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Chiral Atropisomeric Indenocorannulene Bowls: Critique of the Cahn–Ingold–Prelog Conception of Molecular Chirality

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Abstract: *Chiral corannulenes abound, but suffer generally from configurational lability associated with bowl-to-bowl inversion,[1] thus obviating questions of stereogenicity and stereoelement construction.[2] In contrast, peri-annulated corannulenes show greatly increased barriers for bowl-to-bowl inversion; specifically indenocorannulenes invert on a time scale too slow to observe by normal NMR methods and raise the possibility of creating chiral atropisomeric bowl-shaped aromatics.[3] Two methods for preparing indenocorannulene from simple 2-haloarylcorannulenes—silyl cation C–F activation,[4] and Pd-mediated C–Cl activation[5]—enable the synthesis of an array of such chiral atropisomeric indenocorannulenes.[6] Resolution of the enantiomers by high-performance liquid chromatography over chiral support phases motivates the study of chiroptical properties, the assignment of absolute "Cartesian" configuration, and the assessment of configurational stability.[7] These studies bring into question any systematic assignment of nontrivial stereoelements (i.e. not the molecule in its entirety) and refute any assertion of congruence between "Cahn–Ingold–Prelog elements" and the physical or "Cartesian" basis of chirality.*

The minimum-energy static bowl form of indenocorannulene manifests bilateral (C_s) symmetry. All of the hydrogen atoms are chirotopic (local symmetry C_1) and therefore replacement of any single hydrogen atom by a non-hydrogen atom lowers the symmetry of the molecule to C_1. This study focuses on chiral molecules resulting from substitutions to the indeno six-membered ring.

Iodocorannulene couples efficiently with a variety of 2-haloarylboronic acids to provide the immediate synthetic precursors to indenocorannulenes **1a–1f** (Scheme 1). Fluoro precursors were subjected to silyl cation C–F activation/coupling, whereas chloro precursors underwent Pd-catalyzed
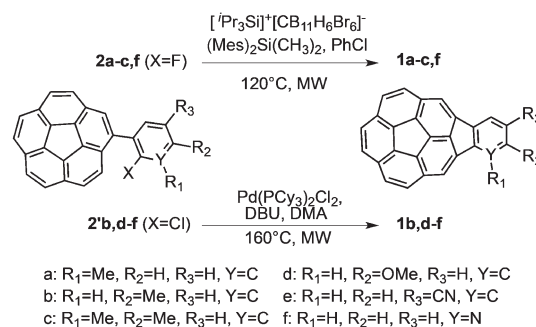
Scheme 1. Chiral indenocorannulenes prepared by C–F or C–Cl activation. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMA = dimethylacetamide, MW = microwave irradiation.

C–Cl activation/coupling. Although both methods cleanly provide product, the yields for Pd-catalyzed C-Cl activation/coupling are in general higher (80% vs. 40%, see the Supporting Information) and the reaction is less sensitive to moisture and oxygen.

Indenocorannulenes in general embody useful photophysical and electrochemical properties. Compared to corannulene with a first reduction potential of −2.49 V, the parent monoindenocorannulene has a first reduction potential of −2.06 V and azaindenocorannulene **1f** has a first reduction potential of −2.00 V.[8] Clearly the effect of introducing an indeno annulation (ca. 0.5 V) outweighs the modulating influence of simple substituents (< 0.1 V). Across the series, the optical spectra display absorption peaks around 270 nm and 300–350 nm, and one broad emission peak at about 580 nm (ca. 100 nm width at half-height). Quantum efficiencies are routinely observed to be less than 1%.

Indenocorannulenes are predicted to have high barriers and low rates for bowl inversion.[3] As such, one expects the products of the reactions described above, monosubstituted derivatives **1a–1f,** to be nonfluxional racemic mixtures. HPLC over a chiral stationary phase effected the resolution of **1a–1f**, specifically using (*S,S*)-WHELK-O1, Chirapak ID, (*S,S*)-WHELK-O1, Chirapak IE, Chirapak IG, and Chirapak IC, respectively (see the Supporting Information).

