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SUPPLEMENTARY MATERIAL TO
**Introductory concept for teaching chirality – Symmetry of the
asymmetric**

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DERIVATION OF EQUATIONS

Derivation of equation for racemization thermodynamics:¹

$$\Delta G^{\circ} = \Delta H^{\circ} - T\Delta S^{\circ} \quad (1)$$

$$\Delta G^{\circ} = -RT \ln K \quad (2)$$

$$\Rightarrow K = e^{-\frac{\Delta H^{\circ} - T\Delta S^{\circ}}{RT}}, \Delta H^{\circ} = 0, \Delta S^{\circ} = 0 \quad (3)$$

$$K = 1, \text{ for every } T \quad (4)$$

where ΔG° is the standard reaction Gibbs energy, ΔH° is the standard reaction enthalpy, T is the temperature, ΔS° is the standard reaction entropy and R is the universal gas constant.

Derivation of an expression for racemization half-times:

Rate constants for enantiomer interconversions are obtained from the Eyring equation, using $\Delta^{\ddagger}G$ values from cited references and with an approximation $\kappa=1$:

$$k = \frac{\kappa k_B T}{h} e^{-\frac{\Delta^{\ddagger}G}{RT}} \quad (5)$$

where κ is the transmission coefficient, k_B is Boltzmann's constant, T is temperature, h is Planck's constant, $\Delta^{\ddagger}G$ is Gibbs free energy of activation and R is the universal gas constant.

Racemization half-times were obtained from kinetic law for the first order reactions approaching equilibrium, $E_1 \rightleftharpoons E_2$, when only E_1 is present at the start of the reaction, using calculated (equation 5) rate constants:²

$$[E_1] = \frac{k_1 + k_2 e^{-(k_1 + k_2)t}}{k_1 + k_2} [E_1]_0 \quad (6)$$

where $[E_1]$ is a concentration of E_1 , k_1 is the rate constant for the direct reaction, k_2 is the rate constant for the reverse reaction, t is reaction time and $[E_1]_0$ is the starting concentration of E_1 .

In the case of enantiomers:

$$k_1 = k_2 = k \quad (7)$$

$$\Rightarrow [E_1] = \frac{1 + e^{-2kt}}{2} [E_1]_0 \quad (8)$$

$$t = \frac{\ln\left(\frac{2[E_1]}{[E_1]_0} - 1\right)}{-2k} \quad (9)$$

Half of the sample is racemized when $\frac{1}{4}$ of $[E_1]_0$ is transformed:

$$\frac{[E_1]}{[E_1]_0} = \frac{3}{4} \quad (10)$$

$$\Rightarrow t_{1/2} = \frac{\ln\left(\frac{3}{4} - 1\right)}{-2k} \quad (11)$$

$$t_{1/2} = \frac{\ln\left(\frac{1}{2}\right)}{-2k} \quad (12)$$

$$t_{1/2} = \frac{0.347}{k} \quad (13)$$

REFERENCES

1. M. Quack, G. Seyfang, G. Wichmann, *Chem. Sci.* **13** (2022) 10598 (<https://doi.org/10.1039/D2SC01323A>)
2. P. Atkins, J. Paula, J. Keeler, *Atkins' Physical Chemistry*, 11th ed.; Oxford University Press, Oxford, United Kingdom, 2018; p. 737 (ISBN: 978-0-19-108255-9).

PROBLEMS

Practice:

Using quantum mechanical calculations, predict the IR spectrum of bromochloromethane molecule and create animations of all vibrations that correspond to bands visible in the predicted IR spectrum.

Task 1:

Using free software Vega ZZ, generate conformational diagrams for the following three biphenyls:

2,2'-dimethyl-1,1'-biphenyl (**A**)

2-tert-butyl-2'-methyl-1,1'-biphenyl (**B**)

2,2'-tert-butyl-1,1'-biphenyl (**C**)

a) All graphs have two maxima with different energies. Does the molecule have to pass through both of these barriers for enantiomer equilibration? Explain.

b) Considering only the lower maximum of generated conformational diagrams, which of these biphenyls could be separated to pure enantiomers on ambient conditions using ordinary laboratory methods? For the energy barrier consider the difference in energy between lower minimum and lower maximum. Energy values in the graphs are in kcal/mol.

c) Explain the trend in energy barrier from **A** to **C**.

