On Protochirons and Known or Predicted Helical Structures

Alexandru T. Balaban

Texas A&M University at Galveston, Marine Sciences Dept., Galveston, TX 77553, USA

(Received November 29, 2010)

Abstract. Axial chirality is present in many interesting structures. Some predicted helical structures may be stabilized by inter- or intra-molecular hydrogen bridges.

1. Introduction

Helical structures in the nanoworld are ubiquitous and of utmost importance for essential classes of natural compounds, allowing life to exist. One should think about (i) the secondary structure of proteins, with Pauling-Corey α-helices that allow fairly linear segments of definite length chosen by evolution to allow membrane crossing or to lead to certain geometrical features [1,2]; (ii) the secondary structures of RNA that also include single helix structures [3-6]; (iii) the well-known DNA double helix allowing, thanks to base pairing, the rapid repair of damaged portions; (iv) the triple collagen superhelix [7] achieving a strength that surpasses that of steel.

Synthetic polymers also form helices, as first proved by Natta and coworkers [8]. Percec and coworkers have made spectacular polymeric helical structures [9-12], and reviewed the field in special issues of Chemical Reviews [13]. Okamoto and Nakano reviewed asymmetric polymerization [14] and synthetic helical polymers [15]. Several reviews on double helices are cited here [16-20].
Compounding the formation of a circular molecular chain with a transversal movement (which prevents closing a ring at each turn) results in the chirality of helices. A book chapter on helical chiral conjugated materials is freely available on the web [21].

One can define a protohelix element if one advances sequentially with the same distance along the Cartesian direction $x$, then $y$, and then choosing the chirality along $z$ in either the positive or negative direction [22]. By repeating this advance one obtains the simplest protohelix. Such helices or more elaborate helices can be described in mathematical terms [23]. If the angles between two adjacent linear segments are $90^\circ$, one can view two enantiomeric protochirons as shown in Fig. 1, and by linking several identical protochirons one obtains a “cubic helix” with $90^\circ$ angles, as shown in Fig. 2 [23].

![Figure 1. Two enantiomeric protochirons](image1)

![Figure 2. Stereo-view of a cubic helix involving points 1 through 8](image2)

If the angle between adjacent segments is $60^\circ$, then protochirons can be viewed as edges of regular tetrahedra. Figures 3 and 4 show such 3-straight-segment protochirons on a free tetrahedron or on a tetrahedron inscribed in a cube. These figures also show that two nonadjacent edges of a regular tetrahedron, which are orthogonal in 3D-space, define a chiral fragment of a twisted ribbon, indicated by red lines.
The tetrahedral 3-straight-segment protochirons can also serve for making the connection between the above axial chirality and the familiar molecular chirality of compounds with stereogenic centers: one pair of enantiomers for an sp$^3$-hybridized atom connected to 4 different ligands with tetrahedral geometry; ten pairs of enantiomers for an sp$^3$d-hybridized atom connected to 5 different ligands with trigonal-bipyramidal geometry; and 15 pairs of enantiomers for an sp$^3$d$^2$-hybridized atom connected to 6 different ligands with octahedral (or trigonal-antiprismatic) geometry. The last two types of structures give rise to spectacular reaction graphs for their intramolecular rearrangements [24,25].
2. Structures composed of triple bonds and benzenoid rings

In this section we will discuss structures composed of triple bonds and benzenoid rings, or only benzenoid rings, with emphasis on helical structures. Compounds related to benzo-annulenes belonging to this class of chemical structures such as dehydrobenzo[12]annulene (1, Fig. 5) have been prepared more than 40 years ago by Wolowsky and Sondheimer [26], Staab and Graf [27], Raphael and coworkers [28,29], and Kloster-Jensen and Wirz [30]. Related dehydro-benzoannulenes having diacetylene linkers between benzenoid systems have been reviewed in 1987 in a 3-volume book [31].

Vollhardt and coworkers [32], Tobe et al. [33], and Haley et al. [33] have synthesized several multiply fused dehydrobenzo[12]annulenes such as 2–4 (Fig. 5).