Kinetic studies on the first-order decay of optical activity allowed determination of activation free energies for racemization by bowl-to-bowl inversion (Table 1). The kinetics of enantiomerization were measured in ethanol at 78°C. Rate constants of enantiomerization were determined assuming first-order decay of the optical activity during the early stages of the reaction. Half-lives of racemization were determined using the first-order rate constants.

| Cmpd	k [×10^5 s^{-1}]	Exptl ΔG [kJ mol^{-1}]	Calcd $\Delta G^{\neq}$ [kJ mol^{-1}][a]	$t_{1/2}$ [h]
1a	3.31	116.6	115.1	2.90
1b	2.09	117.9	117.0	4.60
1c	3.90	116.1	113.4	2.47
1d	1.89	118.2	117.2	5.09
1e	1.14	119.7	119.1	8.41
1f	1.17	118.5	117.6	5.60

[a] B97D/Def2-TZVPP(ethanol)//B97D/Def2-TZVPP.

B97-D/Def2-TZVPP(ethanol)//B97-D/Def2-TZVPP bowl ground state and flat transition state geometries enabled prediction of the energetics of the bowl-flipping model for comparison to experimental free energies of racemization (ΔG^+). Predicted ΔG^+ values for **1a–1f** agree well with experiment (RMS deviation < 1 kJ mol^{-1}) and follow the same trend. All data indicate that the enantiomers of **1a–1f** are configurationally stable on the order of several hours at 60°C (days at room temperature in solution).

Cyano derivative **1e** displays the largest activation energy and longest half-life, whereas the dimethyl derivative **1c** has the smallest activation energy, possibly due to the repulsive interactions between hydrogen atoms of the adjacent methyl groups and the neighboring hydrogen atom of the corannulene rim. The lower barrier of 1-methyl (**1a**) vs. 2-methyl (**1b**) supports this supposition. Albeit a rather small influence, the other three compounds also have low bay region congestion and all display higher barriers. This trend is a local correlation among close cognates that does not hold generally; for example, bowls with flanking helicene character will no doubt display higher barriers to enantiomerization.[9]

In principle, solvent polarity could influence the activation parameters of the bowl-inversion process by stabilization of the bowl state relative to the flat state. For corannulene, the bowl state has a dipole moment along the fivefold symmetry axis and the flat state has a dipole moment of zero, based on D_{5h} symmetry; for indenocorannulene these symmetry restrictions are released but the dipole moment in the bowl form is still substantial (2.74 D) and oriented nearly normal to the bowl-hub plane, whereas in the flat form the dipole moment is small (0.27 D) and is oriented in the plane. In an attempt to address the role of the bowl dipole, the racemization process for **1a** was investigated at three temperatures in ethanol, in carbon tetrachloride, and in cyclohexane. The computations predict a dipole moment of 2.80 D for the bowl state of **1a** roughly "normal" to the best plane of the bowl hub atoms and 0.61 D in the plane of the flat form. Although experimental activation free energies could be determined with reasonable precision (± 1.0 kJ mol^{-1}), the precision of activation enthalpy and entropy is insufficient to establish a causal difference in the barriers to racemization of **1a** as a function of solvent. Computational data on the activation enthalpy as a function of solvent support the classical idea that more polar solvents should lead to higher barriers by stabilization of the more polar bowl state, but only by a very

small amount, ca. 2 kJ mol^{-1} across the series ethanol, hexane, gas phase. (For complete details see the Supporting Information.)

Crystals from enantioenriched **1d** (97 + % *ee*), suitable for X-ray diffraction analysis, were obtained from CH$_2$Cl$_2$/hexane (Figure 1).[10] Two symmetry-independent yet similar mole-
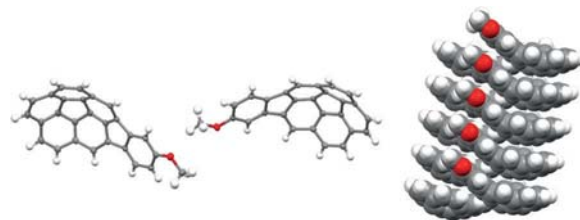

Figure 1. The asymmetric unit (left) and crystal packing (right) in the crystal structure of **1d**.

cules occupy the asymmetric unit (RMS deviation $= 0.029$ Å). Crystal packing ($P2_1$) reveals polar columns of molecules stacked bowl-in-bowl. The experimentally determined bowl depth of **1d** is 1.068 Å. On the basis of the correlation of bowl depth to inversion barrier, a bowl depth of ≈ 1.07 Å should correlate with a barrier of ≈ 120 kJ mol^{-1},[3] in good agreement with experiment. The polar unit cell is consistent with the packing of a chiral enantiopure molecule. Nonetheless, the presence of partial inversion twinning in the selected crystal cannot be unequivocally excluded (Parson's parameter,[11] $z = 0.19(11)$), therefore precluding unambiguous determination of the absolute configuration of the absolute configuration. The best guess configuration is displayed in Figure 1.