Task 2:

Compare the most abundant conformations of 1,2-dibromoethane and 1,2-difluoroethane on the basis of chirality properties.

Task 3:

Enantiomers don't have exactly the same energy content in an achiral environment. The energy difference is so small that it hasn't been yet detected experimentally. If the difference in Gibbs free energy on 23 °C between enantiomers E_1 and E_2 is 2.292×10^{-14} kJ/mol, calculate the excess of the more stable enantiomer in the system consisting of 1 mol of E_1 and E_2 in total, in an equilibrium mixture.

SOLUTIONS

Materials and methods:

To prepare for practical exercises, the instructor and students have to download and install software for running the simulation. The choice of software is not limited to software recommended here.

For drawing the structures you can use any software that generates standard MOL files. We used Avogadro¹ (Avogadro is an open-source molecular builder and visualization tool; Version 1.20, <http://avogadro.cc/> (accessed 25.6.2023.)). Some of the software used have integrated tools for drawing molecules (MoCalc2012, Vega ZZ) and can be used as well.

For quantum mechanical calculations, we recommend either Firefly QC package², which is partially based on the GAMESS (US)³ source code. Firefly (Alex A. Granovsky, Firefly version 8, <http://classic.chem.msu.su/gran/firefly/index.html> (accessed 25.6.2023.)) or NWChem⁴ (<https://nwchemgit.github.io/> (accessed 25.6.2023.)). Firefly can be made available by sending an e-mail (instructions can be found on the website).

As a graphical user interface for input for QM software, we used MoCalc2012 (<https://sourceforge.net/projects/mocalc2012/> (accessed 25.6.2023.)).

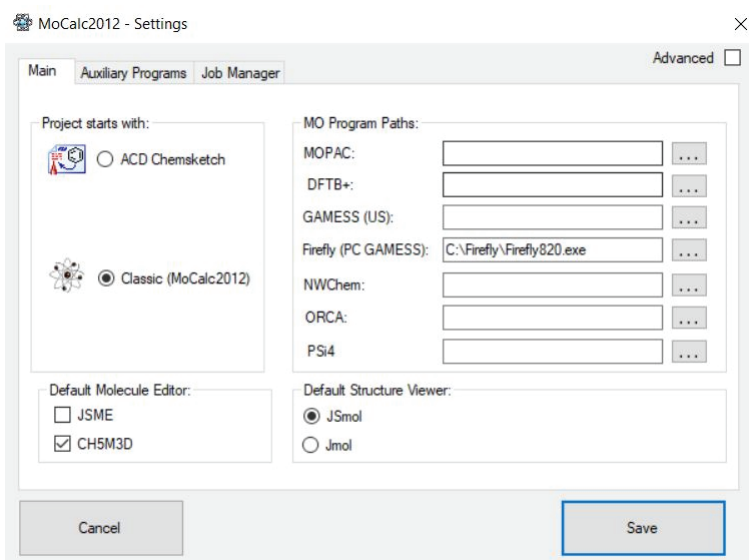
For visualization of the IR spectra in the first exercise, we used ChemCraft (Chemcraft - graphical software for visualization of quantum chemistry computations. Version 1.8, build 648. <https://www.chemcraftprog.com> (accessed 25.6.2023.)), available free of charge for the period of 150 days.

If JSmol is selected as Default Structure Viewer in MoCalc2012 Settings, visualization of IR spectra and isomers can be performed within MoCalc2012.

