Chirality

DOI: 10.1002/ange.200601869

Configurationally Stable Molecular Propellers: First Resolution of Residual Enantiomers**

*Tiziana Benincori, Giuseppe Celentano, Tullio Pilati, Alessandro Ponti, Simona Rizzo, and Francesco Sannicolò**

There is general consensus that three-bladed propeller-shaped molecules are operationally achiral because of the easy reversal of helicity at room temperature. A few attempts to control the specific configuration of the propeller were based on the introduction of chiral substituents.[1–3] We supposed that molecular propellers bearing identical blades devoid of any rigid stereogenic element could be obtained as configurationally stable enantiomers by exploiting residual stereoisomerism,[4–8] a phenomenon discovered by Mislow and up until now considered just as an academic facet of stereochemistry. Strict correlation of the ring torsional motion is a necessary condition for the existence of residual stereoisomerism.[4] We considered that this requirement is well satisfied in tris(2-alkyl-1-methyl-3-indolyl)phosphine oxides **1**, which are readily prepared in good yield from 2-alkyl-1-methylindoles (Scheme 1). The motional correlation is enhanced by increasing the size of the *ortho* group from methyl to ethyl and isopropyl (**1a**–**c**).

There are eight predictable chiral stereoisomers for **1**, which form four enantiomeric pairs[9] (Scheme 2). We used a sequence of four descriptors to describe each stereoisomer,

[*] Prof. F. Sannicolò
Dipartimento di Chimica Organica e Industriale
Università di Milano and CIMaINa—Centro Interdisciplinare Materiali e Interfacce Nanostrutturati
via Venezian 21 and via Celoria 16, 20133 Milano (Italy)
Fax: (+39) 02-5031-4139
E-mail: staclaus@unimi.it

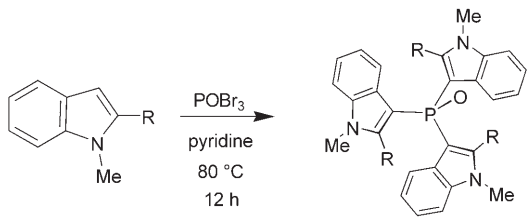
Dr. T. Pilati, Dr. A. Ponti, Dr. S. Rizzo
Istituto di Scienze e Tecnologie Molecolari—CNR
via Golgi 19, 20133 Milano (Italy)

Prof. T. Benincori
Dipartimento di Scienze Chimiche ed Ambientali
Università dell'Insubria
via Valleggio 11, 22100 Como (Italy)

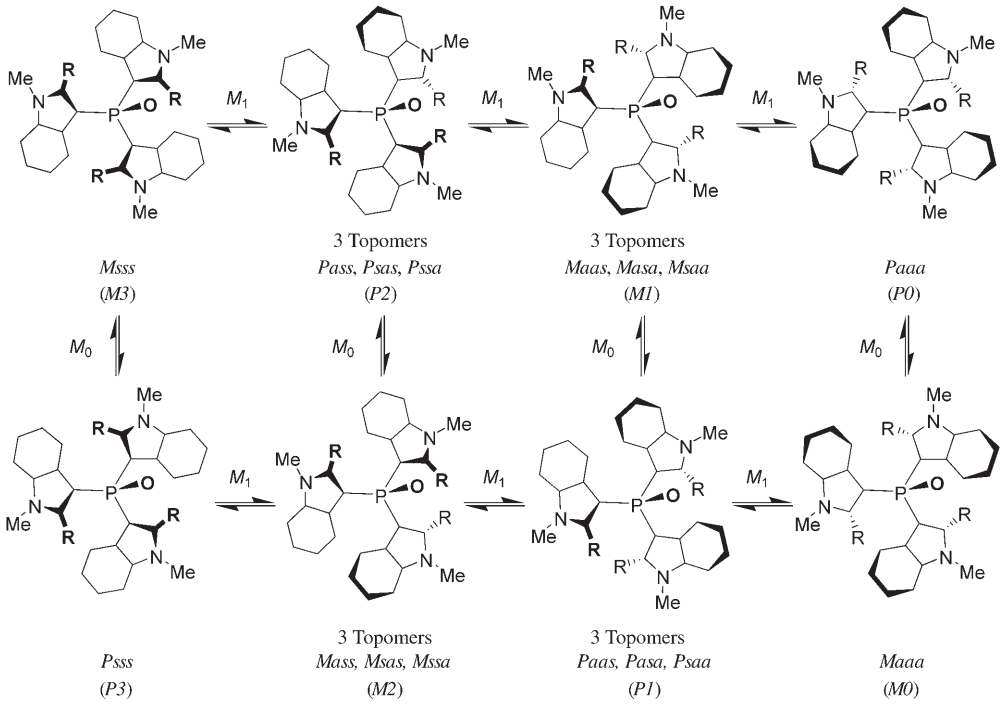
G. Celentano
Istituto di Chimica Organica "A. Marchesini"
Università di Milano
via Golgi 19, 20133 Milano (Italy)

