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The DFT study on racemisation of atropisomeric biaryls

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The process of racemisation of atropisomeric biaryls was modelled by means of DFT calculations at an advanced B3LYP/6-31G* theoretical level. Thus, the detailed protocol of determination of the racemisation rate presented herein provides a practical prediction tool for elucidation of the configurational stability of atropisomers.

1. Introduction

Atropisomeric compounds play an important role in many fields of modern chemistry.[1,2,3,4,5] In an enantiomerically pure form, they are used as catalysts, ligands, liquid crystals, drugs, and valuable building blocks in fine organic synthesis (Fig. 1). By definition, atropisomers are separable rotamers which at a given temperature have a half-life time above 1000 seconds (16.7 minute), which corresponds to the rotation barrier energy ΔG= 93.5 kJ/mol.[6]

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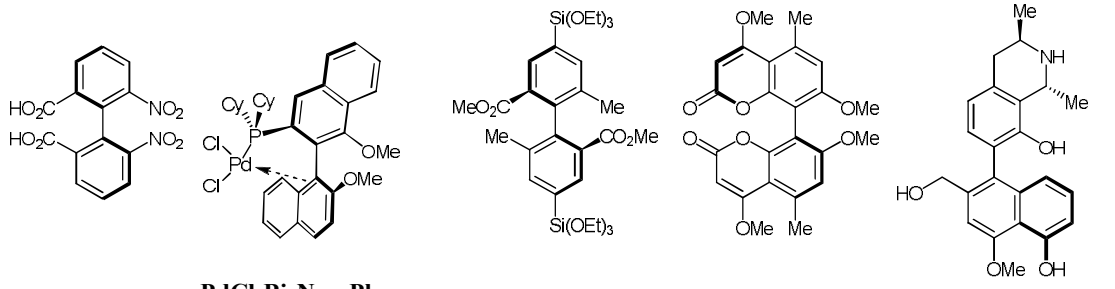


First atropisomers discovered by Kuhn in 1933

$PdCl_2$BisNap-Phos Chiral catalyst for Suzuki-Miyaura and Mizoroki-Heck cross-coupling reaction[7]

Atropisomeric biphenyl dopant for induction of liquid crystal phases[8]

(P)-(+)-Kotanin fungal metabolites[9]

(R)-Dioncopeltine A antimalarial activity[10]

Fig. 1. Some important atropisomers

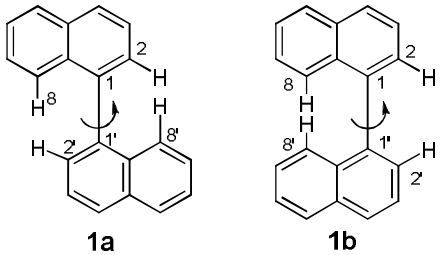
2. Results and Discussion

In the course of our studies on the synthesis and application of biaryl systems,[11, 12, 13, 14, 15] we found that atroposelective synthesis of some biaryls was impossible due to the rapid racemisation of the product during the reaction or storage. Since the desirable properties of the chiral atropisomeric biaryls are determined by their absolute configuration and optical purity, the studies on racemisation of such compounds have a practical value. Detailed analysis of literature indicated that, in the rarely published studies of racemisation of biaryls, authors provide only limited data concerning the racemisation pathway and possibility to predict the stability of newly formed biaryls.[16,17,18] Herein we present a detailed protocol of calculation of the rotation barrier and racemisation rate, which could be performed on a usual desktop PC. The proposed practical protocol could be used for prediction of thermal configurational stability of small atropisomeric molecules.

Possible paths of racemisation of 1,1'-binaphthyl

The mechanism of racemisation studied can be demonstrated on an example of 1,1'-binaphthyl (**1**) and calculated in detail on an affordable regular desktop PC. The DFT calculation at the B3LYP/6-31G* theoretical level was selected as a compromise between prompt calculation time and relevant values of energy in the outcome. It has already been successfully used for examination of several rotation processes around the C-C bonds of diversified chiral compounds.[19, 20]

Racemisation of **1** takes place as a result of rotation around the C-C bond connecting two naphthyl bicyclic moieties and runs via one of two possible paths. The first path leads through the transition ***anti*-TS** state, in which two hydrogen atoms at positions H2, H8' (or H2', H8) and two carbon atoms C1-C1' are located in the same plane where dihedral angle H2-C1-C1'-H8' is equal 0 degree - an ***anti*** path. The other path leads through the transition state ***syn*-TS,** in which two hydrogen atoms in position H8, H8' and two carbon atoms C1-C1' are located in the same plane where dihedral angle H2-C1-C1'-H8' is equal 180 degree - a ***syn*** path (Fig. 2). Obviously, a less energized form in which only H2, H2' and C1-C1' are in the plane does not create sufficient conditions for racemisation, since H8, H8' flattening requires much more energy.