![Figure 5. Dehydrobenzo[12]annulene, C_{24}H_{12} (1) and several multiply fused dehydrobenzo[12]annulenes, namely C_{34}H_{14} (2), C_{42}H_{18} (3), and C_{60}H_{24} (4).](image-url)
More recently, several papers have discussed the yet unknown carbon allotrope graphyne (5 is a fragment of it), and very recently calculations were performed for the interplay of aromaticity and antiaromaticity in the yet unknown polyhedral graphyne substructures (polyhedral phenylacetylenes), in which the benzenoid rings are meta-connected. A Schlegel diagram of the tetrahedron-derived compound C₃₆H₁₂ is shown in Fig. 6; it has four benzenoid rings replacing the tetrahedron vertices and six acetylenic bridges replacing the tetrahedron edges. Analogous “polyhedral phenylacetylenes” have been discussed [34] for all known regular (Platonic) and semiregular (Archimedean) polyhedra except for the octahedron, icosahedron, small rhombicosidodecahedron, and small rhombicuboctahedron.

Figure 6. Schlegel diagram of a tetrahedron-derived phenylacetylenic polyhedral graphyne with four meta-disubstituted benzenoid rings as vertices and six triple bonds (ethynylene groups) as edges.

When ortho-diethynylbenzenoid rings are involved, it is easy to imagine, by analogy with dehydrobenzo[12]annulene (1) how a helical structure could result on adding one more triple bond (6, Fig. 7). The synthesis of 1 by Campbell et al. [28] had started from ortho-iodo-ethynylbenzene (7, Hal = I, Fig. 7) via the corresponding copper acetylide. One may imagine that polymerization of ortho-phenylene-ethynylene may
yield a helical structure along with zig-zag conformers such as 8 (Fig. 7). Evidently, ortho-phenylenic disubstitution leads to a three-fold symmetry of the helix.

Figure 7. Oligomeric ortho-phenylene-ethynylene structures

Grubbs and Kratz [35] prepared in analogous fashion (but using also trimethylsilylacetylene with subsequent treatment with potassium fluoride for replacing aryl-iodine atoms by acetylenic groups) highly unsaturated oligomeric hydrocarbons with three through nine benzenoid rings such as 8 – 10. Interestingly, molecular structures determined by X-ray diffraction (for only two of the new oligomers) revealed that one of them (9) had a zig-zag geometry, but the other one (10) had a partly helical geometry, ascribed to intramolecular π-stacking. A decabeno-decadehydro[40]annulene (11, C₈₀H₄₀) has been prepared and its structure was confirmed by X-ray analysis – in Fig. 8, bond angles for 11 are not indicated correctly for sp-hybridized carbon atoms. The facile rotation about the sp–sp² bonds was supposed to be responsible for the helical orientation of the phenylethynyl moieties [35].
Figure 8. Conjugated oligomeric hydrocarbons comprised of 1,2-ethynediyl units alternately linked together with benzenoid rings at their ortho positions.

A stereo-view of a hypothetical helical oligomeric phenylacetylenic structure with eight benzenoid rings is presented in Fig. 9. In order to visualize the overlapping rings, the top three rings are colorized blue, the next two are red, and the last three are green. Only the red-colored rings are sandwiched between two other benzenoid rings.

Figure 9. Stereo-views of the helical structure of a conjugated oligomeric hydrocarbon comprised of seven acetylenic units and eight benzenoid rings.
In order to increase the intramolecular $\pi$-stacking by adding hydrogen-bonding, one may imagine the use of phenolic and carbonyl groups, as indicated in Fig. 10. Natural evolution has made use of such interactions in chlorophylls and other light-harvesting molecular assemblies, as shown in the reviews by T. S. Balaban et al. [37].

**Figure 10.** Unit for an oligomer similar to the hydrocarbon from Fig. 5, but with added intramolecular forces between stacked benzenoid rings due to hydrogen bonding.

On alternating pyrocatecholic rings with benzenoid rings having two carbonylic groups (aldehyde or acetyl), owing to the geometry of the arrangement, one obtains favorable interactions (as seen in Fig. 11 for the red-colored rings, which are sandwiched between two other benzenoid rings).

