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Unified Generation of Conformations, Conformers, and Stereoisomers: A Discrete Mathematics-Based Approach

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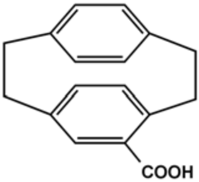
In this feasibility study we propose an approach to a unified generation of stereoisomers including conformers of a molecular structure. The method is based on discrete mathematics, it recognizes and varies the orientation of in principle each quadruple of atoms. The method has potential to also generate stereoisomers that are not describable in terms of stereocenters or single bond rotations. Fundamentals such as the concept of a (partial) orientation function are discussed, and mathematical tools such as Radon partitions and binary Grassmann-Plücker relations are used to construct tests for realizability of abstract orientation functions. Simple examples are treated in detail.

1 Introduction

Stereoisomers are defined as “isomers of identical constitution but differing in the arrangement of their atoms in space”.[1,2] In contrast to this definition, organic chemists for practical reasons often count as stereoisomers those different species of identical constitution only that can be isolated or at least observed spectroscopically as distinct species. Isomers that differ exclusively in torsion angles about single bonds usually cannot be isolated, due to rapid interconversion, and therefore in this usage of the term are not considered stereoisomers but conformers.



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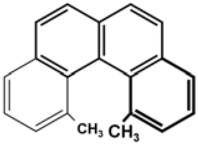

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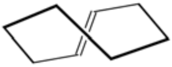


C

Accordingly, attempts to automatically generate all stereoisomers of a given constitution traditionally neglected rotation about single bonds. The pioneering work of Nourse[3] as well as Sasaki's approach[4] concentrated on finding stereocenters (an ill-defined term[5]) and systematically changing their orientations, under consideration of constitutional symmetry. Thus, these methods deal with configuration[1,2] only. Atom coordinates for each configurational isomer so obtained can be calculated by Elyashberg's method.[6] Nourse's approach was implemented and further developed by Munk et al.,[7] by the Bayreuth group,[8] by Jaritz,[9] and by Contreras et al.,[10] without its principal limitation being overcome.

On the other hand, generating all relevant conformers[1,2,11] for a given compound, that is, accounting for single-bond rotations, was considered a task quite different from the first. For that purpose several commercial computer programs were developed, the majority of which systematically or stochastically change torsion angles about all single bonds considered rotatable, coupled with force-field calculations, with or without simultaneous relaxation of bond lengths and bond angles.[12] Ring systems cause problems to such methods, and therefore their conformations were often taken from a preformed library, or rings were initially cut and finally re-closed.[13] Recent alternative approaches based on the distance geometry concept[14a] or genetic algorithms[14b] appear promising.

An approach combining stereocenter inversion and single bond rotation was proposed by Mekenyan et al.[13]

Any stereoisomers whose existence cannot formally be traced to the presence of stereocenters or to rotation about rotatable single bonds are missed by both kinds of programs. Thus, e.g. for [2,2]paracyclophanecarboxylic acid **A**, for 1,12-dimethylbenzo[c]phenanthrene **B**, for (*E*)-cyclooctene **C**, and for chiral fullerenes such as C_{76} the structures' chirality and therefore the existence of enantiomers cannot be detected by any of the current programs, due to their conceptual limitations.

In the present work we introduce a unified approach to the generation of stereoisomers including conformational isomers. In contrast to existing approaches to conformations, that are based on geometrical calculations, ours is completely discrete mathematics-based, it does not depend on the artificial distinction between configuration and conformation, nor on concepts such as stereocenters or stereogenic elements. Our approach is based on the idea of Dreiding and Dress to use chirotopes (strongly related to oriented matroids) as a tool for describing conformations.[15] The idea was pursued by Crippen and Havel in chapter 2 of their book.[16] Similar considerations were put forward by Klin, Tratch and Zefirov[17] and by Kuz'min.[18] The concepts and mathematics involved may be unfamiliar to chemists,[19] short previews were given recently.[20] In particular in references 17c-f generation of molecular conformations is discussed.

The idea is to treat a given conformation of a given molecule of N atoms as a collection of (irregular) tetrahedra, each tetrahedron formed by a quadruple of atoms. Each of the $\binom{N}{4}$ quadruples may be considered, or a selected subset only. Each tetrahedron's volume is described as a real number, easily calculated as the determinant of a matrix obtained from the atom coordinates. The determinant is positive or negative if the three last atoms, seen from the first, are arranged clockwise or anticlockwise, respectively, it is zero if all four atoms lie in one plane. Correspondingly, a $+$ or $-$ or 0 sign attributed to the tetrahedron is called the tetrahedron's or the atom quadruple's *orientation.* In a step of abstraction the conformation can be characterized by a sequence of plus and minus signs and zeros that describe the orientations of all quadruples considered.

By generating all possible such sequences and constructing for each a molecule-like arrangement (if possible), primarily a set of conformations is obtained that covers large parts of the total conformational space. In combination with force field energy minimization conformers may be obtained.

The tasks covered by the existing two types of stereogeneration programs turn out to be special cases of this approach:

- Configurational isomers only are generated by exclusively varying the orientations of all tetrahedra formed by the immediate neighbors of a stereocenter.[9] This is equivalent to Nourse's approach, and ours thus may be considered a generalization thereof.
- Conformations of a particular configurational isomer are obtained by keeping constant the orientations of these same tetrahedra while varying the others.

2 Methods

2.1 Orientations

Dreiding and Dress suggested to use orientations of quadruples of atoms for describing steric and conformational information of a flexible molecular structure. Any quadruple of distinct atoms forms an (irregular) tetrahedron. By the order of the four atoms, an orientation is associated to this tetrahedron (and thus to the quadruple of atoms), i.e. a sign which is +, − or 0. The orientation of the quadruple of atoms a_1, a_2, a_3, a_4 having coordinates $(x_{a_i}, y_{a_i}, z_{a_i})$, $i = 1, 2, 3, 4$, is determined by the sign of the determinant of a 4×4-matrix:

$$\chi(a_1, a_2, a_3, a_4) = \operatorname{sign}(\det \begin{pmatrix} 1 & 1 & 1 & 1 \\ x_{a_1} & x_{a_2} & x_{a_3} & x_{a_4} \\ y_{a_1} & y_{a_2} & y_{a_3} & y_{a_4} \\ z_{a_1} & z_{a_2} & z_{a_3} & z_{a_4} \end{pmatrix}).$$

The absolute value of this determinant divided by 6 provides the volume of the tetrahedron. Clearly, this volume is zero if and only if the four atoms lie in a plane. Otherwise, the volume is nonzero and the sign is either positive or negative.