Vibrational circular dichroism (VCD) offers an alternative way to establish absolute configuration by comparison of experimental and computational spectra.[12] The VCD of **1a–1f** were measured (CHBr$_3$) and compared to B97-D/Def2-TZVPP (CHBr$_3$) determined spectra. Comparison of the regions of the spectra unperturbed by solvent peaks, 800–1000 cm^{-1} and 1250–1600 cm^{-1}, allowed configurational assignment for all enantiomers (Figure 2), which in the case of **1d**, corroborates the crystallographic supposition.

Electronic circular dichroism (ECD) can also provide an enantiomeric spectroscopic signature;[13] however, with fewer transitions it can be less robust than VCD. In light of the assignment by VCD, one can use ECD as an independent confirmatory determination. In the present series, comparison of experimental and TD-CAMB3LYP[10e]/Def2-TZVPP-(ACN)//B97-D/Def2-TZVPP determined ECD spectra for **1a–1f**, arrives at the same configurational assignment as that obtained with VCD (Figure 3).

Although identifying a geometric molecular model as chiral follows from its symmetry, establishing the enantiomeric character of the represented physical compound relies on observation of various chiroptical properties.[14] Neither the symmetry of the model nor observation of chiroptical properties requires a specification of molecular bonding. As such, linking stereoisomerism to a valence-bond model inherently erodes the model's claim to being the basis for molecular chirality.
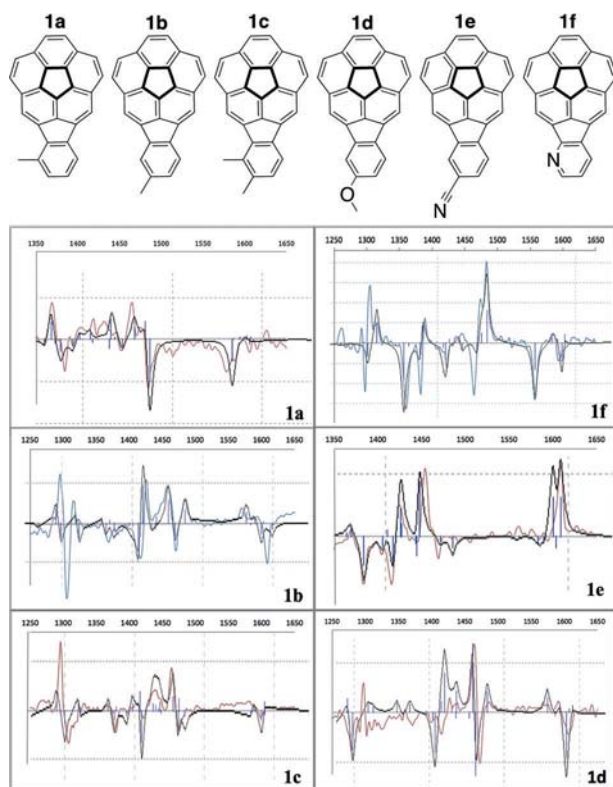
Figure 2. B97-D/Def2-TZVPP (gray) and experimental (first eluted red; second eluted blue) VCD spectra of **1a–1f** (structures in header) from 1350 to 1650 cm^{-1} in CHBr$_3$.
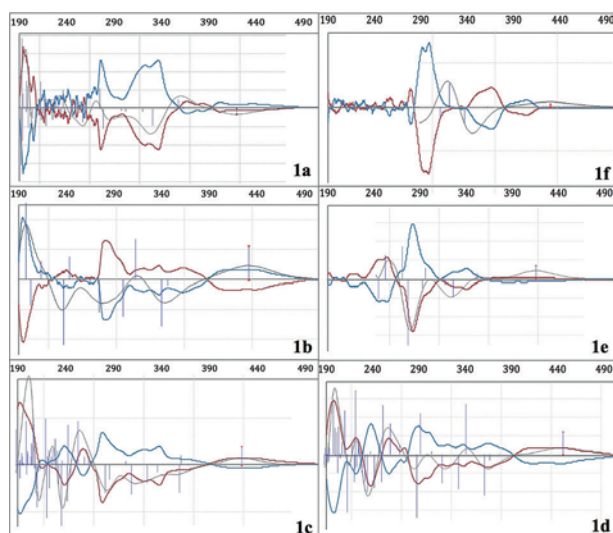
Figure 3. TD-CAMB3LYP/Def2-TZVPP(ACN)//B97-D/Def2-TZVPP (gray) and experimental (first eluted red; second eluted blue) ECD spectra of **1a–1f** from 190 to 490 nm in acetonitrile.