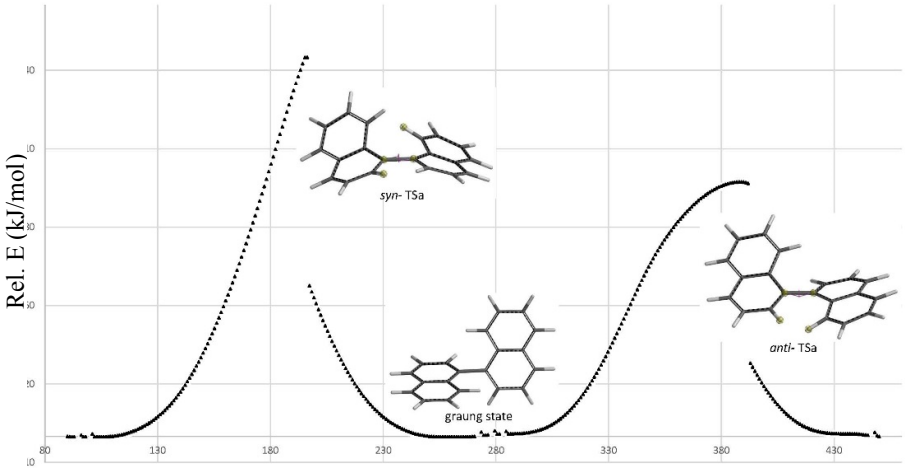


1a **1b**

Fig. 2. *Anti-* and *syn-* 1,1'-binaphthyl

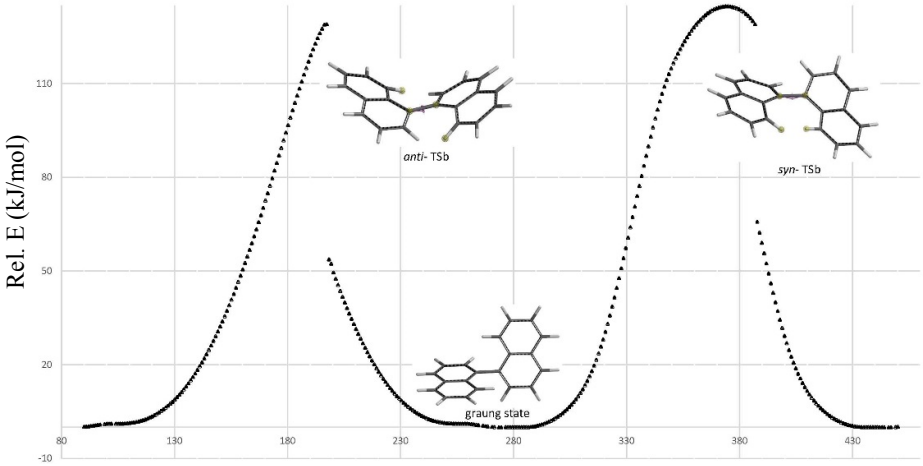
The DFT study of racemisation of 1,1'-binaphthyl

It is not obvious which pairs of four hydrogen atoms (H2-H8' or H8-H8') on the racemisation pathway first approach the plane with carbon atoms C1-C1'. Thus, to evaluate the racemisation paths, two competitive energy profiles **1a** and **1b** were modelled. These energy profiles were built as dependence of energy on restricted dihedral angles H2-C1-C1'-H8' (1a) or H8-C1-C2-H8' (1b) altering from 90 to 450 degrees (Fig. 3, 4). In the energy profiles **1a** and **1b,** maxima that correspond to the theoretically possible ***syn-*** and ***anti-*****TS** transition states of racemisation were observed (Fig. 3, 4).



