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Communication

Spontaneous resolution of chiral bis-sulfoxides with asymmetric atropisomerism

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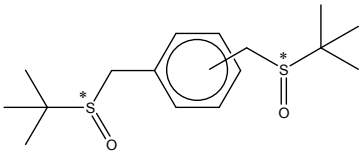
Restricted rotation of the *ortho* sulfinyl groups directs the *trans ortho*-substituted bis-sulfoxide (3) to adopt right-handed (*P*) or left-handed (*M*) conformations and produces symmetric atropisomeric (*R*, *R*)-3/(*S*, *S*)-3 and asymmetric atropisomeric enantiomers (*R,S*)-3, respectively. (*R,S*)-3 exhibits spontaneous resolution and crystallizes as conglomerate (*P,R,S*)-3/(*M,R,S*)-3 with homochiral supramolecular helix (*P/M*-helix) conformation.

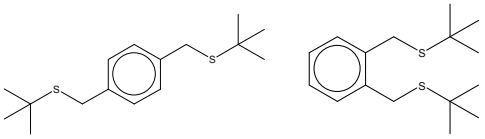
Generally, mixtures of mirror-image configurations or conformations of a racemic compound crystallize via racemic compound. However, some metal complexes,[1-3] organic chiral atropisomers [4,5] and salts of organic compounds[6] crystallize as conglomerates in which molecules forming the crystal are comprised of only one enantiomer. This is applicable in cases where the sample as a whole is racemic. [7,8] This phenomenon is known as spontaneous resolution which refers to the segregation of enantiomers upon crystallization. Spontaneous resolution is generally an unplanned separation of enantiomers.[8] Unfortunately, there is no clear explanation of how the spontaneous homochiral crystallization occurs, and is still one of the great challenges in stereochemistry. [8-10]

In the crystalline phase, hydrogen bonding and π-π stacking are sometimes invoked to explain the extent of spontaneous resolution.[10] On the other hand, some organic chiral compounds[4,5] exhibiting the atropisomeric structure also favor the possibility of spontaneous resolution.

In the field of asymmetric synthsis, atropisomeric sulfoxides, especially bis-sulfoxides, impart excellent chiral selectivity in rhodium-catalyzed asymmetric addition reactions,[11-15] and may act as conformational controllers.[16-23] Furthermore, chiral sulfinyl group has emerged as one of the most efficient and versatile chirality inducer in C-C and C-X bond formation reactions.[24,25]



1 : α,α'-di-*tert*-butylsulfinyl-*para*-xylene
2 : α,α'-di-*tert*-butylsulfinyl-*meta*-xylene
3 : α,α'-di-*tert*-butylsulfinyl-*ortho*-xylene



1s: α,α'-di-*tert*-butylthio-*p*-xylene **3s**:α,α'-di-*tert*-butylthio-*o*-xylene

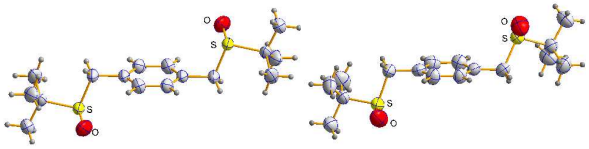
Scheme 1. Structure of bis-sulfoxides and bis-sulfides

In this communication, we wish to report the first spontaneous resolution of racemic atropisomeric bis-sulfoxides. A series of *ortho*-, *meta*- and *para*-disubstituted bis-sulfoxides were synthesized and characterized (Scheme 1). Further investigations revealed that atropisomeric *ortho*-disubstituted bis-sulfoxide (*P*/*M,R,S*)-**3** with asymmetric conformation exhibit an unprecedented spontaneous resolution.

Table 1. Crystal system compounds of **1-3, 1s and 3s**

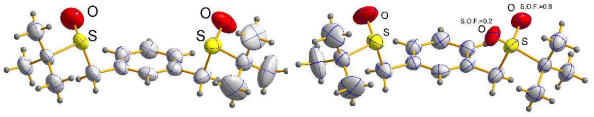
Com-pound	Crystal type	Space group	Confor-mation	Molecular point group
1	*rac*-**1**((*R*, *R*)-**1**, (*S*, *S*)-**1**)	$P2_1/c$	*trans*	C_2[a]
	meso-**1**((*R*, *S*)-**1**)	$P\bar{1}$	*trans*	C_i
1s	**1s**	$P\bar{1}$	*trans*	C_{2h}[a]
2	*rac*-**2**((*R*, *R*)-**2**, (*S*, *S*)-**2**)	$P\bar{1}$	*trans*	C_2[a]
	meso-**2**((*R*, *S*)-**2**)	$P2_1/c$	*cis*	C_s[a]
3	*rac*-**3**((*R*, *R*)-**3**, (*S*, *S*)-**3**)	$C2/c$	*trans*	C_2
	(*P, R, S*)-**3**	$P2_12_12_1$	*trans*	C_1
	(*M, R, S*)-**3**	$P2_12_12_1$	*trans*	C_1
3s	**3s**	$P\bar{1}$	*trans*	C_2[a]

[a] Approximate point group of conformation in the crystal structure.