[**] We thank Prof. M. Pierini (University of Rome "La Sapienza") for a preliminary HPLC simulation, Prof. M. Gullotti (University of Milan) for CD spectra, and Jasco Europe Srl for technical assistance in HPLC experiments with a circular dichroism detector. T.B. is grateful to the Dipartimento di Chimica Organica e Industriale of the Università di Milano for hospitality. Financial support from project FIRB2003-RBNE033 KMIA is acknowledged.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. The preparation of tris(2-alkyl-1-methyl-3-indolyl)phosphine oxides **1**.



Scheme 2. The eight possible stereoisomers of **1** and their interconversion processes. Each row, which comprises four stereoisomers, represents the residual enantiomers. The double bonds of the indole structures are omitted for clarity.

the first one refers to the helicity (*P*, *M*) and the three others describe the orientation of the priority (CIP rules) edge of each ring with respect to the P=O bond. We used indices *s* (contraction of *syn*) and *a* (contraction of *anti*) according to the usual rules for simple rotors. Given the identity of the aryl rings, one can also use a simpler notation *Xn* (in brackets in Scheme 2), *X* is the helicity and *n* is the number of rings with index *s*. There are four stereomerization mechanisms M_k, characterized by the number ($k = 0, 1, 2, 3$) of rings undergoing edge interchange with respect to the reference plane (the plane defined by the three carbon atoms bound to the phosphorus atom). The other rings "flip", that is, they pass through a plane perpendicular to the reference plane. All four isomerizations involve helicity reversal.[9] The M_1 mechanism,[6,7,10–13] which involves one edge interchange and two ring flips is, without known exception, the threshold stereomerization mechanism.[11] It does not allow free interconversion inside the full set of eight isomers, but only within two closed subsets of four isomers each, namely {*M3*, *P2*, *M1*, *P0*} and {*P3*, *M2*, *P1*, *M0*}. As the stereoisomers belonging to one subset are enantiomers of those present in the other one, the two subsets of isomers are residual enantiomers. The M_0 mechanism only inverts the helicity and therefore converts any stereoisomer into its enantiomer; M_2 also converts stereoisomers from different subsets, whereas M_3 converts stereoisomers within a single subset.

Before undertaking the difficult task of the resolution of **1**, we resorted to DFT-B3LYP calculations to check whether the residual enantiomers of **1** could be stable enough to be separated. The main computational results are reported in Table 1 and Table 2. The most stable isomers are *X3* ($X = M, P$) in all cases. The *X3* isomers largely predominate with a molar fraction larger than 98% at 298 K, small amounts of *X2* isomers can be present with a molar fraction of less than 2%, and the *X1* and *X0* isomers are virtually absent. The activation barriers involved in the M_1 mechanism are low enough that the M_1 isomerizations should be fast even at room temperature. The barriers of the M_0 mechanism are higher than 100 kJ mol^{-1}. M_0 stereomerization is slower than M_1 as all three indole moieties are parallel to the P=O bond and steric strain is larger in its transition states. The antipodes of **1a** should be not configurationally stable enough at room temperature to be isolated in a pure state (enantiomerization half-life, $t_{1/2} \cong 2$ days), whereas **1b** ($t_{1/2} \cong 1$ month) and **1c** ($t_{1/2} \cong 10^4$ years) are increasingly stable. The transition