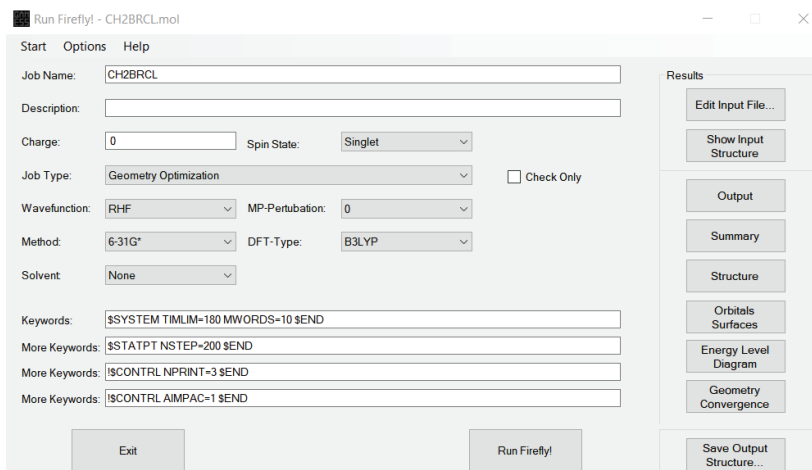
For conformation simulations, VEGA ZZ is used⁵ (<http://www.ddl.unimi.it/> (accessed 25.6.2023.)). Energies calculated using this program are more illustrative than accurate. The goal is to provide pedagogical exercise using free software.

Practice:

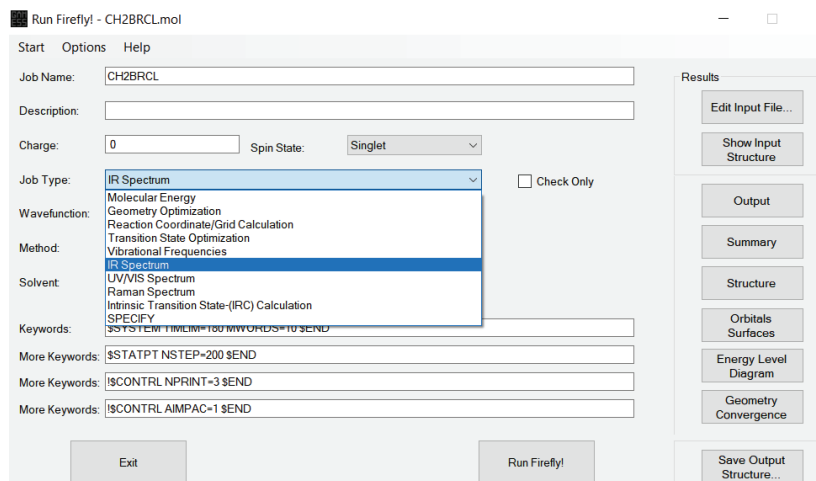
Using Avogadro (or any software that generates standard MOL files (ArgusLab, ChemDraw,...)) draw bromchlormethane. Save the structure as a MOL file. Open MoCalc2012 and attach a file for quantum mechanical calculations to the program: Options -> Settings -> On *Main* dialog, next to Firefly, choose the directory where the file for quantum mechanical calculations is.



Then click *Save* and choose QM program *Firefly* and open saved structure (Start -> Open Structure File; Ctrl+O). In the first step, we have to optimize geometry of molecule. On drop down menu *Job Type*: select Geometry Optimization, then select *Method* 6-31G* and *DFT-Type* B3LYP. Start optimization by clicking on Run Firefly!

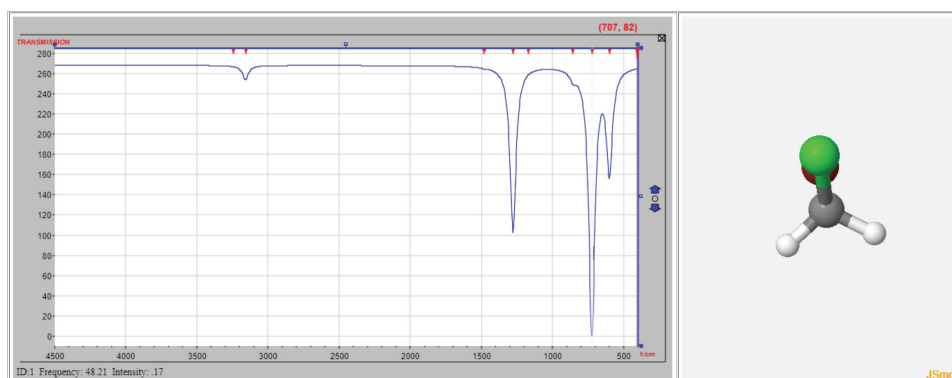


When Firefly finishes optimization, click on *Save Output Structure...* and save optimized molecule. Remember to change name of the molecule. Now open optimized structure and change *Job Type* to IR Spectrum. Leave *Method* and *DFT-Type*. Start calculations. When calculation finishes, you can visualize result.