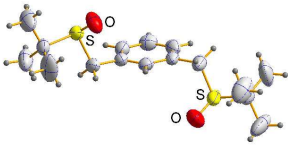


trans - *meso*-**1**((*R*, *S*)-**1**) *trans* - *rac*-**1**((*R*, *R*)-**1**, (*S*, *S*)-**1**)

Figure 1. ORTEP of *meso*-**1** and *rac*-**1** with thermal ellipsoids drawn at the 50% probability level.



cis - *meso*-**2**((*R*, *S*)-**2**) *cis* - **2**(with disorder of sulfinyl)



trans - *rac*-**2**((*R*, *R*)-**2**, (*S*, *S*)-**2**)

Figure 2. ORTEP of *meso*-**2** and *rac*-**2** with thermal ellipsoids drawn at the 50% probability level.

Bis-sulfoxides have been successfully employed in various asymmetric transformations and are gaining increased attention

recently.[11-13] Keeping this in mind, we introduced two *tert*-butylsulfinyl moieties to form potential atropisomeric bis-sulfoxides species **1**, **2**, and **3**, which have provided encouraging results in transition-metal catalyzed asymmetric reactions[14]. With two chiral sulfur center, compounds **1**, **2** and **3** should have at least three isomers with (***R, R***), (***S, S***) and (***R, S***) configurations. The isomers of compounds **1** and **2**, like most of the organic compounds, tend to form a bulk racemic crystal in achiral space group (Table 1). The structure of **1s**, a bis-sulfide, and its oxides *rac*-**1** and *meso*-**1** all show *trans* conformations (Figure 1**)**. The isomer *rac*-**2** exhibits *trans* conformation, while *meso*-**2** shows a *cis* conformation. Another crystal sample also showed a disorder *cis* structure in sulfinyl group of **2**. This means **2** may adopt *cis* or *trans* conformation in crystal steadily with partially restricted rotation (Figure 2**)**.

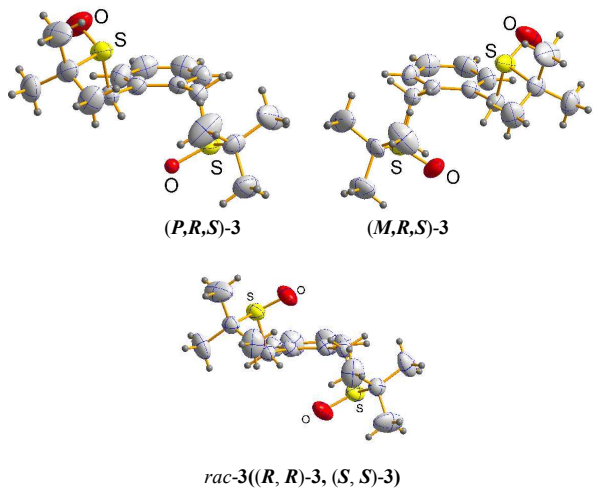


Figure 3. ORTEP of *trans* *rac*-**3** and enantiomers (***P,R,S***)-**3** and (***M,R,S***)-**3** with thermal ellipsoids drawn at the 50% probability level.

Owing to the significant repulsion between two *ortho*-sulfinyl groups, (***R, R***)-**3**, (***S, S***)-**3**, and (***R, S***)-**3** all adopt the *trans* form according to crystal structure analysis, while the (***R, R***)-**3** and (***S, S***)-**3** isomers crystallize to racemic crystal *rac*-3 with C_2-symmetric atropisomeric structures in the achiral *C*2/c space group. On the other hand, the restricted rotation of the *ortho* sulfinyl groups leads *trans* (***R, S***)-**3** to adopt right-handed (*P*) or left-handed (*M*) conformations and produces atropisomeric enantiomers (***P,R,S***)-**3** and (***M,R,S***)-**3** in the same chiral $P2_12_12_1$ space group, respectively (Figure 3). Apparently, spontaneous resolution occurs in the crystallization of (***R, S***)-**3**.