Enantiomers are the one class of stereoisomers that are required by symmetry, independent of the bonding model. Historically, their configuration was labelled with regard to physical properties, such as optical rotation (d/l) or the Cotton effect.[15] If experimental conditions are well defined, then the absolute configuration of a compound can be linked directly

with its properties; however, one cannot easily draw the structure of a specific absolute configuration directly from reading the chiroptical property. Strategies such as octant rules or more sophisticated chirality functions have attempted to link properties to configuration by general procedures.[16]

Since the time of van't Hoff, stereoisomers have been defined specifically with regard to permutations over molecular valence-bond frameworks, e.g., a tetrahedral stereocenter—van't Hoff's classically labelled "asymmetric center".[17] Fischer–Rosenoff conventions (D/L) moved the discussion toward defining configuration on the basis of the geometry of the model rather than on the basis of the properties of the compound, but the reliance of this model on valence bonding weakens its generality as regards chirality.[18]

Believing they had found an underlying set of elements of chirality, Cahn–Ingold–Prelog proposed their famous nomenclature of centers, axes, and planes.[19] However, for a regular tetrahedron, the symmetry group T_d overlaps one-to-one with the maximal permutation group S$_4$, causing some misconception that permutation operations are generally equivalent to symmetry operations.[2] Furthermore, Ruch's topological analysis reveals severe limitations concerning the definability of homochiral taxonomies.[20] As such, Cahn–Ingold–Prelog's bold claim that molecular chirality is reducible to causative "elements of chirality" turns out to be fatuous.

The importance of this historical discussion to the present article lies in the fact that the structures of **1a–1f** possess no tetrahedral atoms suitable for serving as a tetrahedral stereogenic element, and no suitable stereogenic elements within the center, axes, plane paradigm, yet these are chiral molecules which have been prepared and resolved into enantiomeric forms. Thus, they are a fundamental contradiction to the Cahn–Ingold–Prelog basis for chiral factorization.

One could in principle arbitrarily define a set of four atoms specific to this class of structure, but this only underlines the contrived connection between geometric chirality and commonly used chiral-element nomenclature popularized by Prelog and co-workers. There are a myriad of chiral materials that are ill-suited for application of the Cahn–Ingold–Prelog rules. Indeed, the nomenclatural rules applied to bowls,[21] fullerenes,[22] and a host of other systems amply exemplify that Cahn–Ingold–Prelog "elements of chirality" were never more than an ad hoc solution to the configurational labelling problem—neither elementary nor inherently chiral.

For indenocorannulene isomers **1a–1f**, a simple labelling for archival purposes is desirable. To emphasize the distinctly non-Cahn–Ingold–Prelog nature of these names, the symbols 乒 and 乓 are appropriate for denoting the classes of enantiomers (Figure 4).[23,24] If one orients the convex-facing indenocorannulene skeleton with its mirror plane vertical and the benzene ring at 6 o'clock, then substituents to the left are 乒, while those to the right are 乓.[24]

Although one can also use 乒乓 to label pentasubstituted pentaindenocorannulenes, X$_5$-pentaindenocorannulene, it must be acknowledged that 乒乓 is a "whole-molecule" label and not simply ascribable to being five stereogenic elements of type X-**1**. Despite the structural parallel between
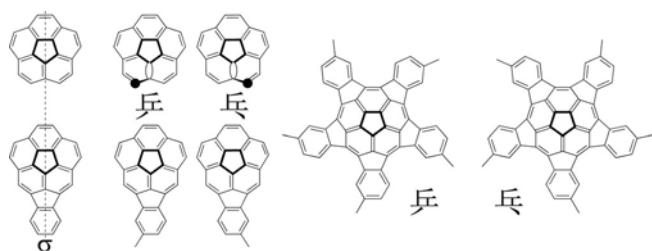
Figure 4. Configurational labels 乒 and 乓 for X-**1** and X₅-pentaindeno-corannulene.[24]

X-**1** and its fivefold symmetric analogue X₅-pentaindeno-corannulene, the five spoke axes do not qualify as independent stereogenic elements; permutation at any one spoke in X₅-pentaindenocorannulene does not yield a diastereomer but rather a constitutional isomer. Thus, 乒乓 can be used for compounds of type X-**1** and X₅-pentaindenocorannulene, but further elaboration is needed before this can generally be applied to bowl compounds.