Dihedral angles H2-C1-C1'-H8' of 1,1'-binaphthyl

Fig. 3. Energy profile **1a**: DFT level - B3LYP/6-31G*, DMF, 50 ^{o}C



Dihedral angles H8-C1-C1'-H8' of 1,1'-binaphthyl

Fig. 4. Energy profile **1b**: DFT level B3LYP/6-31G*, DMF, 50 ^{o}C

The preferred path of racemisation leads through a transition state with a minimum energy, i.e. the ***anti-*****TSa** transition state. The relationship between Gibbs free energy and entropy measurement or calculated at the constant temperature and pressure is defined by Eq. (1) as follows,

$$\Delta G = \Delta H - T\Delta S \quad (1)$$

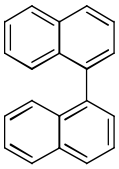
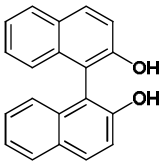
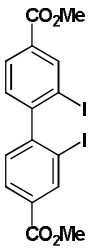
At the constant temperature, the enthalpy change ΔH is approximately equal to the internal energy change ΔE. Then the entropy change ΔS should not be significant in the case where inversion of the absolute configuration takes place; therefore, it is assumed that $\Delta G = \Delta E$.

Based on the data depicted in the energy profile **1a** (Fig. 3), it is possible to determine the activation energy of racemisation ΔG_{rac}. ΔG_{rac} is defined as the difference between the value of Gibbs energy of the transition state ($G^{\ddagger}_{rac}$ = 97.35 kJ/mol) and Gibbs energy of the stationary state (G^{0} = -0.15 kJ/mol). Thus, the calculated ΔG_{rac} of **1** based on the data from Fig. 3 is 97.5 kJ/mol.

Comparison of the experimental and theoretical data

The accuracy of our approach was confirmed by comparison of the theoretic and experimental kinetic data presented in Table 1.

Table 1. Comparison of experimental and calculated energies of racemisations

Entry	Biaryls	ΔG_{rac}, experimental	ΔG_{rac}, calculated
1	 **1**	98.5 kJ/mol (50 °C in DMF)[17]	97.5 kJ/mol (50 °C in DMF)
2	 **2**	155.5 kJ/mol (195 °C in naphthalene)[16]	162.2 kJ/mol (195 °C in toluene)
3	 **3**	93.5 kJ/mol (25 °C in DMF)[18]	94.5 kJ/mol (25 °C in DMF)

Calculation of the racemisation rate

Based on the calculated (or measured) value of ΔG_{rac}, we next determined the racemisation half-time applying the Eyring-Polanyi equation:

$$\kappa = \frac{\kappa_B T}{h} e^{-\frac{\Delta G^{\mp}}{RT}} \qquad (2)$$

where k is the reaction rate constant [s^{-1}]; T, measured temperature [K], ΔG_{rac}– energy of racemisation [J/mol]; R, universal gas constant, 8.314 [J/K·mol]; k_B, Boltzmann's constant, $1.38 \cdot 10^{-23}$ [J/K]; and h, Planck's constant, $6.63 \cdot 10^{-34}$ [J·s]

In the case of **1**, the calculated racemisation rate in DMF at 50 °C constant k is $6.72 \cdot 10^{12}$ s^{-1}. Racemisation of biaryls is a first-order reaction. Thus, the half-time of racemisation could be defined as a time after which enantiomeric excess (ee) of the compound is reduced to half of its initial value.

The half-time of the first order reactions does not depend on the initial concentration, so it can be calculated by the equation:

$$\kappa\tau_{1/2} = -\ln\left(\frac{\frac{1}{2}[A]_0}{[A]_0}\right) = -\ln\frac{1}{2} = \ln 2 \quad \text{and} \quad \tau_{1/2} = \frac{\ln 2}{\kappa} \tag{3}$$

where k is the reaction rate constant [s^{-1}], and $\tau_{½}$ is the half-time of racemisation. The half-time of 1,1'-binaphthyl (**1**) calculated in this way is 10.1 minutes. The relation between enantiomeric excess of **1** and the time of racemisation was drawn based on the definition of racemisation half-time (Fig. 5). This plot allows reading the enantiomeric composition of **1** at a given time.