As a visualization, in a right-handed coordinate system,[21] the orientation of four atoms a_1, a_2, a_3, and a_4, not all lying in one plane, may be determined manually by the "right hand rule": Identifying atom a_1 with the back of the right hand, the orientation is positive if and only if it is possible to point with thumb, index and middlefinger in direction to atoms a_2, a_3, and a_4, respectively. Equivalently, looking from atom a_1 to the plane containing a_2, a_3 and a_4, the latter three atoms are arranged clockwise.

For practical reasons, we provide a tolerance for zero orientations: Quadruples of atoms with a corresponding tetrahedron volume less than or equal to a given tolerance value are assigned orientation 0. This allows, for example, nearly planar rings or nearly eclipsed bonds to be recognized as planar or eclipsed, respectively.[22]

In previous articles[20a,b] orientations with plus and minus signs only were considered (i.e. no zero orientations). It was argued that small deformations of a planar arrangement of four atoms will result in very similar conformations having no zero orientations. However, this leads to difficulties when considering symmetry: For an achiral conformation, there may exist enantiomorphic chiral deformations. In order to avoid this breaking of the chiral/achiral property, we decided to allow zero orientations explicitly and even to allow a relatively large tolerance therefore.

2.2 The orientation function of a conformation

In the following, we consider a molecule made of N atoms in a given conformation. Atom numbers $1, 2, \ldots, N$ are arbitrary but fixed. (In section 2.3 we will discuss the influence of a renumbering of the atoms on the orientations.)

The function χ mapping each quadruple of atom labels to the orientation of the corresponding atoms is called the *orientation function* of the given conformation. One crucial point of describing conformational information by an orientation function is that we obtain a classification of all conformations into a discrete set of possible orientation functions.

Thus by identifying conformations with the same orientation function, we reduce an infinite set of conformations to a finite set of distinct orientation functions.

We could write down the orientation function by listing the function values for all quadruples. However, the number N^4 of all quadruples is huge already for medium-sized N and thus this seems impractical. We will show the following:

1. It is not necessary to write down the orientation of each quadruple explicitly, as the orientations are interdependent. Some are easily obtained from others.
2. Not all orientations of quadruples are of equal relevance. We may restrict our investigations to a selection of most relevant orientations, and by so doing we may describe a conformation on various levels of accuracy.

Note that the reduction of explicitly stored information according to item 1 is without loss of information, in contrast to that according to item 2.

Because of determinant rules, permutation of two atoms in the quadruple (a_1, a_2, a_3, a_4) will reverse the sign of its orientation. This corresponds to the reversal of configuration on exchange of two ligands at a stereocenter. In mathematical terms, mappings fulfilling this property are called *alternating mappings.* Once we know $\chi(a_1, a_2, a_3, a_4)$, we also know the following orientations:

$$\begin{aligned}
&\chi(a_1,a_2,a_3,a_4) = \chi(a_1,a_3,a_4,a_2) = \chi(a_1,a_4,a_2,a_3) = \\
&\chi(a_2,a_1,a_4,a_3) = \chi(a_2,a_3,a_1,a_4) = \chi(a_2,a_4,a_3,a_1) = \\
&\chi(a_3,a_2,a_4,a_1) = \chi(a_3,a_1,a_2,a_4) = \chi(a_3,a_4,a_1,a_2) = \\
&\chi(a_4,a_3,a_2,a_1) = \chi(a_4,a_1,a_3,a_2) = \chi(a_4,a_2,a_1,a_3)\,.
\end{aligned}$$

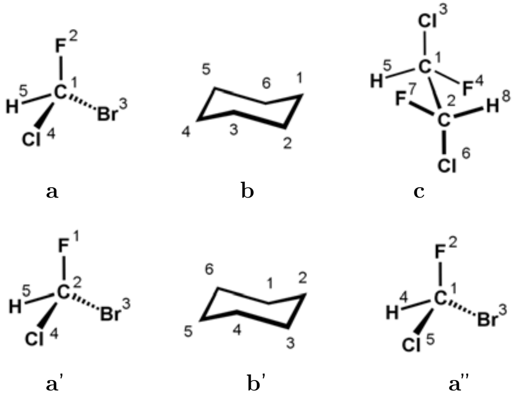
The twelve remaining permutations of (a_1, a_2, a_3, a_4) all have the opposite orientation $-\chi(a_1, a_2, a_3, a_4)$. Thus it suffices to write down the orientation of quadruple (a_1, a_2, a_3, a_4) of increasing atom numbers $a_1 < a_2 < a_3 < a_4$.

For formal reasons we below will need to consider quadruples (a_1, a_2, a_3, a_4) where one of the atoms occurs multiply. However, as the determinant of a matrix having two identical columns is zero, $\chi(a_1, a_2, a_3, a_4) = 0$ in such a case. This corresponds to flattening a tetrahedron into a triangle by identifying two of its vertices, thereby nullifying its volume.

Thus, instead of N^4 orientations of all quadruples, we only need to specify

$$\tbinom{N}{4} = \tfrac{N(N-1)(N-2)(N-3)}{24}$$

orientations of *increasing quadruples* of distinct atoms, in order to specify an orientation function without loss of information. For example, for $N = 10$, we have $10^4 = 10\,000$ and $\tbinom{10}{4} = 210$.



a **b** **c**

a' **b'** **a''**

Figure 1: Example conformations

Listing the quadruples of atom indices in lexicographic order,[23] we specify the mapping χ by writing down the orientations of quadruples (a_1, a_2, a_3, a_4) with $a_1 < a_2 < a_3 < a_4$. Thus, the orientation function is described by a sequence of length $\binom{N}{4}$ that consists of plus and minus signs and zeros.