Figure 4 shows that (***P,R,S***)-**3** and (***M,R,S***)-**3** have very analogous geometries. With a 2_1-screw axis, molecules of (***P,R,S***)-**3** link together through bifurcated C-H…O hydrogen bonds ($d_{C...O}$ and $\theta_{C\text{-}H...O}$ are 3.259 Å and 135.1°; and 3.327 Å and 155.7° respectively) and C-H…π interaction ($d_{C...\pi}$ =3.799 Å), while an intramolecular hydrogen bond ($d_{C...O}$=3.244 Å) stabilizes its staggered molecular structure. The Flack parameter for (***P,R,S***)-**3** and (***M,R,S***)-**3** was 0.20 and 0.11, respectively. Figure 5 shows that (***R, S***)-**3** adopts a homochiral right/left-handed supramolecular helix (***P/M***-helix) held together by hydrogen bonds along the *a*-axis, which causes (***P,R,S***)-**3***/*(***M,R,S***)-**3** to crystallize as conglomerate. The precursor compound of **3** is α,α'-di-*tert*-butylthio-*o*-xylene (**3s**), a bis-sulfide, and its crystal is in the achiral $P\bar{1}$ space group. This suggests that the oxygen atoms of the sulfinyl groups in (***R,S***)-**3** are necessarily in the spontaneous resolution of (***P,R,S***)-**3** and (***M,R,S***)-**3**.

The observed atropisomerism in this case is obviously the result of the restricted rotation around the *ortho*-disubstituted benzene ring caused by the steric hindrance of *tert*-butylsulfinyl substituent. It is noteworthy that this atropisomerism leads to a conformational symmetry breaking of (***R,S***)-**3** with a C_1 molecular point group (Table 1), though the structures of the *rac*-**3(**(***R***, ***R***)-**3**, (***S***, ***S***)-**3)** have symmetric conformations with C_2 molecule point groups.

Importantly, in the *tert*-butylsulfinyl group of (***R,S***)-**3**, the maximum steric hindrance does not appear at *alpha* atom,[16,17] but at the remote *beta* atom of the substituent. This provides a new example of atropisomerism in *ortho*-disubstituted bis-sulfoxides, differing from *ortho*-substituted benzene, [16,17] biaryls[12,26] and 1,1`-binaphthyl[11] derivatives.

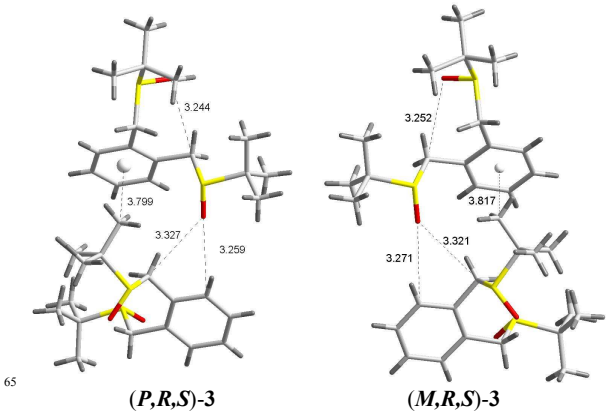


Figure 4. Distance of intermolecular interactions of (***P,R,S***)-**3** and (***M,R,S***)-**3**

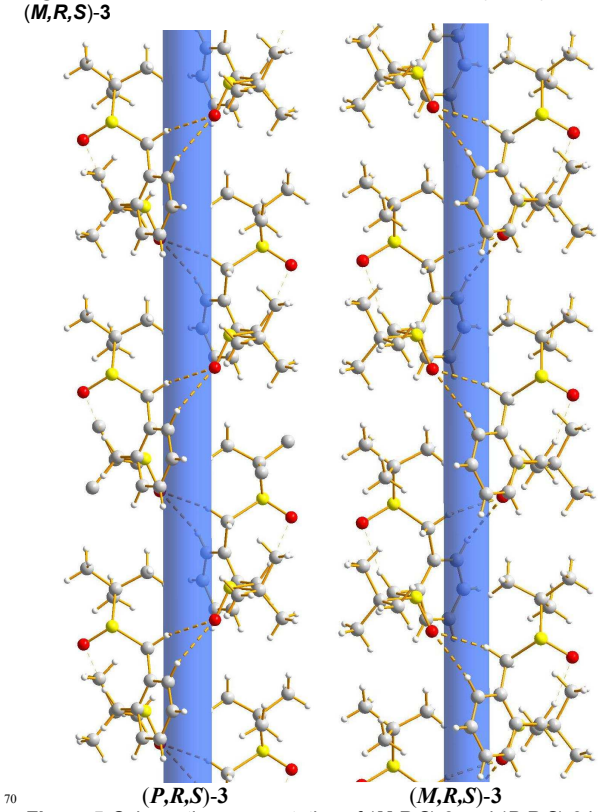


Figure 5. Schematic representation of (***M,R,S***)-**3** and (***P,R,S***)-**3** in crystals with homochiral helical structures.

