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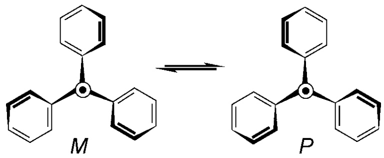
Trityl Ethers: Molecular Bevel Gears Reporting Chirality through Circular Dichroism Spectra**

*Jacek Ściebura, Paweł Skowronek, and Jacek Gawronski**

Dedicated to Professor Kurt Mislow

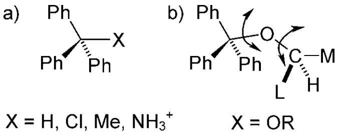
The study of the fascinating static and dynamic stereochemistry of molecular propellers was launched by Mislow and coworkers over 30 years ago and was followed by unprecedented intellectual and experimental efforts of other groups.[1] It is generally agreed that triarylmethyl systems exist in enantiomeric propeller structures in which all three aryl rings of a given molecule have the same sense of twist, either *P* or *M* (Scheme 1).



Scheme 1. Enantiomerization of the C_3-symmetric triphenylmethane propeller.

The transition structure (TS) of the enantiomerization of the triarylmethyl group can be achieved by correlated rotation of the rings.[2,3] Extensive dynamic NMR studies have shown that except for certain special cases, triarylmethyl derivatives with substituted phenyl or naphthyl rings[4] have a rotational barrier sufficiently low to prevent separation of residual (conformational) stereoisomers.[5] Although the process of enantiomerization can in principle involve four different pathways (zero-, one-, two-, and three-ring flip paths), the two-ring flip pathway[6] is considered a general rotational mechanism for C_3-symmetric propellers.[7,8] Zero- and one-ring flips are not seen as real pathways to enantiomerization since side-to-side orientation of the aryl substituents in the transition state would contribute enormously to the energy of the molecule (see Figure S1 in the Supporting Information).

Despite detailed stereochemical studies of elaborate triaryl entities, surprisingly little is known about the conformational properties of the triphenylmethyl (trityl) group. Trityl systems are apparently less suitable for dynamic NMR studies because of the low energy barriers to stereoisomers interconversion. The paucity of stereochemical studies is in contrast to the importance of the trityl group in synthetic chemistry. The trityl group attached to a heteroatom (O, S, N) is widely used as a versatile, acid-labile protecting group for hydroxy (e.g. in sugars and nucleosides), thiol, and amine groups.[9] Trityl derivatives often show interesting properties, either biomedical[10] or in designing supramolecular clusters,[11] helical nanotubes,[12] stators,[13] and disulfide cages.[14] We anticipated that the trityl ethers of chiral secondary alcohols would act as molecular bevel gears (Scheme 2), transmitting chiral information from the alcohol to the trityl system, enabling its ready deciphering by means of induced circular dichroism within the electronic transitions of the phenyl groups. This observation could then be confirmed by comparison with the calculated structural models and their corresponding calculated CD spectra. Despite its conceptual simplicity, this type of study has not been undertaken until now, although a few examples of optically active C_3-symmetric propellers have been reported.[15]



Scheme 2. Propeller (a) and bevel gear (b) models of triphenylmethyl group.

A brief literature survey of structures of triphenylmethyl derivatives Ph_3CX determined by X-ray diffraction showed that while the derivatives with formal C_3 symmetry (X = H, Me, Cl, NH_3^+; Table 1) have indeed the structures of molecular propellers (dihedral angles ω_1–ω_3[16] are of the same sign), it is not true for the trityl ethers (X = OR), for which we observe a breakdown of C_3 symmetry; that is, the two dihedral angles are of opposite sign to the sign of the third.

To test this hypothesis, we examined the trityl derivatives **1**–**12** of representative chiral alcohols. They show surprisingly strong, characteristic Cotton effect patterns in their CD spectra, as a result of a preferred helicity of the trityl group (Table 2).

The derivatives of *S* configuration (**1**–**4**, **6**) at the carbinol carbon atom give rise to a negative Cotton effect within the

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[*] J. Ściebura, Dr. P. Skowronek, Prof. J. Gawronski
Department of Chemistry, A. Mickiewicz University
Poznań (Poland)
E-mail: gawronsk@amu.edu.pl

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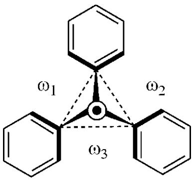
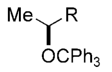
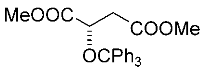
Table 1: Dihedral angles ω_1, ω_2, and ω_3 in Ph_3CX structures determined by X-ray diffraction.