If you use ChemCraft, find a file with a name of optimized structure and extension .gam. Open it and you will see the list of absorptions in cm^{-1} . Selecting one of the bands, you can see the appropriate vibration animated. You can enlarge movements by changing *Scale displacement* and/or show vibrational vectors by switching *Show displacement vectors* and *Scaled vectors* on and off.

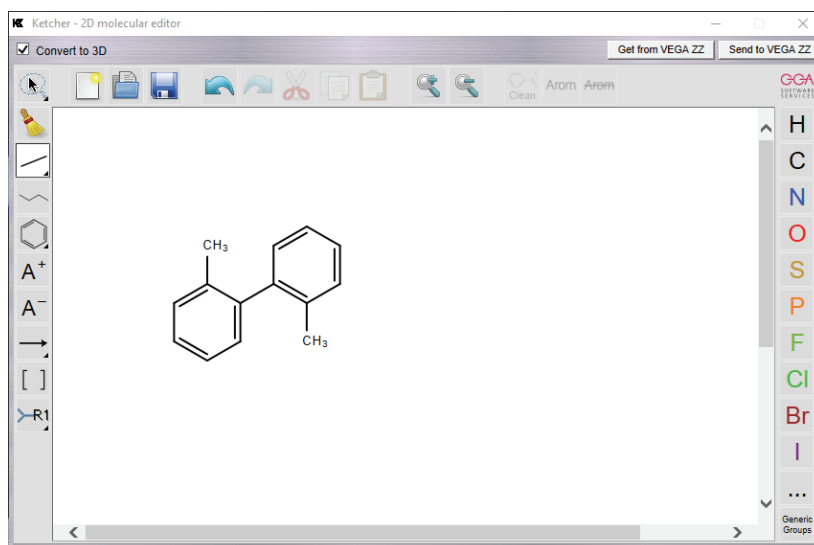
If you use MoCalc2012, when the calculation finishes, you can click on *IR Spectrum*. You will see absorption bands indicating absorption of specific energy from the spectrum, correlating with a specific vibration. If you click on *Vibrations* and select *Interactive correlation of animated vibrations to bands* you will be able to see spectra on the left, with marked absorption bands (red marks at the upper axis of the spectra), frequency related to the specific absorption (lower left part of the spectra window) and animated molecular vibrations corresponding to selected absorption band. Using the right mouse click on the animation window and selecting *Vibrations* menu, you can change the look and movements on screen.



Task 1:

Using available tools (Ketcher (Edit -> Ketcher) from Vega ZZ) to draw different 1,1'-biphenyl derivatives from the list.

- A - 2,2'-dimethyl-1,1'-biphenyl
- B - 2-*tert*-butyl-2'-methyl-1,1'-biphenyl
- C - 2,2'- *tert*-butyl -1,1'-biphenyl



Save them in suitable format (.mol2) or open it directly with Vega ZZ (*Send to VEGA ZZ* option). Every molecule is processed in same way:

After importing/opening molecule in Vega ZZ, run Conformational search (*Calculate -> Amp -> Conformational search*).

Torsion	Base	Steps	End

Torsion parameters		Search parameters	
Base:	0.00	Method:	Systematic
Steps:	6	Steps:	1000
End:	360.00	Temp.:	300.0
		RMSD:	60.00

Apply to:

Previous

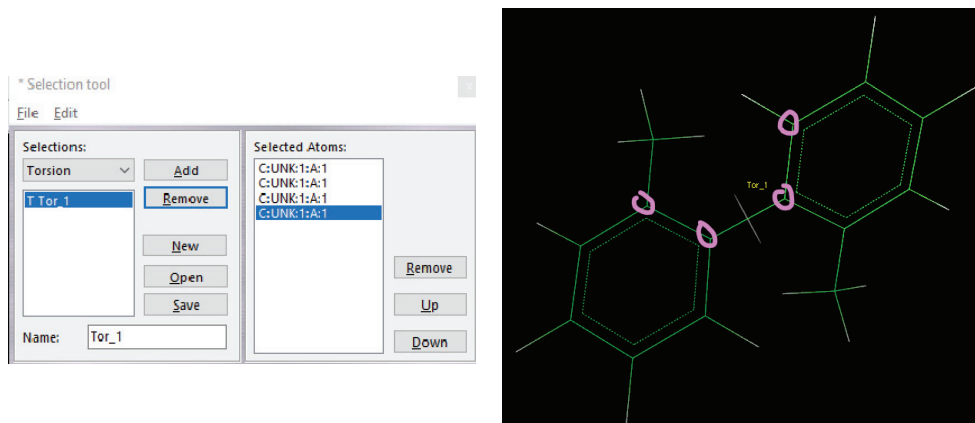
Minimized

Minimize all conformations

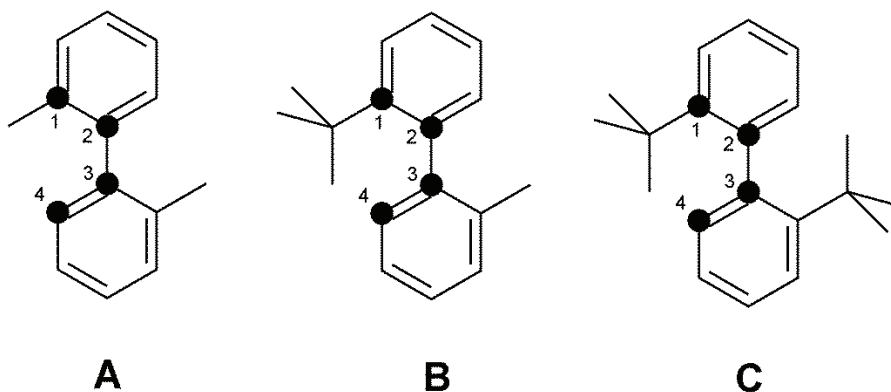
Steps: 50 Toler: 0.0100

On *Conformational search* dialog, click *Edit torsions* and then select torsion angle.

Torsion angle is selected on *Selection tool*. Click on *Add* and then select atoms in molecule on screen. As a *Torsion angle*, select C2-C1-C1'-C6'.

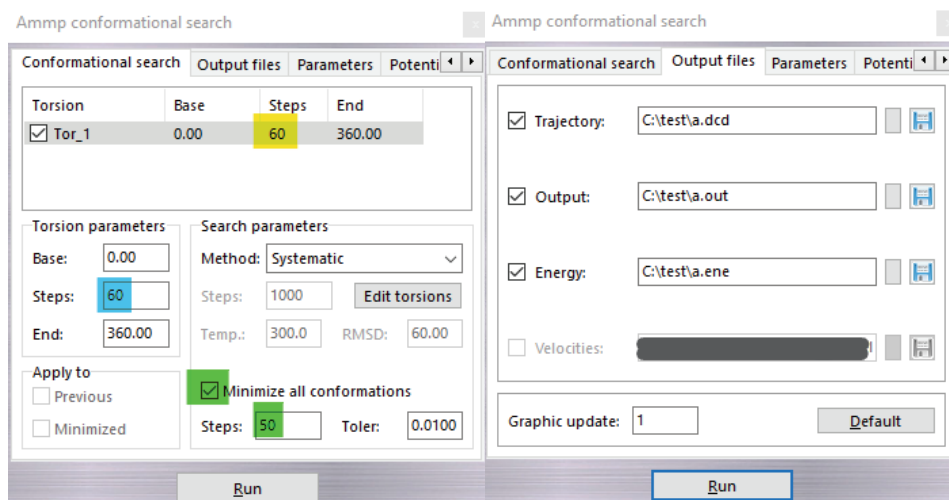


In this program, results can be dependent on the atoms chosen for defining the torsion angle. In the following Scheme 1 are presented ways of defining the torsion angles for **A**, **B** and **C** that we used:

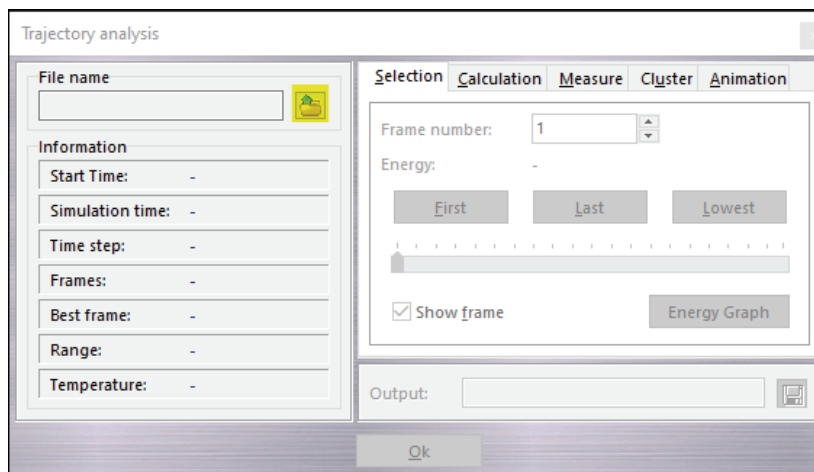


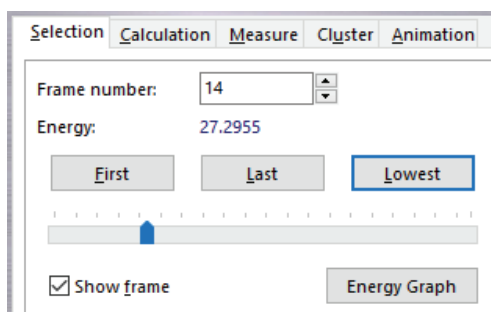
Scheme S-3.

When you selected the torsion angle, click on *Steps* in dialog window (yellow) and increase steps to 60 (blue). Select *Minimize all conformations* and input 50 steps. After that, on the tab *Output files*, select saving output files you need to disk.

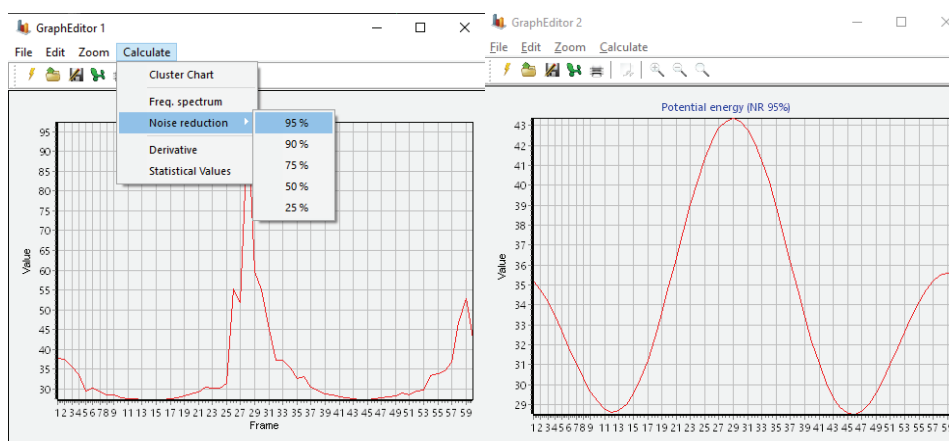


Then click *Run*. Calculations are finished very fast. Now select *Calculate* -> *Analysis*. Dialog box *Trajectory analysis* pops up. Click on *Open* icon, select .dcd file named as your compound that computer saved. Now you have option to see all conformations and their energies by moving the slider or changing the frame number.

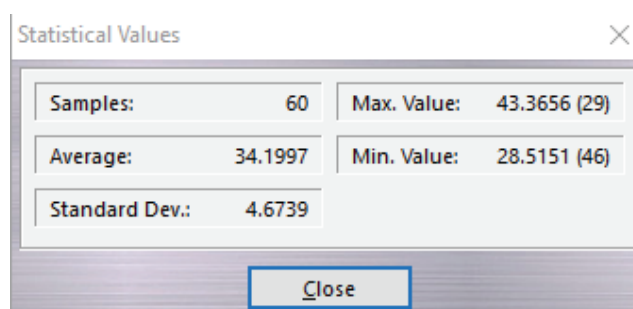




Clicking on Energy Graph, you will have a graphical representation of conformational analysis. If you switch on *Select conformation (Edit -> Sel. Conformations or CTRL+F)* your energy graph will be interactive, changing the conformation when you click on line on graphic.