In order to evaluate barrier energies of the above three sulfoxide, *ab initio* (MP2(FC)/6-31g(d,p))[27] calculations of the structure of (***R,S***)-**1,** (***R,S***)-**2** and (***P,R,S***)-**3** in the gas phase were carried out. Their X-ray crystal structures were used as a starting

point and energy minimizations were carried out for structures resulting from successive 10° rotations about the dihedral [S-C-C(Ar)-C(Ar)]. The resulting energies are shown in Figure 6, and indicates that in the gas phase the *trans* conformer (with dihedral [S-C-C(Ar)-C(Ar)] angle of around -100°) of (***P,R,S***)-**3** is more stable than the *cis* conformer (with dihedral angle of about 80°) by about 17 kJ·mol^{-1}. The calculated rotated barrier energies of 43.8 and 34.0 kJ·mol^{-1} for conversion of *tran* to *cis* conformation are significantly larger than that of (***R,S***)-**1** (20.0 and 19.7 kJ·mol^{-1}) and (***R,S***)-**2** (22.7 and 20.8 kJ·mol^{-1}). This suggests that (***R,S***)-**3** is easy to become atropisomer at a low temperature.

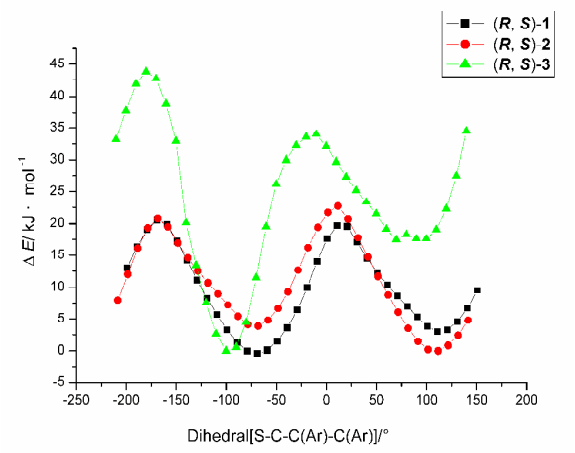


Fig.6 Optimized potential energy scan (MP2(FC)/6-31g(d,p)) along the dihedral [S-C-C(Ar)-C(Ar)] of (***R,S***)-**1,** (***R,S***)-**2** and (***R,S***)-**3**.

In summary, we report the first spontaneous resolution in chiral sulfoxides. Although, it is difficult to predict the occurrence of spontaneous resolution, it becomes obvious from the study that some of the properties, such as bifurcated C-H…O hydrogen bonding, π-π stacking and atropisomeric systems, may contribute towards the existence of spontaneous resolution.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental details, IR spectra, ^{1}H/^{13}C NMR spectrum, MS spectrum. CCDC 755516 (*rac*-**1**), 766255 (*meso*-**1**), 766254 (**1s**), 810941 (*rac*-**2**), 810942 (*meso*-**2**), 755513(**2** with disorder structure), 755514 (**3s**), 755515 ((*P,R,S*)-**3**), 833342(*rac*-**3**), and 833343 ((*M,R,S*)-**3**)]. These supplementary crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

‡ The crystal structures of the above compounds were determined by X-ray diffraction, measured with a CCD Bruker APEX II diffractometer using graphite monochromated Mo *K*α radiation (λ= 0.71073Å). The structure was solved and refined by direct methods using SHELXL.[28]

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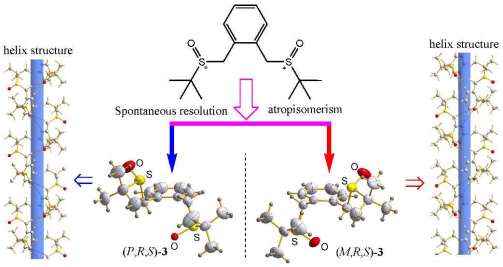
Graphical abstract



Atropisomeric *ortho*-disubstituted bis-sulfoxide (***P*/*M*,*R*,*S*)-3** with asymmetric conformation adopts a homochiral right/left-handed supramolecular helix and exhibit an unprecedented spontaneous resolution.