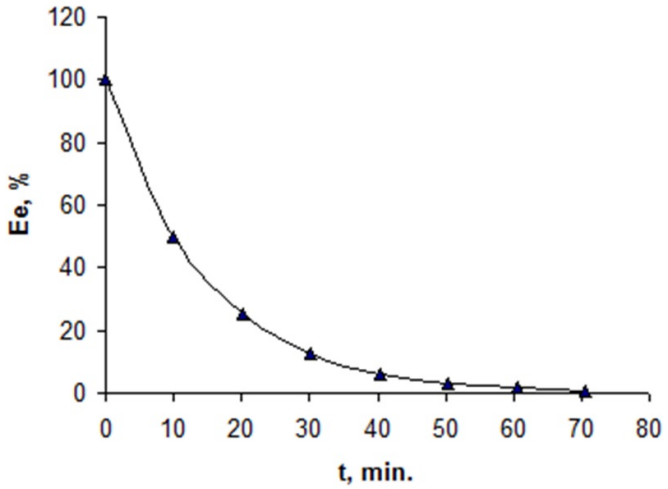


Fig. 5. Relationship between ee and the time of racemisation of **1**

Seeking dependence between ΔG_{rac} and ee of obtained products.

The deeper understanding of the process of racemisation of atropisomeric biaryls made it possible to design their rational synthesis and predict behaviour of such compounds in a variety of solvents and temperatures.

The easiest way to obtain atropisomeric biaryls is the Suzuki-Miyaura reaction (Fig.6). By utilisation of chiral catalysts in this reaction, formation of chiral non-racemic products can be expected.[6],[7] Nevertheless, the optical yield of the reaction depends not only on the efficiency of the catalysts used but also on the thermal configurational stability of formed products.

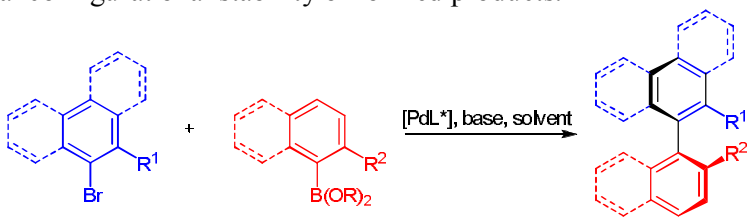


Fig. 6. Synthesis of biaryls by asymmetric Suzuki-Miyaura reaction

The configurational stability of tetra-*ortho*-substituted biaryls at moderate temperature is a rather obvious phenomenon; at the same time, tri- and especially di-*ortho*-substituted biaryls may undergo racemisation even under reaction conditions or during storage. Therefore, we performed DFT

calculation of the activation energies and half-times of racemisation of some products of the model asymmetric Suzuki-Miyaura reaction obtained in lower enantiomeric excesses. In the calculations we also considered the temperature at which the reactions were carried out (50 °C) (**Fig. 7**).[21]

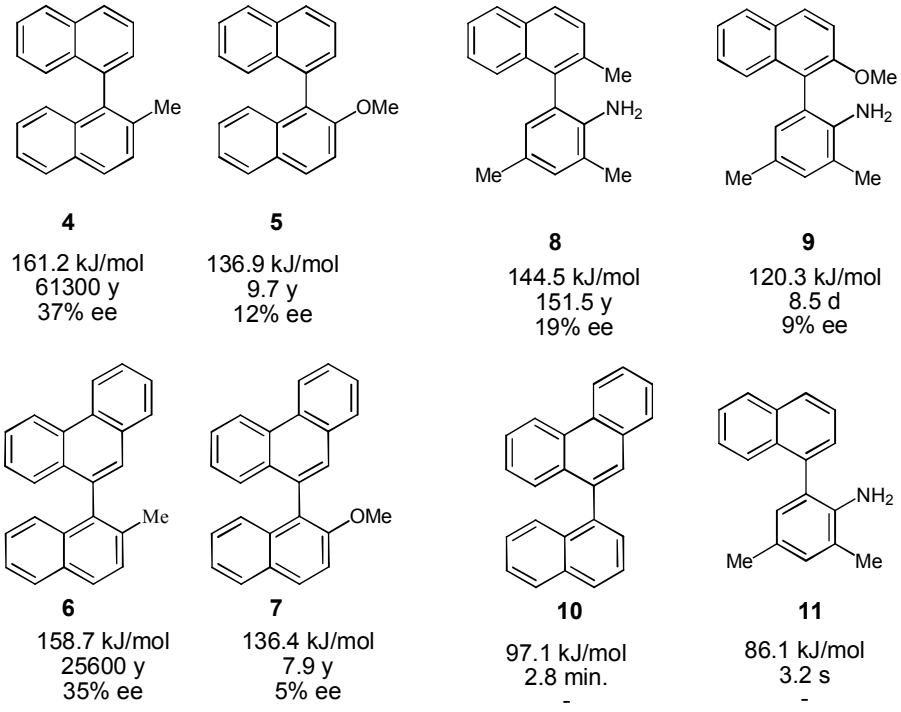


Fig. 7. ΔG_{rac} of biaryls obtained in model asymmetric Suzuki-Miyaura reaction[21]