Table 1: Computed relative energies and Boltzmann population of the stereoisomers of tris(2-alkyl-1-methyl-3-indolyl)phosphine-oxides **1a**–**c**.[a]

Isomer	**1a**		**1b**		**1c**	
	ΔE [kJ mol^{-1}]	Population [%]	ΔE [kJ mol^{-1}]	Population [%]	ΔE [kJ mol^{-1}]	Population [%]
X3	0	98.6	0	99.4	0	97.8
X2	13	1.4	15	0.6	12	2.2
X1	27	0.0	39	0.0	27	0.0
X0	39	0.0	58	0.0	37	0.0

[a] DFT B3LYP/3-21G* calculations with thermal correction within the harmonic approximation; relative energies ΔE and percentage Boltzmann population are given.

Table 2: Computed activation parameters for the *M3*⇌*P2* and *M3*⇌*P3* stereomerizations by the M_1 and M_0 mechanisms, respectively, in **1a–c**.[a]

Process	Parameter	**1a**	**1b**	**1c**
M3⇌*P2* via M_1	$\Delta E^{\neq}$ [kJ mol^{-1}]	33	38	36
	$\Delta H^{\neq}$ [kJ mol^{-1}]	29	34	33
	$\Delta S^{\neq}$ [J K^{-1} mol^{-1}]	−30	−54	−26
	$\Delta G^{\neq}_{25^\circ C}$ [kJ mol^{-1}]	38	51	40
M3⇌*P3* via M_0	$\Delta E^{\neq}$ [kJ mol^{-1}]	98	104	122
	$\Delta H^{\neq}$ [kJ mol^{-1}]	95	100	130
	$\Delta S^{\neq}$ [J K^{-1} mol^{-1}]	−33	−36	−47
	$\Delta G^{\neq}_{25^\circ C}$ [kJ mol^{-1}]	105	111	144
	$t_{1/2}$ (25 °C)	≈2 days	≈1 month	≈10^4 years

[a] DFT B3LYP/3-21G* calculations with thermal correction within the harmonic approximation: Activation enthalpy ($\Delta H^{\neq}$), entropy ($\Delta S^{\neq}$), free energy at 25 °C ($\Delta G^{\neq}_{25^\circ C}$), and enantiomerization half-life at 25 °C ($t_{1/2}$(25 °C)).

states for the M_2 and M_3 mechanisms could not be located as a result of the huge steric overcrowding between edge exchanging rings. Hence, the picture that arises from the computational results is that 1) *M3* and *P3* are the major isomers in all cases; 2) M_1 isomerizations within each residual enantiomer are fast at room temperature in all cases; 3) the rate of the M_0 isomerization, and thus the configurational stability of residual antipodes, is very sensitive to the size of the *ortho* alkyl substituent and small enough that the more sterically crowded terms are configurationally stable.

In agreement with the calculations, only *X3* isomers were observed by X-ray diffraction (XRD) studies in the crystals of **1a–c** (see Figure 1a and the Supporting Information). Also ^{1}H and ^{13}C NMR spectroscopic analysis revealed the presence of a single C_3-symmetric enantiomeric pair in solution down to −90 °C.