X	ω_1	ω_2	ω_3	Ref.
H	−61	−51	−45	[19]
	66	62	47	
Me	−72	−66	−59	[20]
Cl	−66	−58	−57	[21]
	−67	−66	−60	
	−73	−72	−69	
$NH_3^+ PhSO_3^-$	−75	−61	−53	[11]
OEt	−56	−54	40	[22]
OCH(Me)Ph	69	−56	5	[23]



1 R = Et
2 R = *n*-C_6H_{13}
3 R = COOEt



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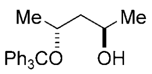

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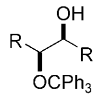
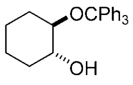


6 R = Me
7 R = COOMe
8 R = CONMe$_2$



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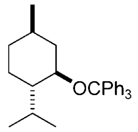

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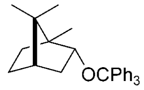

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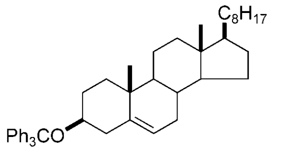

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Table 2: Selected CD ($\Delta\varepsilon$ [nm]) and UV data (ε [nm]) for chiral trityl ethers (in cyclohexane).

	$\Delta\varepsilon$ [nm]		ε [nm]
1	−3.8 (208)	16.7 (194)	84 500 (193)
2	−5.4 (205)	17.4 (194)	90 900 (195)
3	−9.8 (205)	40.2 (195)	80 600 (193)
4	−7.6 (204)	8.6 (195)	78 400 (194)
5	7.2 (209)	−21.4 (194)	74 300 (193)
6	−6.6 (210)	41.7 (196)	82 000 (195)
7	27.5 (205)	−40.4 (193)	75 000 (194)
8	66.4 (203)	−81.7 (191)	103 000 (193)
9	6.0 (210)	−42.2 (196)	73 600 (192)
10	25.6 (208)	−80.4 (194)	71 700 (193)
11	−15.8 (203)	36.4 (193)	79 600 (193)
12	−4.7 (217)	13.5 (197)	85 300 (192)

^1L_b transition range (ca. 225 nm) and a negative CD couplet within the strong ^1B band (195–210 nm), the opposite being true for *R* configuration (**5**, **7**–**10**). The only exception is the derivative (**11**) of (−)-borneol, because of its bicyclic structure. The insensitivity of sign of the Cotton effects to molecular conformation in the case of *R*,*R*-tartaric acid derivatives **7** and **8** is notable.[17] The sensitivity of the trityl probe to remote molecular chirality is illustrated with the derivative of cholesterol **12**. Although the C–O bond is flanked by the two CH_2 groups, the signs of the Cotton effects due to the trityl ether correctly follow the configurational scheme mentioned above because of the stereodifferentiation of the CH_2 and the CH=groups in the β position. Therefore, the trityl ethers constitute nearly ideal chromophores, superior to those previously reported,[18] for sensing chirality, that is, the difference in bulkiness of the substituents at the nearby chiral center. This is also the first example of using a trichromophoric derivative for sensing molecular chirality at one chiral center.

Molecular modeling, using a Monte Carlo search followed by DFT structure optimization, was carried out for a few achiral triphenylmethane derivatives Ph_3CX of formal C_3 symmetry and for representative chiral trityl ethers of formal C_1 symmetry (acyclic **1**, monocyclic **10**, and bicyclic **11**). Ph_3CX molecules are represented by single minimum energy propeller conformers of C_3 symmetry ($\omega_1 = \omega_2 = \omega_3$), and the dihedral angle ω increases in the order X = H (53°), X = F (59°), X = Cl (69°), according to the size of substituent X. In contrast, five conformers of **1**, differing in the conformation of the four-carbon-atom chain (*T*, G^-, G^+), one conformer of **10**, and two conformers of **11**, all of C_1 symmetry of the trityl group, were found within the 3 kcal mol^{-1} energy window (Table 3).