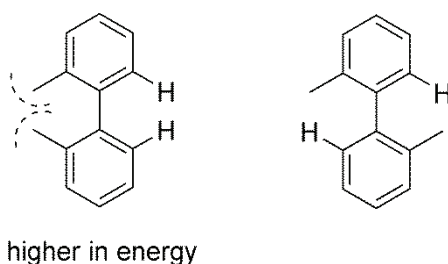


To smooth the graph, select *Calculations -> Noise reduction -> 95%*. Using *File* menu, you can export values to Excel or CSV file. If you want to calculate potential barrier, click on *Calculate -> Statistical Values*.



a) Conformational diagrams have two maxima because steric repulsion significantly increases in two conformations during full rotation, because

substituents on the biphenyl moiety get close to each other. These two conformations of **A** are depicted in Scheme 2.



Scheme S-4. The two conformations of 2,2'-dimethyl-1,1'-biphenyl (**A**) that are highest in energy

Enantiomers can interconvert by passing only through one of the barriers (because rotation about the C–C bond can happen in either direction). Interconversion is faster through the barrier of lower energy.

b) Whether a compound can be separated to enantiomers depends on its racemization half-time on the temperature of separation. Formulae for conversion of rotation barrier energy to racemization half-times are provided in Supporting Information 1 (along with their derivation).

A: 33.47 kJ/mol (8 kcal/mol)

$$k = \frac{\kappa k_B T}{h} e^{-\frac{\Delta \ddagger G}{RT}} \quad (1)$$

$$\Rightarrow k = 8.4 \times 10^6 \text{ s}^{-1} \quad (2)$$

$$t_{1/2} = \frac{0.347}{k} \quad (3)$$

$$t_{1/2} = 4.1 \times 10^{-8} \text{ s} \quad (4)$$

B: 67 kJ/mol (16 kcal/mol)

$$k = 11.2 \text{ s}^{-1} \quad (5)$$

$$t_{1/2} = 0.031 \text{ s} \quad (6)$$

C: 155 kJ/mol (37 kcal/mol)

$$k = 4.2 \times 10^{-15} \text{ s}^{-1} \quad (7)$$

$$t_{1/2} = 2.6 \times 10^6 \text{ years} \quad (8)$$

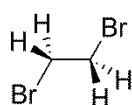
Based on these values, it can be concluded that **C** can be isolated as pure enantiomer on ambient conditions, while **A** and **B** cannot.

c) Tert-butyl group is bulkier than methyl group and consequently causes greater steric repulsion with methyl and hydrogen atom, so both of the barriers of

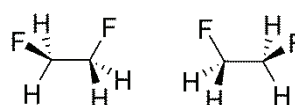
B are expected to be higher in energy than in **A**. By analogy, **C** is expected to have greater conformational barriers than **B**.

Task 2:

Task 2: The most stable conformer of 1,2-dibromoethane is anti (same as in *n*-butane). It is achiral. The most stable conformer of 1,2-difluoroethane is gauche.⁶ This conformation is chiral, so two enantiomeric conformations are a dominant form of 1,2-difluoroethane (Scheme 3).



the most stable conformation of
1,2-dibromoethane (achiral)



the most stable conformations of
1,2-difluoroethane (chiral)

Scheme S-5. 1,2-Dibromoethane and 1,2-difluoroethane are similar molecules, but a sample of 1,2-dibromoethane is dominantly composed of achiral structures and a sample of 1,2-difluoroethane is dominantly composed of chiral structures.