**Figure 11.** Stereo-views of the same helical structure as in Fig. 9 but with added intramolecular hydrogen-bonding due to carbonyl and hydroxyl groups.
3. Helical structures composed of benzenoid or heterocyclic aromatic rings

\([h]\)Helicenes are cata-condensed polycyclic aromatic hydrocarbons with \(h\) benzenoid rings, which are isoarithmic with other fibonacenic isomers such as zigzag catafusenes. They have huge specific rotations and surprisingly low racemization barriers. Martin synthesized, studied, and reviewed helicenes up to \(h = 13\). Unlike acenes which are unstable thermally when \(h > 7\) and react with oxygen affording cyclic peroxides, helicenes have no energetic penalty for increasing \(h\) values Fig. 12 displays \([9]helicene\). Such structures without stereogenic centers have axial chirality, when the enantiomers are designated by \(R_a / S_a\), or plus (P) / minus (M), or alternatively \(\Delta / \Lambda\). In the helical P enantiomer the sense is clockwise on viewing along the helical axis and moving from the front to the rear, whereas for the M enantiomer the sense is anticlockwise [38].

![Figure 12. Stereo-views of M-[9]helicene](image)

Poly(\(ortho\)-phenylene) [39], like the oligomeric phenylacetylenic compounds discussed earlier, yield helices with a three-fold periodicity because the angles between \(ortho\)-situated bonds of benzene is 60°, which is the angle between edges of equilateral triangles. Examples are presented in Figures 13 and 14. In the latter figure it is
anticipated that intramolecular hydrogen bonds between C=O and OH groups, such as those indicated in Fig. 10 (but devoid of triple bonds), would favor and stabilize the helix.

![Stereo-views of poly-(ortho-phenylene) with 6 benzenoid rings plus 2 phenyl endgroups which are colored in blue.](image1)

**Figure 13.** Stereo-views of poly-(ortho-phenylene) with 6 benzenoid rings plus 2 phenyl endgroups which are colored in blue.

On replacing biphenyl units in *ortho*-phenylenes by [1,10]phenanthrolines, the helical distortion is enhanced [40]. Many heterohelicenes (oxa-, thia-, aza-, azoniahelicenes) have also been prepared (see Rajca’s review [21]). Interestingly, the racemization barrier of oxahelicenes is appreciably lower than that of the corresponding thiahelicenes [41].

![Stereo-views of poly-orho-phenylene (with 6 benzenoid rings plus 2 blue end-group rings) with intramolecular hydrogen bonds between red acetyl and alcohol groups.](image2)

**Figure 14.** Stereo-views of poly-orho-phenylene (with 6 benzenoid rings plus 2 blue end-group rings) with intramolecular hydrogen bonds between red acetyl and alcohol groups.
When poly(meta-phenylene) geometry is constrained to be helicoidal, a six-fold symmetry results in theory, as seen in Fig. 15 [42-48]. In such a case the above strategy for intramolecular interactions would not work. However, X-ray data proved that helices are fairly disordered and have only five benzenoid rings per turn, so that alternating catecholic and vicinal dicarbonylic phenylene groups should again be effective.

![Figure 15. Stereo-view of a poly-(meta-phenylene) with 6-fold symmetry having a total of 12 benzenoid rings. The two terminal phenyl groups are colored in blue.](image)

In 2002 Sharpless [49] and Meldal [50] discovered independently how to accelerate Huisgen’s 1,3-dipolar cycloadition between azides and alkynes [51] by using cuprous compounds (e.g. cupric salts and ascorbic acid in aqueous solution). This reaction allows to link together organic moieties via 1,2,3-triazole rings, and because it runs smoothly it has been called ‘click reaction’ [52,53]. Using two meta-difunctional moieties, helical structures were obtained by Hecht and coworkers [54] as seen in Fig. 16; the R and R’ substituents include triethyleneglycol ether and ester groups, respectively. Monofunctional endcaps of 4-azidotoluene and 4-ethynyltoluene were successively used. Because the triazole rings introduces additional bond angles, the sixfold screw axis characteristic for meta-disubstituted 6-membered rings may no longer apply for this polymer with molecular weight 1600-5300 a.m.u. and a dispersity index of 1.5–2.3.
Figure 16. Structure of the helix obtained by the click reaction.

An easy access to a short helical hetero-analog involving ortho- and meta-linked rings should be the reaction product between meta-phenylenediamine and 2,4,6-triphenylpyrylium tetrafluoroborate. It is known that pyrylium salts react readily with primary amines affording pyridinium salts [55-59]. The resulting bis-pyridinium salt (Fig. 17) would have a helical structure involving nine 6-membered aromatic rings.