Resolution by chiral HPLC with a circular dichroism (CD) detector provided the experimental proof that **1a** is a residual racemate. The first eluted enantiomer shows negative ellipticity at $\lambda = 230$ nm and positive ellipticity at $\lambda = 280$ nm. The opposite behavior is obviously exhibited by its residual antipode (Figure 1b). These experiments are direct evidence of the first successful resolution of a residual racemate. Variable-temperature (VT; 0–70 °C) HPLC experiments with UV detection demonstrated, however, the interconversion between the residual enantiomers (Figure 1c). A small plateau is observed at 0 °C and the peaks coalesce at 70 °C. The dynamic HPLC profiles have been accurately fitted by exploiting the stochastic theory of chromatography.[14,15] This approach provided the M_0 enantiomerization activation parameters for **1a** (Table 3), which is not configurationally stable at room temperature, in satisfactory agreement with the calculations.

Table 3: Experimental activation parameters for the *M3*⇌*P3* stereomerization by the M_0 mechanism in **1a–c**.[a]

Parameter	**1a**[b]	**1b**[c]	**1c**[c]
$\Delta H^{\neq}$ [kJ mol^{-1}]	77 ± 3	102.5 ± 0.1	127 ± 4
$\Delta S^{\neq}$ [J K^{-1} mol^{-1}]	−87 ± 10	−86.5 ± 0.1	−93 ± 3
$\Delta G^{\neq}_{25^\circ C}$ [kJ mol^{-1}]	103 ± 4	128.2 ± 0.1	155 ± 4
$t_{1/2}$(25 °C)	≈7 h	≈20 years	≈10^6 years

[a] Activation enthalpy ($\Delta H^{\neq}$), entropy ($\Delta S^{\neq}$), free energy at 25 °C ($\Delta G^{\neq}_{25^\circ C}$), and enantiomerization half-life at 25 °C ($t_{1/2}$(25 °C)). [b] Dynamic HPLC analysis. [c] Dynamic ^{1}H NMR spectroscopic analysis.

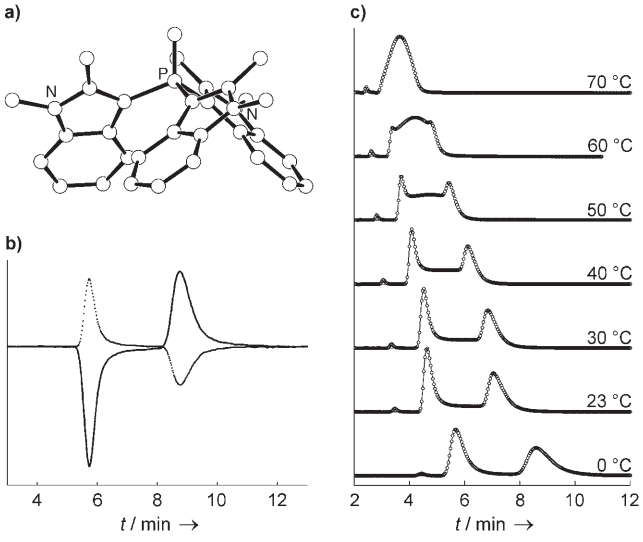


Figure 1. a) XRD structure of tris(1,2-dimethyl-3-indolyl)phosphine oxide (**1a**) at 90 K (hydrogen atoms are omitted; the N atom on the indole (front right) is eclipsing the N atom on the indole ring behind it). b) Chiral HPLC with CD detection of **1a** at room temperature (solid line: detection at 230 nm; dotted line: detection at 280 nm). c) VT dynamic HPLC of **1a** (open circles: experimental; solid line: optimized).

Also in the case of **1b**, chiral HPLC proved very efficient in resolving the racemate (Figure 2a), but the enantiomerization plateau is not observed in this case, so **1b** has a larger configurational stability than **1a**. The methylene protons in **1b** are diastereotopic as long as the enantiomerization by the M_0 mechanism is slow, otherwise they are enantiotopic. Hence, they are effective probes for dynamic ^{1}H NMR experiments[16] (Figure 2b). The shape variation of their complex multiplet near $\delta = 3$ ppm with increasing temperature allowed us to estimate the M_0 barrier parameters that are reported in Table 1.[17] The enantiomerization half-life time is about 20 years at room temperature, therefore **1b** is the racemate of configurationally stable residual enantiomers.