Example. Let us consider the conformations shown in Figure 1. The orientation functions are:

$$\begin{array}{lccccc} & 1234 & 1235 & 1245 & 1345 & 2345 \\ \chi_{1a} = & - & + & - & + & + \end{array}$$

$$\begin{array}{lccccccccccccccc} & 1234 & 1235 & 1236 & 1245 & 1246 & 1256 & 1345 & 1346 & 1356 & 1456 & 2345 & 2346 & 2356 & 2456 & 3456 \\ \chi_{1b} = & + & + & + & 0 & + & + & - & 0 & + & + & - & - & 0 & + & + \end{array}$$

$$\begin{array}{lccccccccccccccccccc} & 1234 & 1235 & 1236 & 1237 & 1238 & 1245 & 1246 & 1247 & 1248 & 1256 & 1257 & 1258 & 1267 & 1268 & 1278 & \cdots \text{(altogether 70 quadruples)} \cdots & 4578 & 4678 & 5678 \\ \chi_{1c} = & - & + & 0 & + & - & - & - & 0 & + & + & - & 0 & - & + & - & & - & - & - \end{array}$$

Before discussing further ideas to reduce the amount of necessary explicit information for representing steric and conformational properties, we will consider the influence of the chosen atom numbering on the orientation function.

2.3 Symmetry, the orientational automorphism group

Renumbering atoms of a molecule, without affecting configuration and conformation, may lead to an orientation function different from the initial one. For example, exchanging the numbers of atoms 1 and 2 in the conformation shown in Figure **1a**, compare **1a**', results in the modified orientation function

$$\chi_{1\mathrm{a}'} = \begin{array}{ccccc} 1234 & 1235 & 1245 & 1345 & 2345 \\ + & - & + & + & + \end{array}$$

Note that there is no 1:1 correspondence between orientation and Cahn-Ingold-Prelog (CIP) designation. The orientation of a particular quadruple depends on the numbering of atoms, not on their nature. Thus, exchanging atom numbers 4 and 5 in conformation **1a**, compare **1a**'', will result in orientation $\chi_{1\mathrm{a}''}(2,3,4,5) = -$ instead of $\chi_{1\mathrm{a}}(2,3,4,5) = +$, while the configuration of stereocenter atom 1 remains R, of course.

The orientation function may change under a renumbering even if the molecular graph remains the same, i.e. even if the renumbering is a graph automorphism. For example, if we change the labels of the cyclohexane conformation **1b** in a cyclic manner ($1 \rightarrow 2$, $2 \rightarrow 3$, $3 \rightarrow 4$, $4 \rightarrow 5$, $5 \rightarrow 6$, $6 \rightarrow 1$) as shown in **1b**', the molecular graph remains the same: renumbered atoms 1 and 2 are still bonded, there is still no bond between atoms 1 and 3, etc., i.e. the cyclic renumbering is a graph automorphism. However, after renumbering we obtain the orientation function

$$\chi_{1\mathrm{b}'} = \begin{array}{ccccccccccccccc} 1234 & 1235 & 1236 & 1245 & 1246 & 1256 & 1345 & 1346 & 1356 & 1456 & 2345 & 2346 & 2356 & 2456 & 3456 \\ - & - & - & 0 & - & - & + & 0 & - & - & + & + & 0 & - & - \end{array} ,$$

which is exactly the negative of the original orientation function. Orientation functions obtained from each other by a graph automorphic renumbering are called *isomorphic.*

It is worth remarking that here is a nice test for chirality: A conformation is achiral if and only if its orientation function is isomorphic to its negative.[15b,16,17c,f] Thus, the fact that the orientation function of the cyclohexane conformer is isomorphic to its negative indicates the achirality of the conformer.

Note that achirality does *not* imply a balanced relation between plus and minus signs in an orientation function. Note further that also the exchange of atom numbers 4 and 5 in chiral conformations **1a** and **1a**'' above results in the negative orientation function. However, this renumbering is not a graph automorphism.

A graph automorphism that does not change the orientation function is called an *orientational automorphism.* The set of all orientational automorphisms is called the *orientational automorphism group.* It is a subgroup of the graph automorphism group[24].

Isomorphic orientation functions differ only due to the chosen atom numbering, they belong to essentially equivalent conformations. Thus, when generating conformations, we would like to generate exactly one representative from each class of isomorphic orientation functions. This is achieved by defining *canonic* orientation functions. Within each class of isomorphic orientation functions, we declare one as canonic. There should be an efficient test to recognize whether a given orientation function is canonic or not.

A simple choice is to declare the lexicographically minimal one within a class of isomorphic orientation functions as canonic. However, the particular choice is not essential. Essential is the ability to test for canonicity efficiently: Minimality can be tested by calculating and comparing the orientation functions of all graph automorphic renumberings. For small graph automorphism groups this is practicable.

For a large graph automorphism group, a more sophisticated algorithm is available:[25] One of the authors developed a general algorithm for a canonicity test and thus for testing isomorphism of mappings such as orientation functions with respect to a prescribed group of possible relabellings (the graph automorphism group). The canonic form used with this algorithm has the advantage to be compatible with the orderly generation[26] algorithm for such mappings implemented in the same work. This generation algorithm is used below for generating partial orientation functions and thus conformers of chemical structures.

2.4 Partial orientation functions (POFs)

As already obvious in example structure **1c**, the full orientation function is overly complex for larger molecules. So we generally restrict our considerations to a few relevant orientations by selecting a subset S of atom quadruples. The partial orientation function (POF) with respect to S of a conformation is the orientation function χ of the conformation restricted to the subset S. Thus, a POF χ is an alternating mapping $\chi\colon S \to \{+,-,0\}$.

We request S to be closed under permutations of the quadruples and under application of graph automorphisms of the molecule. In other words, if $(a_1, a_2, a_3, a_4) \in S$, then each permutation of this quadruple should be contained in S, and for each graph automorphism π (a renumbering of the atoms) the renumbered quadruple should also be in S. This way, applying a graph automorphism π to a POF with respect to S will result in a POF with respect to the same selection S. We can introduce canonic forms for POFs with respect to S, and generate canonic representatives only, avoiding the generation of isomorphic conformations.

We suggest to select for various purposes various types of quadruples, and further selections are of course possible.

i) Quadruples consisting of the four (immediate) neighbors of a stereocenter. These will distinguish classical stereocenter-based stereoisomers.

ii) Quadruples of four atoms linked in a row with a single bond as the central bond. These will distinguish conformations that arise by rotation about single bonds.

iii) Further quadruples are required to distinguish stereoisomers in examples **A**-**C**.