Enantiomers **1a**–**1f** can also address the ill-conceived notion of quantification of chirality.[25,26] Whereas phenomena arising from a specific chiral diastereomeric relationship can be quantified through a selected measurable, there is no assurance that another chiral diastereomeric relationship among the same set of compounds will give rise to the same order. In other words, the compound with the highest optical rotary power need not also show the largest separation factor on a chiral HPLC column.

To exemplify, consider a few phenomena upon which a ranking of "more chiral" could be made, but which bring home the contradiction inherent in such rankings: 1) configurational stability; 2) chiroptical power; 3) enantioselective recognition. For bowl-shaped enantiomers **1a**–**1f**, configuration stability is limited by the bowl-inversion barrier, which is also the barrier to enantiomerization. On the basis of this criterion, **1e**, with the highest barrier, would be the most chiral (cf. Table 1). Chiroptical power could be viewed as the largest absolute $[\alpha]_D$, in which case **1d** is most chiral, or the largest ECD $\Delta\varepsilon$, which would favor **1e**. Enantioselective recognition, if gauged by the degree of separation over a chiral chromatographic substrate, could favor **1f**; but what substrate should be the reference? Ultimately, fanciful schemes devoted to quantification of chirality reveal more about the scientific biases of the proponents than the geometrical or physical nature of the structures in question. They are further obviated by the excellent job modern electronic structure theory does at predicting molecular properties including chiroptical properties, as can be seen from the comparison of experiment and theory above (cf. Table 1 and Table 2).

Given our epistemological position that chirality in molecules is different from that in molecular models, because molecular chirality requires observable anisochrany, we arrive at the issue of crypto-dissymmetry.[27] In a chiral molecule, all points are chirotopic and the local symmetry across any region is also chiral. Therefore, although the hydrogen atoms straddling the 12–6 o'clock axis in indeno-corannulene are symmetry equivalent and enantiotopic, those

Table 2: High-order effects for two-spin systems (400 and 600 MHz).

Cmpd	$2 \times i_2$[a]	$2 \times i_1$[b]	$v_1 - v_4$[c]	$v_2 - v_3$[d]	Calcd[e]
1d	1.76	0.15	19.2	1.64	7.80
	2.00	0.08	21.6	0.86	5.20
1e	1.95	0.10	18.0	0.92	7.14
	1.80	0.06	18.0	0.60	4.76
1f	1.84	0.05	18.0	0.49	3.42
1b					2.34
1c					0.48
1a					0.48

[a] Integration of protons at the 12 o'clock position. [b] Integration of wing peaks. [c] Coupling constant of wing peaks in Hz. [d] Coupling constant of protons at the 12 o'clock position in Hz. [e] CSGT B97-D// Def2-TZVPP (dichloromethane).

same positions in **1a**–**1f** are not (Table 2). The symmetry nonequivalent diastereotopic hydrogen atoms straddling 12 o'clock should manifest in the ¹H NMR spectrum as a doublet of doublets, rather than as a singlet anticipated for enantiotopic hydrogen atoms. When the chemical shift difference between the two sites approaches zero (in a practical sense, when it is less than the coupling constant) the spectrum becomes non-first order and manifests a pseudo-singlet, which masks the anisochrony. When we examine **1a**–**1f** at 400 and 600 MHz, all except **1d** appear to manifest a singlet; however, closer examination shows tiny wing peaks at the coupling constant distance from the central peak revealing the cryptoclastic chiral character and allowing one to deduce the chemical shift difference. With this method, one sees the strongest effect for **1d**, followed by **1e** and **1f**. For **1a**–**1c** the effect is indiscernible at these field strengths. Ab initio computational methods predict the trend of these effects well.[28]

In conclusion, this new set of chiral bowl-shaped molecules opens an avenue to the study of chiral materials obviating the discussion of chiral elements. They underline the distinction between chirality and stereoisomerism pointed out three decades ago. Their general physical properties and propensity for shape-selective molecular recognition bodes well for the development of cognates capable of replacing classical chiral scaffolds.

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[24] In the future more keyboards will include "pinyin-simplified" options. The chosen symbols are Chinese pinyin "ping" "pang" 乒乓, and well represent the concept discussed here. They avoid confusion with other heavily used symbols (e.g., " < " and " > " already have well-known meanings). However, to facilitate useage, a suitable alternative might be BOLD "**p**" and "**q**" in a cerif-free font.

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