The significant racemisation half-times obtained indicate that compounds **4-9** may exist as single enantiomers at this temperature of the reaction. This observation is indirectly confirmed in the model asymmetric Suzuki coupling reaction, where significant enantiomeric excess of the products obtained was found. Apparently, not only thermal stability determines the optical outcome of the reaction and additional efforts should be made towards obtaining compound **7** with higher stereoselectivity. In the case of compounds **10**, **11**, which were obtained with ee below the secure level of detection, the short racemisation half-times were predicted. Thus, we could speculate that those compounds may rapidly racemise and their asymmetric synthesis has not much sense (Fig. 7). This assumption was confirmed by experimental data showing that racemic mixtures were obtained in a reaction run under different conditions and mediated by all (ten available in our labs, based on ligands BINAP, DIOP, *BisNap*-Phos, Tol-BINAP, MOP, PFNH, DPCA, PFNME, PROPHOS and CHIRAPHOS) chiral catalysts based on chiral ligands of different structure and nature.

3. Conclusions

Visualisation of the racemisation process and the possible transition states provides deeper understanding of the studied phenomenon. The presented study demonstrates a practical and affordable approach to determination of thermal configurational stability of biaryl atropisomeric compounds by the investigation of the racemisation process using the user-friendly interface molecular modelling and computational chemistry application SPARTAN`10.[22, 23] The method described gives reliable results confirmed by independent experimental data; moreover, its applicability could be easily extended to other classes of atropisomeric compounds and relatively stable conformers.

Acknowledgements

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4. Experimental

4.1. Methodology

All calculations were carried out on a regular 32-bit desktop PC with processor IntelCore i3, 3.20 GHz and 5GB RAM. The computer program SPARTAN 10 (Windows edt.) of Wave function Inc. was selected because of its simple and user-friendly interface, while DFT calculation at the B3LYP/6-31G* theoretical level was chosen as a compromise between short calculation time and relevant values of energy of the stationary and transition states. The conditions of the model asymmetric Suzuki coupling reaction were also taken into account and the solvent (DMF) and temperature (50 ^{o}C) were considered in the calculations of the energies.

4.2. General procedure

Racemisation of 1,1'-binaphthyl. First of all, the stationary state of 1,1'-Binaphthyl was found as a result of Equilibrium Geometry calculation without any restriction at a PM3 level followed by DFT recalculation at an advanced B3LYP/6-31G* theoretical level with consideration of the DMF solvent and 50 ^{o}C temperature. In the calculation, we used a universal continuum solvation model SM8 developed by Truhlar and Cramer, which may be applied to compute partition coefficients, acidity constants, redox potentials, solubilities, temperature-dependent absolute free energies of solvation, and solvent effects on the solute structure and reactivity in aqueous and non-aqueous solvents and at complex interfaces.[24] Next, the dihedral angle formed by H2-C1-C1'-H8' atoms was restricted and a deviation of the value of this angle was set up in a range from 90 to 450 ^{o} in 200 steps. The Energy Profile was calculated at the B3LYP/6-31G* theoretical level with consideration of the solvent (DMF) and temperature (50 ^{o}C). As an outcome of the last calculation, a spreadsheet of 200 molecules with different restricted dihedral angles H2-C1-C1'-H8' was obtained. The Equilibrium Geometries of those molecules were recalculated respecting constraints and the curve of dependence between the constrained dihedral angle and energy (**Fig. 3**: energy profile **1a**) was built. Energy profile **1b** (**Fig. 4**) was built analogously as a dependence between dihedral angles H8-C1-C1'-H8' and energy. The activation energies of racemisation were read from the profiles as a difference between maximal and minimal values of the energies. The racemisation rate was calculated according to the Eyring-Polanyi equation, while the half-times of racemisation were calculated with an assumption that racemisation is a first-order reaction.

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