In example **B**, we could add the quadruple consisting of the two methyl carbon atoms together with their immediate neighbors. In fact, the atoms of a quadruple not at all need to be bonded to each other (those in type i quadruples are not, either). Thus, the methyl carbon atoms together with any two atoms in the aromatic system could serve as well. To detect stereoisomerism that is not describable in terms of stereocenters or butane fragments, it even seems advisable to select quadruples of atoms far apart.

Example. Selecting quadruples of type i and ii, we obtain the following POFs for the conformations shown in Figure 1:

$$\begin{array}{ll} & \scriptstyle 2345 \\ \chi_{1\mathrm{a}} = & + \end{array}$$

$$\begin{array}{lcccccc} & \scriptstyle 1234 & \scriptstyle 1236 & \scriptstyle 1256 & \scriptstyle 1456 & \scriptstyle 2345 & \scriptstyle 3456 \\ \chi_{1\mathrm{b}} = & + & + & + & + & - & + \end{array}$$

$$\begin{array}{lccccccccccc} & \scriptstyle 1236 & \scriptstyle 1237 & \scriptstyle 1238 & \scriptstyle 1246 & \scriptstyle 1247 & \scriptstyle 1248 & \scriptstyle 1256 & \scriptstyle 1257 & \scriptstyle 1258 & \scriptstyle 1678 & \scriptstyle 2345 \\ \chi_{1\mathrm{c}} = & 0 & + & - & - & 0 & + & + & - & 0 & - & + \end{array}$$

The amount of stored information is reduced drastically compared to the full orientation function. Still, different conformations are distinguished, as we will see in the next sections.

A POF may still be highly redundant. In example **1c**, there are nine strongly interdependent quadruples describing the torsion about the rotatable central bond. Along with the stereocenter quadruples (1,6,7,8) and (2,3,4,5), even a single orientation such as that of (1,2,3,6) is sufficient to completely describe a particular conformer of **1c**. However, the chosen quadruples as an automatically computer-generated selection S are practical, since this set is certainly closed under graph automorphisms.

2.5 Generation of abstract POFs

So far, we considered a way of describing steric information of a given conformation using POFs, i.e. sequences of plus and minus signs and zeros. By writing down all possible such sequences, referred to as *abstract (partial) orientation functions*, we can therefore *generate* quite a lot of conformations. Each abstract POF is a candidate for the POF of a conformation. We call the following approach

Dreiding's approach for stereoisomer generation. We obtain conformers and stereoisomers of a molecule by constructing all abstract POFs with respect to a suitable set S of atom quadruples, i.e. by considering the set of alternating mappings $\chi\colon S \to \{+,-,0\}$, and selecting those that are realizable in 3D space using reasonable bond lengths, bond angles and dihedral angles.

Thus the generation is split into two steps:

1. Combinatorial level:
   Generate all abstract POFs that are eligible (by means of simple combinatorial tests) for a chemical conformation.
2. Geometrical level:
   For each of these candidates, try to find a conformer as realization.

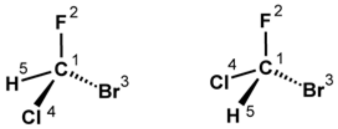
Note that there may exist no realization for an abstract POF even if the function fulfills all tested criteria of step 1. We distinguish three kinds of abstract POFs:

- χ is not realizable:
  There is no embedding of the atoms in space such that χ is the POF of this embedding.
- χ is geometrically realizable:
  There exists an embedding of the atoms into 3D space having χ as POF. However, bond lengths, bond angles and torsion angles are not considered, i.e. the molecule is assumed to have unlimited flexibility.
- χ is chemically realizable.
  There is (at least) one conformer[1] having χ as POF.

It is crucial to provide a set of combinatorial tests on level 1 to exclude as many as possible non-realizable and not chemically realizable abstract POFs. We distinguish two kinds of tests:

- Tests excluding non-realizable abstract POFs only may be used without any concern. Their validity can be proven in the mathematical sense.
- Tests excluding geometrically realizable but not chemically realizable abstract POFs have to be justified chemically. Depending on the problem given, a particular rule may or may not be acceptable.

The computer program `origen`, a generator of alternating functions, was developed by one of the authors for solving step 1.[25] This program accepts as input among other parameters a set of tuples as relevant function domain (i.e. the set S), a group of possible relabellings (the automorphism group of the molecular graph), and possibly further restrictions (allowing a variety of tests for geometrical and chemical realizability). It generates all non-isomorphic partially defined alternating functions, i.e. all non-isomorphic abstract POFs.



1 **2**

Figure 2: Stereoisomers generated for structure **1a**.

For step 2, a sophisticated solution does not yet exist. Nevertheless we are able to demonstrate the conformer generation according to the proposed strategy for very simple examples. For this purpose we used a constrained optimization algorithm[27] to optimize a random arrangement of atoms via a simple energy function similar to MM2,[28] restricting the allowed conformations by the prescribed orientations. Note that, unfortunately, such an optimization procedure may fail to find a conformer though it exists.

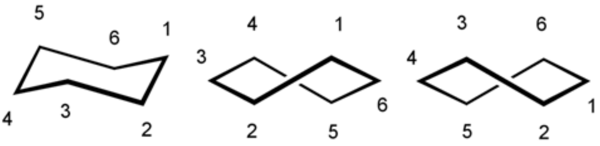
Example. In the following we consider the numbers of abstract POFs for the structures (constitutions) from Figure 1. As set S, we select again the quadruples of type i and ii. For a first run, we will not consider any combinatorial tests reducing the number of candidates on level 1.

1a: This example is trivial: The graph automorphism group is trivial, i.e. there are no graph-automorphisms except the identity. All possible (partially defined) alternating mappings are:

$$\begin{array}{rl} & 2345 \\ \chi_1 = & + \\ \chi_2 = & - \\ \chi_3 = & 0 \end{array}$$

POFs χ_1 and χ_2 correspond to the two enantiomers shown in Figure 2. POF χ_3 is not chemically realizable. However, it is geometrically realizable: Any planar placement of the five atoms has χ_3 as its POF.