Following the same line of reasoning and exploiting the diastereotopism of the isopropylic methyl groups, the M_0 barrier parameters could be estimated for **1c** as well (Figure 2e and Table 1). In agreement with our calculations, **1c** is the racemate of extremely stable residual enantiomers: the M_0 barrier is estimated to be much larger than that of **1b** and the half-life time of **1c** is estimated to be about 10^6 years. As expected, chiral HPLC experiments carried out on **1c** do not show any evidence of enantiomerization up to 60 °C. In this case, we have been able to obtain some milligrams of almost enantiopure residual antipodes of **1c** by semipreparative HPLC (Figure 2c). The first eluted enantiomer is dextrorotatory (589 nm, CH_2Cl_2) and has been isolated in

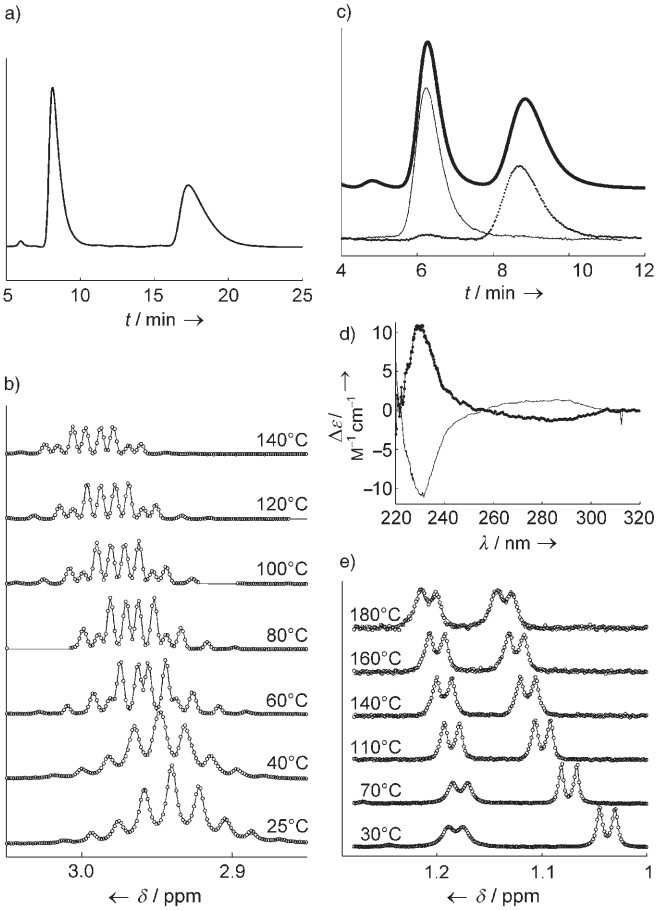


Figure 2. a) Chiral HPLC with UV detection of **1b** at 23 °C. b) VT ^{1}H NMR ([D$_6$]DMSO) spectra of the methylene protons of **1b** (open circles: experimental; solid line: optimized). c) Control of the enantiomeric purity of the residual enantiomers of **1c** obtained from semi-preparative chiral HPLC resolution (thick line: residual racemate; thin line: dextrorotatory residual enantiomer; dotted line: levorotatory residual enantiomer (see text)). d) CD spectra (CH_2Cl_2) of the residual enantiomers of **1c** (solid line: dextrorotatory residual enantiomer; dotted line: levorotatory residual enantiomer). e) VT ^{1}H NMR ([D$_6$]DMSO) spectra of the isopropylic methyl protons of **1c** (open circles: experimental; solid line: optimized).

very high enantiomeric purity (e.r. $> 99.5\,\%$). The enantiomeric ratio of the second eluted enantiomer was 95 %. Their CD spectra ($c = 5 \times 10^{-4}$ M, CH_2Cl_2) are identical in shape and opposite in sign (Figure 2d). These experiments are direct evidence of the successful isolation of residual enantiomers.