Task 3:⁷



$$\Delta G^\circ = 2.292 \times 10^{-14} \text{ kJ/mol} \quad (10)$$

$$\Delta G^\circ = -RT \ln K \quad (11)$$

$$\Rightarrow K = 0.99999999999999990316 \quad (12)$$

$$K = \frac{E_2}{E_1} \quad (13)$$

$$0.99999999999999990316 = \frac{E_2}{1-E_2} \quad (14)$$

$$E_2 = 0.49999999999999997579 \text{ mol} \quad (15)$$

$$E_1 = 1 - E_2 = 0.50000000000000002421 \text{ mol} \quad (16)$$

Excess of E_1 :

$$E_1 - E_2 = 4.842 \times 10^{-15} \text{ mol} \text{ or } 2.9052 \times 10^9 \text{ molecules} \quad (17)$$

REFERENCES

1. M. D. Hanwell, D. E. Curtis, D. C. Lonie, T. Vandermeersch, E. Zurek, G. R. Hutchison; *J. Cheminform.* **4** (2012) (<https://doi.org/10.1186/1758-2946-4-17>)
2. A. A. Granovsky, Firefly version 8, <http://classic.chem.msu.su/gran/firefly/index.html> (accessed 25.6.2023.)
3. M. W. Schmidt, K. K. Baldrige, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis, J.

- A. Montgomery, *J. Comput. Chem.* **14** (1993) 1347 (<https://doi.org/10.1002/jcc.540141112>)
4. E. Aprà, E. J. Bylaska, W. A. de Jong, N. Govind, K. Kowalski, T. P. Straatsma, M. Valiev, H. J. J. van Dam, Y. Alexeev, J. Anchell, V. Anisimov, F. W. Aquino, R. Atta-Fynn, J. Autschbach, N. P. Bauman, J. C. Becca, D. E. Bernholdt, K. Bhaskaran-Nair, S. Bogatko, P. Borowski, J. Boschen, J. Brabec, A. Bruner, E. Cauët, Y. Chen, G. N. Chuev, C. J. Cramer, J. Daily, M. J. O. Deegan, T. H. Dunning Jr., M. Dupuis, K. G. Dyall, G. I. Fann, S. A. Fischer, A. Fonari, H. Früchtl, L. Gagliardi, J. Garza, N. Gawande, S. Ghosh, K. Glaesemann, A. W. Götz, J. Hammond, V. Helms, E. D. Hermes, K. Hirao, S. Hirata, M. Jacquelin, L. Jensen, B. G. Johnson, H. Jónsson, R. A. Kendall, M. Klemm, R. Kobayashi, V. Konkov, S. Krishnamoorthy, M. Krishnan, Z. Lin, R. D. Lins, R. J. Littlefield, A. J. Logsdail, K. Lopata, W. Ma, A. V. Marenich, J. Martin del Campo, D. Mejia-Rodriguez, J. E. Moore, J. M. Mullin, T. Nakajima, D. R. Nascimento, J. A. Nichols, P. J. Nichols, J. Nieplocha, A. Otero-de-la-Roza, B. Palmer, A. Panyala, T. Pirojsirikul, B. Peng, R. Peverati, J. Pittner, L. Pollack, R. M. Richard, P. Sadayappan, G. C. Schatz, W. A. Shelton, D. W. Silverstein, D. M. A. Smith, T. A. Soares, D. Song, M. Swart, H. L. Taylor, G. S. Thomas, V. Tipparaju, D. G. Truhlar, K. Tsemekhman, T. Van Voorhis, Á. Vázquez-Mayagoitia, P. Verma, O. Villa, A. Vishnu, K. D. Vogiatzis, D. Wang, J. H. Weare, M. J. Williamson, T. L. Windus, K. Woliński, A. T. Wong, Q. Wu, C. Yang, Q. Yu, M. Zacharias, Z. Zhang, Y. Zhao, R. J. Harrison, *J. Chem. Phys.* **152** (2020) 184102 (<https://doi.org/10.1063/5.0004997>)
 5. A. Pedretti, A. Mazzolari, S. Gervasoni, L. Fumagalli, G. Vistoli, *Bioinformatics* **37** (2021) 1174 (<https://doi.org/10.1093/bioinformatics/btaa774>)
 6. I.E. E. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley-Interscience, United States, 1994, p. 609 (ISBN: 9780471016700)
 7. A. Guijarro, M. Yus, *The Origin of Chirality in the Molecules of Life: A Revision from Awareness to the Current Theories and Perspectives of this Unsolved Problem*, The Royal Society of Chemistry, Cambridge, UK, 2009, p. 46 (ISBN: 9780854041565).