1b: There are $3^6 = 729$ abstract POFs for structure **1b** (each of the 6 selected increasing quadruples can independently be chosen to have orientation plus, minus, or zero). However, cyclohexane has 12 graph automorphisms. Considering relabellings according to these permutations, some of the abstract POFs are isomorphic. Using `origen`, we obtain 92 non-isomorphic candidates. Using constrained conformation optimization, we found chemical realizations for exactly three of these:



1 **2** **3**

Figure 3: Conformers generated for structure **1b**.

$$\begin{array}{rcccccc} & 1234 & 1236 & 1256 & 1456 & 2345 & 3456 \\ \chi_1 = & + & + & + & + & - & + \\ \chi_2 = & + & + & + & - & + & - \\ \chi_3 = & + & + & - & - & - & - \end{array}$$

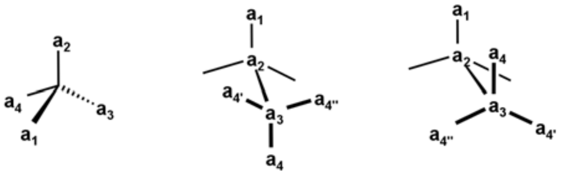
These correspond to the chair and the two enantiomorphic twist conformers, see Figure 3. Further examination shows that among the 92 generated abstract POFs, there is also

$$\begin{array}{rcccccc} & 1234 & 1236 & 1256 & 1456 & 2345 & 3456 \\ \chi_4 = & + & 0 & - & - & - & 0 \end{array}$$

corresponding to the boat conformation. However, as the boat is not a conformer, this is not a chemical realization.

The example cyclohexane was presented in more detail in earlier articles.[20a,b] In these, however, zero orientations were not considered. This led to 13 abstract POFs containing positive and negative orientations only,[29] the three chemically realizable ones among them. If we assume that in saturated rings of size ≥ 6 there are no conformers with four adjacent atoms in one plane, we can use this as a criterion for chemical realizability: We restrict the number of 92 non-isomorphic abstract POFs to 13 abstract POFs without any zero orientation.

1c: Structure **1c** has a nontrivial graph automorphism: (1,2)(3,6)(4,7)(5,8). From the $3^{11} = 177147$ abstract POFs, 89667 non-isomorphic candidates remain. In the next sections, we will discuss combinatorial tests to reduce this number to a manageable size.



a **b** **b'**

Figure 4: Kinds of quadruples considered in tests

2.6 Tests for chemical realizability

In example structure **1c**, we have to handle 89667 abstract POFs. In this section we provide criteria allowing to exclude most of these from further examination. A first criterion is that the four neighbors of a carbon atom certainly should not be placed in one plane, see Figure 4a. Thus we apply

Test 1. If (a_1, a_2, a_3, a_4) are four immediate neighbors of a carbon atom, then we accept an abstract POF as candidate only if $\chi(a_1, a_2, a_3, a_4)$ is not zero.

This test excludes the only chemically non-realizable POF of example **1a**. It has no effect on example **1b**, since there are no such atom quadruples explicitly considered in **1b**. (We do not care about the hydrogen atoms in this example.) For example **1c**, we postulate $\chi(1, 6, 7, 8) \neq 0$ and $\chi(2, 3, 4, 5) \neq 0$, whereby the number of generated candidates reduces to 40095.

The following tests are without influence on examples **1a** or **1b**. However, they allow to further reduce the number of candidates for example **1c**. We can restrict the orientations around a rotatable single bond. Consider the situation shown in Figure 4b. The following should be commonly accepted:

Test 2a. Suppose a_2 and a_3 are carbon atoms connected by a single bond, a_1 is a neighbor of a_2, and a_3 has another three neighbors. Among the neighbors of a_3, there is at most one atom a_4 with $\chi(a_1, a_2, a_3, a_4) = 0$.

Using this rule on example **1c** we postulate that e.g. among $\chi(1, 2, 3, 6)$, $\chi(1, 2, 3, 7)$, and $\chi(1, 2, 3, 8)$, there is at most one function value zero. Using tests 1 and 2a for generation of abstract POFs, the number of generated candidates for example **1c** reduces to 11368. A stronger version of this test is to enforce that in realizations of candidates, there is at least one atom on the one side of the plane defined by atoms a_1, a_2, and a_3, and there is at least one atom on the other side.

Test 2b. Suppose a_2 and a_3 are carbon atoms connected by a single bond, a_1 is a neighbor of a_2, and a_3 has another three neighbors a_4, a'_4, and a''_4. Among $\chi(a_1, a_2, a_3, a_4)$, $\chi(a_1, a_2, a_3, a'_4)$, and $\chi(a_1, a_2, a_3, a''_4)$, there occurs at least one plus and at least one minus sign.

Note that test 2b implies test 2a. Using tests 1 and 2b on example **1c**, we obtain 956 candidates. Finally, as an even more restrictive variant of this test, we could use the following one allowing as realizations of candidates only fully staggered and fully eclipsed conformations at C_{sp3}-C_{sp3} single bonds, with a given tolerance for the zero orientation. Tolerance was discussed above at the end of section 2.1.

Test 2c. Suppose a_2 and a_3 are carbon atoms connected by a single bond, a_1 is a neighbor of a_2, and a_3 has another three neighbors a_4, a'_4, and a''_4. Then $\chi(a_1, a_2, a_3, a_4)$, $\chi(a_1, a_2, a_3, a'_4)$, and $\chi(a_1, a_2, a_3, a''_4)$ are pairwise not equal.

By test 2c, it follows that among $\chi(a_1, a_2, a_3, a_4)$, $\chi(a_1, a_2, a_3, a'_4)$, and $\chi(a_1, a_2, a_3, a''_4)$ all three possible values $+$, $-$ and 0 occur. Using tests 1 and 2c on example **1c**, we retain no more than 30 abstract POFs. Among these, there are nine chemically realizable ones, i.e. nine that describe fully staggered conformers. A deeper analysis shows that among the 30 candidates, there are another nine POFs corresponding to fully eclipsed conformations.

If we want to restrict generation to fully staggered conformations of C-C single bonds, we can provide a further rule that excludes the eclipsed ones.

Test 3. Suppose a_2 and a_3 are carbon atoms connected by a single bond, a_1 is a neighbor of a_2, and a_3 has another three neighbors. If a_4 and a'_4 are two of these neighbors and $\chi(a_1, a_2, a_3, a_4) = 0$, then $\chi(a_1, a_2, a_3, a'_4) = -\chi(a_4, a_2, a_3, a'_4)$.