We have thus demonstrated that configurationally stable residual enantiomers can be rationally designed and easily synthesized.

As triarylphosphine oxides can be transformed into the corresponding phosphines, we performed preliminary computations of the M_0 barrier of tris(2-alkyl-1-methyl-3-indolyl)phosphines. This barrier is 15–30 kJ mol^{-1} lower than that for the corresponding oxides, thus suggesting that at least the most crowded term is configurationally stable, although enantiomerization by pyramidal inversion was not assessed. Therefore, it seems that a novel class of chiral phosphines could be available to synthetic organic chemists. The transition-metal complexes of these phosphines could represent a new series of asymmetric homogeneous catalysts for stereoselective reactions.[18]

Received: May 11, 2006
Published online: August 23, 2006

Keywords: chirality · dynamic NMR spectroscopy · liquid chromatography · phosphine oxides · residual enantiomerism

[1] M. R. Whitnall, K. K. Hii, M. Thornton-Pett, T. P. Kee, *J. Organomet. Chem.* **1997**, *529*, 35 – 50.
[2] M. T. Powell, A. M. Porte, K. Burgess, *Chem. Commun.* **1998**, 2161 – 2162.
[3] R. Dorta, L. Shimon, D. Milstein, *J. Organomet. Chem.* **2004**, *689*, 751 – 758.
[4] K. Mislow, *Acc. Chem. Res.* **1976**, *9*, 26 – 33.
[5] P. Finocchiaro, D. Gust, K. Mislow, *J. Am. Chem. Soc.* **1973**, *95*, 8172 – 8173.
[6] P. Finocchiaro, D. Gust, K. Mislow, *J. Am. Chem. Soc.* **1974**, *96*, 3198 – 3205.
[7] P. Finocchiaro, D. Gust, K. Mislow, *J. Am. Chem. Soc.* **1974**, *96*, 3205 – 3213.
[8] C. A. Johnson, A. Guenzi, K. Mislow, *J. Am. Chem. Soc.* **1981**, *103*, 6240 – 6242.
[9] D. Gust, K. Mislow, *J. Am. Chem. Soc.* **1973**, *95*, 1535 – 1547.
[10] J. D. Andose, K. Mislow, *J. Am. Chem. Soc.* **1974**, *96*, 2168 – 2176.
[11] J. P. Hummel, D. Gust, K. Mislow, *J. Am. Chem. Soc.* **1974**, *96*, 3679 – 3681.
[12] J. F. Blount, P. Finocchiaro, D. Gust, K. Mislow, *J. Am. Chem. Soc.* **1973**, *95*, 7019 – 7036.
[13] P. Finocchiaro, D. Gust, K. Mislow, *J. Am. Chem. Soc.* **1974**, *96*, 2176 – 2182.
[14] R. A. Keller, J. C. Giddings, *J. Chromatogr.* **1960**, *3*, 205 – 220.
[15] O. Trapp, G. Schoetz, V. Schurig, *Chirality* **2001**, *13*, 403 – 414.
[16] A. D. Bain, *Prog. Nucl. Magn. Reson. Spectrosc.* **2003**, *43*, 63 – 103.
[17] ^{1}H DNMR spectroscopy yields an estimate of the activation barrier, rather than an accurate measure, for the following reasons: 1) the whole dynamical range could not be observed and 2) the thermal variation of the chemical shift, as a result of changing solvent–solute interactions, may contribute to the lineshape variation with temperature.
[18] The authors' contributions are as follows: F.S. conceived the project and designed the synthesis; T.B. and S.R. carried out all experimental work, including semipreparative HPLC experiments; G.C. carried out analytical HPLC experiments; T.P. determined the X-ray structures; A.P. designed and carried out the DFT calculations and the analysis of the dynamic HPLC and NMR data; and A.P. and F.S. wrote the Communication.