Figure 17. Stereo-view of the anticipated reaction product from meta-phenylenediamine and 2,4,6-triphenylpyrylium tetrafluoroborate (only the bis-pyridinium dication is shown).

4. Twisted coronoids

It was shown earlier [60] that some twisted coronoids gave rise to interesting stereoisomerisms. The simplest such coronoid with the shape of digit 8 is chiral (Fig.18).
Figure 18. Stereo-view of a chiral coronoid with 12 benzenoid rings having the shape of digit eight.

Two isomeric twisted coronoids with 18 benzenoid rings should exist either in a chiral (Fig. 19) or in an achiral form (Fig. 20).

Figure 19. Stereo-views of one chiral coronoid with 18 benzenoid rings
Figure 20. Stereo-views of one achiral coronoid with 18 benzenoid rings which is a topological stereoisomer of the coronoid from Fig. 19.

5. Anticipated expanded helicenes

One can enlarge helicenes (which are fibonacenes, i.e., strips of condensed benzenoid rings devoid of anthracenic stretches involving linearly-condensed rings) in several ways. One way is to enlarge the “hole” around which the helix is wound. On looking at the usual helicenes along the helical axis, one sees the structure of coronene, with a “hole” of a single benzenoid ring. Taking into account that the coronenic hydrocarbon called kekulene, prepared by Staab and Diederich [61], has a ‘hole’ that is equivalent to coronene, one can conceive an expanded helicene with a width of one benzenoid ring that can be regarded as a ‘kekulenic helix (Fig. 21) with a larger ‘hole’. The distance between two successive turns of this helix is 3.59 Å, according to the geometry optimized with the MM2 program.
A different mode of expanding helicenes is to replace the cata-condensed fibonacene (with a width of one benzenoid ring as in phenanthrene) by a wider peri-condensed benzenoid such as pyrene, with a width of two benzenoid rings (Fig. 22). One might expect the distance between two successive turns of this strengthened helix to decrease. However, the similarly optimized geometries of usual helicenes and of the ‘width-two’ helicenes present identical distances between two successive turns, namely 3.26 Å. Of course, one may increase the width even more, e.g. for width-three (Fig. 23).
Finally, one may combine these two ways by constructing a ‘width-two’ helix around a ‘coronenic hole’ which would look like the peri-condensed benzenoid presented in Fig. 24 when seen along the helical axis.

Figure 24. A peri-condensed coronene with a ‘hole’ similar to the kekulene hydrocarbon.
6. Elemental helices

Intertestingly, some of the pure elements (especially at higher pressure) form helical chains. In the comprehensive review on high-pressure crystal chemistry by Prewitt and Downs [62], these authors formulated nine “rules of thumb” for high-pressure effects on bonding and coordination number in order to update the earlier Pauling’s Rules. Thus, the weakest (according to rule 1) and longest bonds (rule 2) distort most easily, rule 3 indicates that compressed bonds become more covalent, rule 4 states that increasing pressure increases coordination number, and according to rule 9 elements at high pressure behave like elements below them in the Periodic System at lower pressures. Roald Hoffmann, Neil Ashcroft and their coworkers [63] reformulated these rules as follows: “

A) Van der Waals space is most easily compressed;
B) Ionic and covalent structures, be they molecular or extended, respond to pressure by increasing coordination;
C) Increased coordination is achieved relatively easily through donor-acceptor bonding, which shades over into multicenter bonding. Such multicenter bonding, electron-rich or electron-poor, is a mechanism for compactification (hence, a response to elevated pressure) for elements across the Periodic Table;
D) Orbital-symmetry considerations will affect the chance that a high-pressure product survives return to metastability in the ambient-pressure world;
E) In ionic crystals, the anions are more compressible than the cations; therefore. The coordination number (especially that of the cations) increases at high pressure;
F) All materials become metallic under sufficiently high pressure;
G) Thinking about Peierls distortions (their enhancement and suppression) is helpful in understanding symmetrization (or its absence) in solids under high pressure.”
H to J) Under extremely high pressure, electrons may move off atoms, and new ‘non-nucleocentric’ bonding schemes need to be devised; close packing is the way; pressure may cause occupation of orbitals that a chemist would not normally think are involved.
As an example for the last three rules, one can mention that the monatomic crystal of xenon (melting point $T_m = -112^\circ$C at 1 atm, equivalent to about 0.1 MPa) becomes a high-melting solid with $T_m = 3000^\circ$C at a mere 50 GPa.

