimum energy pathways between the stable conformations presented in S3A.

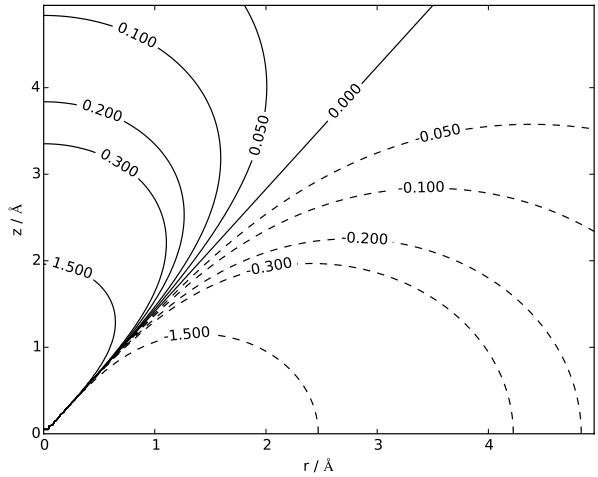

Figure S4. Pople ring current model map.

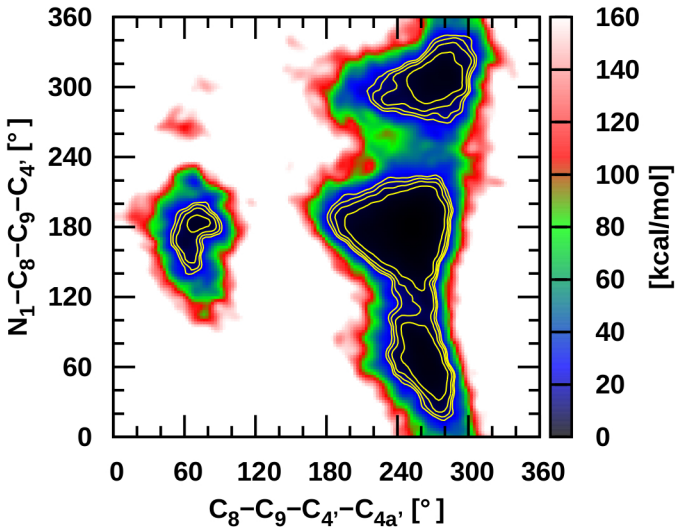

Figure S5. Free energy map of the diasteromer of the cinchona alkaloid catalyst. As expected, this map is the mirror of the map presented in Figure 6.

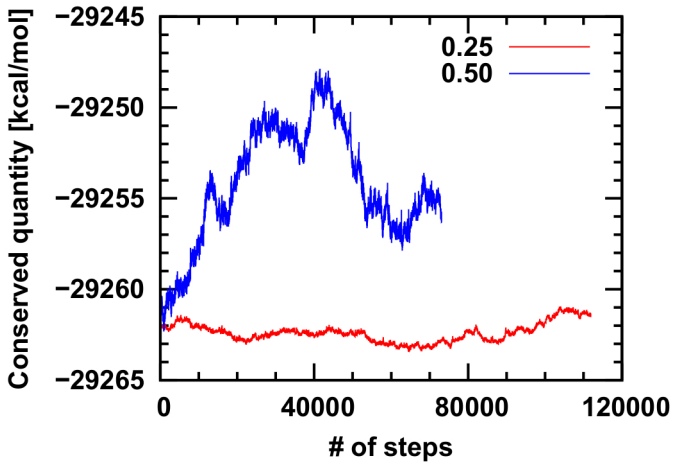

Figure S6. The energy conservation over simulation time at two different time steps (0.25 fs in red and 0.50 fs in blue) at 1500 K for the dithiacyclophane example.