Note that $\chi(a_1, a_2, a_3, a'_4)$ is necessarily nonzero by either of the tests 2a, 2b or 2c. The postulated property of test 3 is true for POFs of staggered conformations, as in this case, atoms a_1 and a_4 lie on different sides of the plane through a_2, a_3, and a'_4, see Figure 4b. In an eclipsed conformation, see Figure 4b', atoms a_1 and a_4 lie on the same side of that plane, thus for the corresponding POF we have $\chi(a_1, a_2, a_3, a'_4) = \chi(a_4, a_2, a_3, a'_4)$ and the test fails.

However, with the proposed selection S, this test is not directly applicable: We did not select the quadruple (a_4, a_2, a_3, a'_4). By using the fact that a carbon atom is within the tetrahedron formed by its four neighbors,[30] the required information on the orientation of (a_4, a_2, a_3, a'_4) can be derived from (a_2, a_4, a'_4, a''_4). This latter quadruple consists of four neighbors of a central atom and thus is selected. As atoms a_3 and a''_4 lie on the same side of the plane through a'_4, a_4, and a_2, the orientations $\chi(a_4, a_2, a_3, a'_4)$ and $\chi(a_4, a_2, a''_4, a'_4) = \chi(a_2, a_4, a'_4, a''_4)$ are identical. Thus we can replace the postulated property in test 3 by $\chi(a_1, a_2, a_3, a'_4) = \chi(a_2, a_4, a'_4, a''_4)$, which can be evaluated for the abstract POFs.

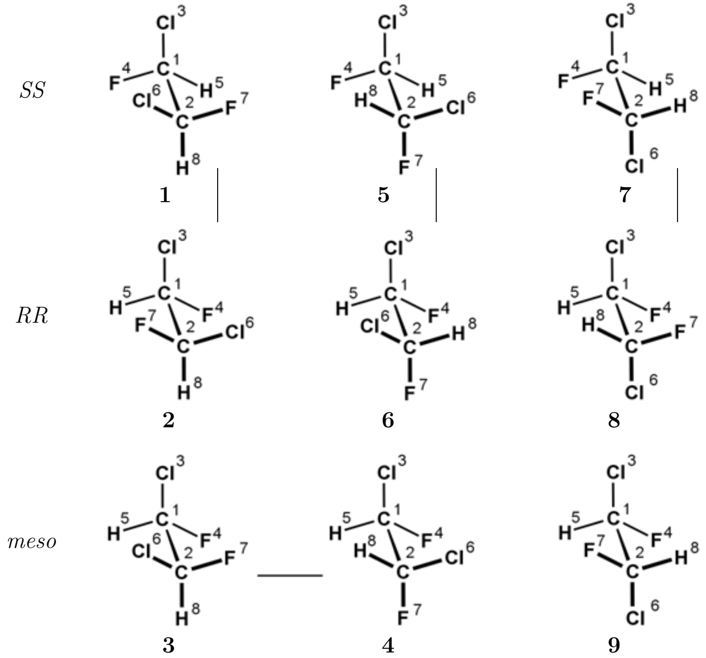
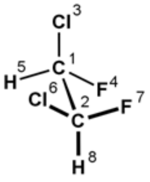


Figure 5: Stereoisomers and conformers generated for structure **1c**.

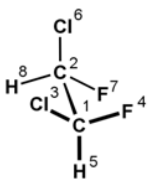
Example. Using tests 1, 2c, and 3 on example **1c**, we retain exactly 9 candidate POFs:

$$\begin{array}{rccccccccccc}
 & 1236 & 1237 & 1238 & 1246 & 1247 & 1248 & 1256 & 1257 & 1258 & 1678 & 2345 \\
\chi_1 = & + & - & 0 & - & 0 & + & 0 & + & - & - & - \\
\chi_2 = & - & + & 0 & + & 0 & - & 0 & - & + & + & + \\
\chi_3 = & + & 0 & - & - & + & 0 & 0 & - & + & + & - \\
\chi_4 = & - & 0 & + & + & - & 0 & 0 & + & - & - & + \\
\chi_5 = & - & 0 & + & 0 & + & - & + & - & 0 & - & - \\
\chi_6 = & + & 0 & - & 0 & - & + & - & + & 0 & + & + \\
\chi_7 = & 0 & + & - & + & - & 0 & - & 0 & + & - & - \\
\chi_8 = & 0 & - & + & - & + & 0 & + & 0 & - & + & + \\
\chi_9 = & 0 & - & + & + & 0 & - & - & + & 0 & + & -
\end{array}$$

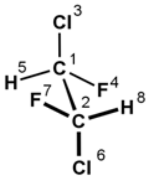
All of these are chemically realizable. The realizations turn out to correspond to exactly three staggered conformers for each of the three stereoisomers, as shown in Figure 5. These correspond to the orientation functions as indicated by the numbers.



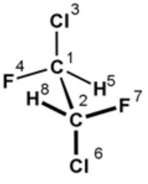
3



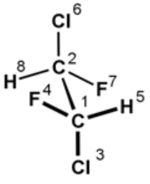
3’



9



9’



9’

It should be an easy exercise for the reader to verify that POFs χ_1, χ_2, and χ_4 – χ_8 describe conformers **1**, **2**, and **4** – **8**. For POFs χ_3 and χ_9 recall that a conformer may be correctly described by more than one orientation function, depending on which automorphic numbering was chosen (χ_{1b} and $\chi_{1b'}$ in sections 2.2 and 2.3). Consider conformer **3**’, which is identical to **3** except for the numbering. The numbering of **3**’ is obtained from that of **3** by application of the graph automorphism (1,2)(3,6)(4,7)(5,8). POF χ_3 describes conformer **3**’, and thus conformer **3** (since atoms in real molecules do not bear numbers).[31]

Similarly, POF χ_9 describes conformer **9**’, which is the mirror image of **9**. Since **9** is achiral, mirror image **9**’ is identical with original **9**, except for the numbering. Again, numbering of **9**’ is obtained from that of **9** by application of the graph automorphism.

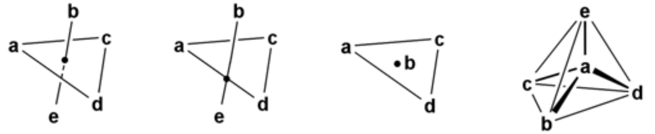
Note that of the nine conformers, the first eight form four pairs of enantiomorphic conformers, as indicated by thin lines in Figure 5. The last conformer is achiral. In this example enantiomorphic conformers are easily recognized from the abstract POFs, in that for them all + and − signs are reversed (e.g. in χ_1 and χ_2). However, due to automorphisms and canonization rules, this is not generally the case. Thus, in example **1b** (section 2.5), abstract POFs χ_2 and χ_3 describe enantiomorphic conformers.