A simple example for helical structures is provided by elemental sulfur and other chalcogens: the 8-membered crown form that exists at ambient pressure yields at 1.5 GPa on heating a covalent helix with 3-fold symmetry (three atoms per turn, phase II, as seen in Fig. 25, apparently similar to Fig. 3, but here the angles are smaller than 90\(^\circ\)), and on heating at 300\(^\circ\)C under pressures higher than 36 GPa it forms a different helix (phase III) with a fourfold screw axis (Fig. 26). By contrast, selenium and tellurium form analogs of phase II at ambient pressure, whereas phase III of sulfur resembles the structure of Se at moderately elevated pressure [64-67].

**Figure 25.** Stereo-view of phase II for elemental sulfur at pressures from 1.5 to 36 GPa.

**Figure 26.** Stereo-view of phase III for elemental sulfur at 300\(^\circ\)C and pressures between 36 and 83 GPa

With the recent advent of advanced materials, methods, and synchrotron radiation it has been possible to investigate properties of materials at high pressures and temperatures, finding that many elements, including B, O, and S, become superconductors. With increasing pressure, scandium passes through several structural-phase transitions, and at 240 GPa is acquires a 6-screw helical chain structure (Sc-V
phase) [68]. One of the scenarios for the origin of life on Earth situates it in the depth of the proto-ocean of the Haldean Earth, about 4 billion years ago, under high pressure [68].

7. Interaction between polycyclic benzenoids and peptide helices

Among other nonviral methods for gene transfer, dendronized polymers based on poly-l-lysine backbone offer a promising avenue. Eric Clar [69] developed his theory of the aromatic sextet by observing that, among all isomers, exceptional stability is associated with polycyclic benzenoids which have only ‘empty rings’ and ‘sextet rings’ such as triphenylene (for such systems we introduced the name ‘claromatic’ with Prof. D. J. Klein [70]). Taking advantage from Clar’s theory, Klaus Müllen [71] synthesized a wide range of giant perifused claromatic benzenoids using the Scholl-type dehydrogenation as modified by Kovacic by using CuCl₂ both as Lewis acid and as oxidant [72]. Müllen and coworkers also prepared poly(para-phenylene) and poly(dialkylfluorene) derivatives that are step-ladder photoemissive materials [73]. By building benzenoid dendrimers around fluorescent moieties such as perylenediimide, Müllen and coworkers were able to investigate the conformation of poly-Z-l-lysine, combining ¹³C-NMR spectroscopy with fluorescence. They observed that on increasing the number of lysine residues beyond 15, the peptide secondary conformation changes from β-sheets to α-helices [74-78].

Hamilton and coworkers used substituted para-terphenyl derivatives as helical proteomimetics that interact with peptidic α-helices involved in cancer cell apoptosis [79]. Two turns of the α-helical region of a protein (with three hydrophobic amino-acid residues) that regulates cancer cell death (apoptosis) are mimicked by a substituted para-terphenyl derivative. The α-helix binding protein B-cell lymphoma-2 (Bcl-2) has an antiapoptotic family member (Bcl-xL) which is successfully inhibited by the para-terphenyl derivative illustrated in Fig. 27. The advantage of polyphenylene derivatives is the low rotation barrier around two aryl groups, allowing close approach to the peptidic α-helices. This is a promising avenue for small-molecule anti-cancer drugs.
8. Conclusion

Helical structures are ubiquitous from the simplest chemical substances, namely the elements, to some of the most complex compounds such as synthetic and natural polymers like proteins and polynucleotides. The three-dimensional molecular geometry of helices leads to various consequences of chirality spanning the different kinds of stereoisomerism (enantiomerism, atropisomerism, helicity, etc.). One can define several protochirons for 3D-ensembles of points, lines, surfaces, or cylindrical tubes. In the present communication a prominent emphasis was ascribed to structures having aromatic and heterocyclic rings. We should also mention self-organizing chiral molecules such as cholesteric liquid crystals which have many practical applications in reflection color displays, tunable lasers, etc. [81].

Acknowledgement. Discussions with Prof. Dr. Teodor Silviu Balaban are gratefully acknowledged.

References