Table 3: Calculated conformer population for trityl ethers **1**, **10**, and **11**.

	Chain conformation	Conformer population [%]	ω_1	ω_2	ω_3	Conformer type
1a	*T*	55.5	−74	56	−6	*MPM*
1b	G^+	17	−79	54	−23	*MPM*
1c	G^+	15	79	−54	22	*PMP*
1d	G^-	6.5	−77	54	−17	*MPM*
1e	G^-	6	81	−54	25	*PMP*
			MPM/*PMP* = 79:21			
10		> 99	73	−56	5	*PMP*
11a		76.5	−79	55	−25	*MPM*
11b		23.5	76	−57	15	*PMP*
			MPM/*PMP* = 76.5:23.5			

With respect to the helicity of the trityl group, only two types of conformers were found, *MPM* (two ω angles negative, one positive) and *PMP* (two ω angles positive, one negative). One of the equal-sign dihedral angles ω is large (above 60°), the other is small (less than 30°), and the opposite sign ω angle is around 55° (see Figure S2 in the Supporting Information). The calculated CD spectra for the separate conformers of **1**, **10**, and **11** are distinct with regard to their helicity, either *MPM* or *PMP*, and population-averaged calculated CD spectra show satisfactory agreement with the experimental ones (see Figures S3 and S4 in the Supporting Information).

An additional benefit of the analysis of chirality transmission from the chiral atom to the trityl group through the difference of bulkiness of the L and M groups is the possibility of correlation of the pattern of the CD spectrum with the absolute configuration (Figure 1). In the cases studied herein (except for **11**), the order of L and M substituents follows the *R*/*S* configurational assignment; that is, the dominant *MPM* conformer corresponds to the *S* configuration, while the *PMP* conformer results from an *R* configuration at the chiral center.

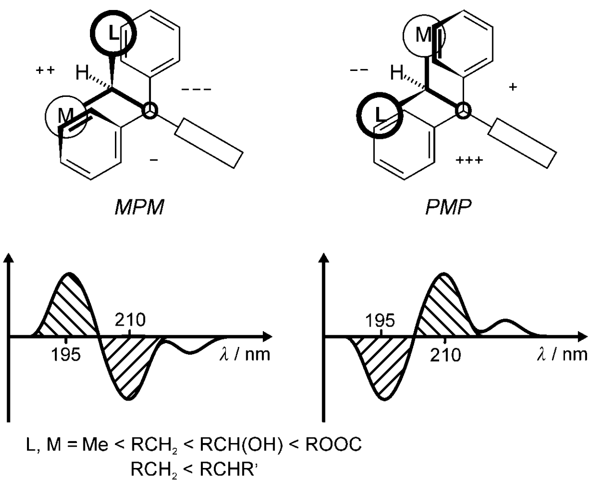

Figure 1. Correlation model of CD spectrum with the dominant conformation for chiral trityl ethers (projections down the O–CPh_3 bond).

However, the case of the bornyl derivative **11** requires more consideration. Molecular modeling results show that in the bicyclic skeleton the L group is the C7-*gem*-dimethyl group, rather than the C1 atom (C3 being the M group), resulting in the apparent reversal of the order of substituents according to their size.

A rather unexpected outcome of molecular modeling of individual conformers of **1** and the transition structures to diastereoisomerization is that while the structures of the low-energy conformers resemble the two-ring flip TS for triphenylmethane, the TS for diastereoisomerization is of propeller structure with uneven ω angles (Figure S5 in the Supporting Information). This result shows that the dynamic behavior of chiral trityl ether bevel gears differs from the classical Mislow model of C_3-symmetric propellers.

In summary, we demonstrated that the trityl group is not just a widely used protecting group. While the trityl moieties undergo virtually unhindered dynamic gearing through a transition state of C_s symmetry, we were able to observe residual stereoisomerism in trityl ethers by the combined use of CD spectra and computational methods. Trityl ethers behave as molecular bevel gears to sense and report chirality. It is worth mentioning that trityl ethers have a very favorable dissymmetry factor ($\Delta\varepsilon/\varepsilon$ up to 10^{-3}) for CD measurements. Our finding opens new possibilities of using CD spectroscopy as a tool for sensing dynamic equilibria of chiral residual stereoisomers of triarylmethanes and related systems, such as helical trityl-substituted isotactic polymers.[24]

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