Note also that within the first row and within the second row of Figure 5 the orientations of $(2,3,4,5)$ and $(1,6,7,8)$ are constant. This is necessarily so since $(2,3,4,5)$ and $(1,6,7,8)$ are just the quadruples describing the stereocenters. Within the last row, there is always one + and one − for these orientations.

2.7 Advanced concept I: Radon Partitions

In the following we formalize the considerations used above to make test 3 applicable. A *Radon partition*[32] is a pair $\{A, B\}$ of disjoint subsets of atoms, such that their convex hulls intersect. The *convex hull* of a point is the point itself, the convex hull of two points is the line between them, the convex hull of three points is the triangle formed by them and the convex hull of four points is a tetrahedron.[33]

For example, in Figure 6a the convex hulls of $A = \{a, c, d\}$, a triangle, and of $B = \{b, e\}$, a line, do intersect, thus $\{\{a, c, d\}, \{b, e\}\}$ is a Radon partition. A similar situation



$\{\{a,c,d\},\{b,e\}\}$ $\{\{a,c,d\},\{b,e\}\}$ $\{\{a,c,d\},\{b\}\}$ $\{\{a\},\{b,c,d,e\}\}$

a **b** **c** **d**

Figure 6: Radon partitions; thin lines clarify geometrical relations, while thick lines (in **d**) represent chemical bonds.

is shown in 6b, where the intersection point lies on an edge of the triangle. In example 6c, the convex hull of the three points a, c, and d intersects with the one of point b. Finally, a chemical example of a Radon partition is a central carbon atom on the one hand and its four neighbors on the other, as shown in Figure 6d. As the central atom is inside the tetrahedron of its four neighbors, the convex hulls intersect.

We call a Radon partition $\{A,B\}$ *minimal* iff it is not possible to remove an atom from either set A or B without destroying the Radon partition property. In other words, the Radon partition $\{A,B\}$ is minimal iff there is no Radon partition $\{A',B'\} \neq \{A,B\}$ with $A' \subseteq A$ and $B' \subseteq B$.

All Radon partitions shown in Figure 6 are minimal except 6b. A minimal Radon partition in Figure 6b is $\{\{a,d\},\{b,e\}\}$. Note that a minimal Radon partition contains at most five atoms. Radon's theorem[34] states that any 5-set of atoms can be partitioned into a Radon partition. Furthermore, each 5-set of atoms that are not all in one plane contains exactly one minimal Radon partition.

One fascinating and very useful feature of minimal Radon partitions is that they can be obtained from the orientation function, i.e. on a purely combinatorial level, without considering coordinates. For this purpose we introduce *abstract minimal Radon partitions* for an abstract orientation function. It will turn out that a pair $\{A,B\}$ is a minimal Radon partition of a conformation if and only if it is an abstract minimal Radon partition of the corresponding orientation function. Before giving a formal definition of abstract minimal Radon partition, we first consider an example:

Example. Consider the following abstract full orientation function as a candidate for structure **1b**:

$$\begin{array}{rccccccccccccccc} & 1234 & 1235 & 1236 & 1245 & 1246 & 1256 & 1345 & 1346 & 1356 & 1456 & 2345 & 2346 & 2356 & 2456 & 3456 \\ \chi = & + & + & + & + & + & - & + & + & - & + & + & + & + & + & + \end{array}$$

For each quintuple $(a_1,\ldots,a_5)$ of atoms the following procedure will result in an abstract minimal Radon partition. Consider e.g. the quintuple $(a_1,\ldots,a_5) = (1,3,4,5,6)$. For the

i-th atom a_i, we compare the sign $\chi(a_1, \ldots, a_{i-1}, a_{i+1}, \ldots, a_5)$ with the sign β_i which is $+$ if i is odd, and $-$ if i is even:

atom a_i	$\chi(a_1, \ldots, a_{i-1}, a_{i+1}, \ldots, a_5)$	β_i
$a_1 = 1$	$\chi(3,4,5,6) = +$	$+$
$a_2 = 3$	$\chi(1,4,5,6) = +$	$-$
$a_3 = 4$	$\chi(1,3,5,6) = -$	$+$
$a_4 = 5$	$\chi(1,3,4,6) = +$	$-$
$a_5 = 6$	$\chi(1,3,4,5) = +$	$+$

We obtain an abstract minimal Radon partition as the pair $\{A, B\}$ of sets of atoms where set A consists of all atoms a_i whose two signs agree, and set B consists of all atoms with opposite signs. In the example, we have

$$\{A, B\} = \{\{1, 6\}, \{3, 4, 5\}\}\,.$$

This result will be resumed in section 2.9.

Definition. An abstract minimal Radon partition of an abstract orientation function χ over atoms $\{1, \ldots, N\}$ is a pair $\{A, B\}$ of disjoint subsets of the set of atoms, such that there is a quintuple $(a_1, a_2, a_3, a_4, a_5)$ with $A \cup B \subseteq \{a_1, a_2, a_3, a_4, a_5\} \subseteq \{1, \ldots, N\}$, and

$$\begin{aligned} a_i \in A \quad &\Longleftrightarrow \quad \chi(a_1, \ldots, a_{i-1}, a_{i+1}, \ldots, a_5) = \ \ \beta_i \\ a_i \in B \quad &\Longleftrightarrow \quad \chi(a_1, \ldots, a_{i-1}, a_{i+1}, \ldots, a_5) = -\beta_i\,, \end{aligned}$$

where $\beta_i = \begin{cases} + & \text{if } i \text{ is odd,} \\ - & \text{if } i \text{ is even.} \end{cases}$

Note that if $\chi(a_1, \ldots, a_{i-1}, a_{i+1}, \ldots, a_5) = 0$, then a_i is neither in A nor in B, i.e. an abstract minimal Radon partition $\{A, B\}$ may contain fewer than five atoms. Still, as for non-abstract minimal Radon partitions, to each 5-set of atoms is assigned exactly one abstract minimal Radon partition. Now, considering a conformation and its orientation function (which is, for sure, also an abstract orientation function), we can formulate the following theorem:

Theorem 1. A pair $\{A, B\}$ of disjoint subsets of the set of atoms $\{1, \ldots, N\}$ is a minimal Radon partition of a conformation if and only if it is an abstract minimal Radon partition of its orientation function.[35,36]

This theorem can be applied to deduce unknown orientations from known ones of an abstract POF.