Cartesian Coordinates of Relevant Structure

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40
Dithiacyclophane (1, Closed Configuration)
C      -1.02184     -2.39924      0.87577
C      -1.63316     -1.80133     -0.22393
C      -0.84692     -1.39415     -1.29582
C       0.53432     -1.56442     -1.28795
C       1.12024     -2.19775     -0.20046
C       0.34608     -2.61006      0.87727
H      -1.62173     -2.68595      1.73175
H      -1.31456     -0.91987     -2.15186
H       2.19320     -2.34620     -0.18076
H       0.82001     -3.07799      1.73098
C       1.39862     -1.12018     -2.44450
H       1.40916     -1.89559     -3.21434
H       2.42940     -0.98879     -2.11223
C      -3.11240     -1.55482     -0.24307
H      -3.46323     -1.38426     -1.26059
H      -3.65898     -2.40622      0.16314
S       0.88183      0.36311     -3.34888
S      -3.63526     -0.15539      0.80294
C       1.50958      1.74537     -2.36120
H       2.58996      1.64771     -2.25414
H       1.34105      2.59554     -3.02377
C      -2.65112      1.19006      0.08638
H      -3.32694      1.88475     -0.41215
H      -2.00011      0.75371     -0.66915
C      -1.82533      1.94567      1.13303
H      -1.37912      2.81898      0.64973
H      -2.50273      2.33115      1.89742
C       0.82538      2.01206     -1.02056
H      -0.24095      1.81615     -1.13497
H       0.91954      3.07948     -0.79224
C       1.35830      1.23278      0.15219
C       2.63617      0.78432      0.26872
C       0.58911      0.90825      1.32630
H       3.44299      0.89095     -0.43841
C       1.34371      0.20492      2.24871
C      -0.75037      1.14157      1.80910
C      -0.93072      0.57000      3.02727
S       2.95923     -0.04300      1.74962
S       0.46634     -0.22981      3.64960
H      -1.83428      0.58380      3.61656
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40
Dithiacyclphane (2, Open Configuration)
C       1.08766      2.41122     -1.74663
C       0.14248      1.79029     -2.55975
C       0.41796      0.52739     -3.06956
C       1.60804     -0.12654     -2.77083
C       2.53954      0.50819     -1.95385
C       2.28239      1.77413     -1.44693
H       0.87714      3.39167     -1.33562
H      -0.33416      0.01731     -3.66314
H       3.46916      0.00631     -1.71182
H       3.00869      2.25892     -0.80773
C       1.86193     -1.52101     -3.26656
H       2.89258     -1.81392     -3.06654
H       1.69496     -1.59381     -4.34197
C      -1.19120      2.43701     -2.80858
H      -1.19990      3.46165     -2.43664
H      -1.42648      2.46375     -3.87310
S       0.74384     -2.77352     -2.55927
S      -2.56733      1.50581     -2.06585
C       0.94392     -2.45354     -0.78423
H       0.96575     -3.42843     -0.29564
H       1.91838     -1.98643     -0.62935
C      -2.03790      1.49098     -0.33483
H      -2.21235      2.46612      0.12307
H      -0.96605      1.29246     -0.30060
C      -2.79158      0.40424      0.43484
H      -3.84101      0.68454      0.53815
H      -2.76312     -0.52326     -0.13922
C      -0.17370     -1.59419     -0.20513
H      -1.12640     -2.09690     -0.39328
H      -0.22014     -0.65187     -0.75653
C      -0.03704     -1.32235      1.26827
C       0.96044     -1.80111      2.05686
C      -0.96770     -0.53840      2.04285
H       1.79391     -2.41776      1.76070
C      -0.61270     -0.48920      3.37786
C      -2.18145      0.19480      1.79012
C      -2.67034      0.73929      2.93350
S       0.82389     -1.35288      3.72161
S      -1.71259      0.40910      4.33347
H      -3.56342      1.33625      3.03707
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40
Dithiacyclophane (3, Disarticulated Configuration)
C      -1.21395     -0.05493     -2.57969
C      -1.67637     -0.06526     -1.26900
C      -1.07129     -0.91514     -0.34725
C       0.00620     -1.71916     -0.70127
C       0.45673     -1.69616     -2.01838
C      -0.16141     -0.87990     -2.95387
H      -1.66715      0.61542     -3.30055
H      -1.43198     -0.92846      0.67657
H       1.30624     -2.30648     -2.30097
H       0.18930     -0.87370     -3.97793
C       0.69992     -2.54088      0.34634
H       0.81089     -3.57750      0.02420
H       0.13459     -2.53272      1.27761
C      -2.73417      0.88776     -0.80603
H      -3.53651      0.97785     -1.53887
H      -3.16017      0.55410      0.13806
S       2.41988     -2.01452      0.65539
S      -2.12239      2.60853     -0.64287
C       2.24504     -0.24897      1.02292
H       3.16222      0.21089      0.65386
H       1.42185      0.14272      0.42417
C      -0.48003      2.42923      0.10100
H       0.08474      3.27392     -0.29580
H      -0.02462      1.52615     -0.30301
C      -0.40628      2.46970      1.63310
H       0.64786      2.47937      1.91494
H      -0.82550      3.42049      1.96681
C       2.06239      0.08624      2.50727
H       2.13414      1.16846      2.63524
H       2.89011     -0.35167      3.06672
C       0.77116     -0.42788      3.06974
C       0.70733     -1.60095      3.75094
C      -0.54037      0.15471      2.90869
H       1.53646     -2.24921      3.98907
C      -1.51378     -0.65169      3.47901
C      -1.11931      1.35394      2.34829
C      -2.46393      1.38184      2.54514
S      -0.88966     -2.07121      4.20240
S      -3.09154     -0.00304      3.35812
H      -3.14005      2.16180      2.22919
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16
Semibullvalene (Reactant/Product)
C      -0.36223      1.23397     -1.22210
C      -0.93186     -0.17916     -1.25801
C      -0.12162     -1.02424     -0.61783
C       1.12574     -0.35494     -0.20982
C       1.11024      1.00999     -0.81704
C       1.08060      0.94889      0.67541
C      -0.20922      1.51499      1.10633
C      -0.99887      1.75951      0.05871
H      -0.52972      1.83342     -2.11406
H      -1.93829     -0.39681     -1.58963
H      -0.35592     -2.05116     -0.37387
H       2.04454     -0.91603     -0.11548
H       1.93718      1.42010     -1.37832
H       1.97537      1.11020      1.25959
H      -0.48373      1.65638      2.14251
H      -2.02464      2.09988      0.10611

16
Semibullvalene Cope Rearrangement TS
C      -0.30099      1.26151     -1.25953
C      -0.98066     -0.06307     -1.12022
C      -0.10143     -1.01473     -0.63270
C       1.14998     -0.45941     -0.42856
C       1.14871      0.99189     -0.78873
C       1.09301      1.19130      0.69218
C      -0.18912      1.52608      1.09238
C      -1.03762      1.58727      0.00028
H      -0.46166      1.86055     -2.15001
H      -2.00536     -0.23077     -1.41198
H      -0.38157     -2.01757     -0.34435
H       2.03451     -0.98220     -0.10062
H       1.97264      1.40784     -1.35948
H       1.96193      1.12080      1.32721
H      -0.50690      1.61394      2.12126
H      -2.07791      1.87154      0.01538
```