Example. We already mentioned that a central carbon atom on the one hand and its four neighbors on the other form a minimal Radon partition. We have such a situation in example **1c**. Thus, $\{A, B\} = \{\{1\}, \{2, 3, 4, 5\}\}$ is a minimal Radon partition of conformation **1c**. According to the theorem, $\{A, B\}$ is also an abstract minimal Radon partition of its orientation function. Knowing only the partial orientation function shown in section 2.4, we have the following situation, corresponding to the quintuple $(1, 2, 3, 4, 5)$:

atom a_i	$\chi(a_1, \ldots, a_{i-1}, a_{i+1}, \ldots, a_5)$	β_i
$a_1 = 1$	$\chi(2, 3, 4, 5) = +$	$+$
$a_2 = 2$	$\chi(1, 3, 4, 5) = \ ?$	$-$
$a_3 = 3$	$\chi(1, 2, 4, 5) = \ ?$	$+$
$a_4 = 4$	$\chi(1, 2, 3, 5) = \ ?$	$-$
$a_5 = 5$	$\chi(1, 2, 3, 4) = \ ?$	$+$

As we know that the minimal Radon partition separates a_1 from the remaining four atoms, and as the signs in the table corresponding to a_1 are equal, it follows that the signs for atoms a_2 – a_5 need to be opposite in the table. Thus we conclude:

$$\chi(1, 3, 4, 5) = +, \quad \chi(1, 2, 4, 5) = -, \quad \chi(1, 2, 3, 5) = +, \quad \chi(1, 2, 3, 4) = -.$$

Similarly, by knowing $\chi(1, 6, 7, 8) = -$ the following values ensue by the minimal Radon partition $\{A, B\} = \{\{2\}, \{1, 6, 7, 8\}\}$:

$$\chi(2, 6, 7, 8) = -, \quad \chi(1, 2, 7, 8) = -, \quad \chi(1, 2, 6, 8) = +, \quad \chi(1, 2, 6, 7) = -.$$

This result is not surprising, since above, using chemical intuition, we classified as important no more than one out of five such function values. On the other hand, this allows to replace in tests orientations of non-selected quadruples by those of selected ones, as done in test 3 above.

2.8 Advanced concept II: Binary Grassmann-Plücker Relations

From the orientations being signs of determinants it follows that the orientation function of any conformation fulfills the *binary Grassmann-Plücker-Relations*:[37]

Binary Grassmann-Plücker Relation. If two quadruples of atoms $(a_1, \ldots, a_4)$ and $(b_1, \ldots, b_4)$ have the same nonzero orientation, then there is at least one atom b_i in the second quadruple such that quadruples (b_i, a_2, a_3, a_4) and $(b_1, \ldots a_1, \ldots, b_4)$, arising by exchange of a_1 and b_i, have the same nonzero orientation.[38]

The “same orientation“ of the first-mentioned two quadruples may or may not differ from the “same orientation” of the second two quadruples. In formal terms:

$$\chi(a_1, a_2, a_3, a_4) = \chi(b_1, b_2, b_3, b_4) \neq 0 \Longrightarrow$$
$$\exists\, i \in \{1, \ldots, 4\} : \chi(b_i, a_2, a_3, a_4) = \chi(b_1, \ \ldots, \underset{\substack{\uparrow \\ i\text{th position}}}{a_1}, \ldots, b_4) \neq 0\,.$$

Example. Consider the constitution of **1c** and the set of its abstract POFs. The binary Grassmann-Plücker relation corresponding to atom quadruples $(4,3,1,2)$ and $(6,7,2,1)$ is as follows:

$$\begin{array}{rll} & \chi(4,3,1,2) = \chi(6,7,2,1) \neq 0 & \Longrightarrow \\ (i=1): & \chi(6,3,1,2) = \chi(4,7,2,1) \neq 0 & \text{or} \\ (i=2): & \chi(7,3,1,2) = \chi(6,4,2,1) \neq 0 & \text{or} \\ (i=3): & \chi(2,3,1,2) = \chi(6,7,4,1) \neq 0 & \text{or} \\ (i=4): & \chi(1,3,1,2) = \chi(6,7,2,4) \neq 0 & \end{array}$$

The last two possibilities are false for any orientation function χ, as $(2,3,1,2)$ and $(1,3,1,2)$ both contain one atom twice, thus these orientations are zero. We reformulate the condition by bringing each quadruple in increasing order:

$$\begin{array}{ll} (-\chi(1,2,3,4)) = (-\chi(1,2,6,7)) \neq 0 & \Longrightarrow \\ (-\chi(1,2,3,6)) = (-\chi(1,2,4,7)) \neq 0 & \text{or} \\ (-\chi(1,2,3,7)) = (+\chi(1,2,4,6)) \neq 0 & \end{array}$$

or equivalently,

$$\begin{array}{rl} \chi(1,2,3,4) = \chi(1,2,6,7) \neq 0 & \Longrightarrow \\ \chi(1,2,3,6) = \chi(1,2,4,7) \neq 0 & \text{or} \\ -\chi(1,2,3,7) = \chi(1,2,4,6) \neq 0 & \end{array}$$

We can use minimal Radon partitions to replace non-selected quadruples by selected ones: Any conformer of constitution **1c** has the minimal Radon partitions $\{\{1\},\{2,3,4,5\}\}$ and $\{\{2\},\{1,6,7,8\}\}$. Thus, as argued in the example at the end of the previous section, $\chi(1,2,3,4) = -\chi(2,3,4,5)$ and $\chi(1,2,6,7) = \chi(1,6,7,8)$. The condition may be reformulated as follows:

$$\begin{array}{rl} -\chi(2,3,4,5) = \chi(1,6,7,8) \neq 0 & \Longrightarrow \\ \chi(1,2,3,6) = \chi(1,2,4,7) \neq 0 & \text{or} \\ -\chi(1,2,3,7) = \chi(1,2,4,6) \neq 0 & \end{array}$$

This condition is true for the POF of *any* conformer of **1c**. We may check it for the POF of the one shown in Figure 1.

$$\chi_{1c} = \begin{array}{ccccccccccc} 1236 & 1237 & 1238 & 1246 & 1247 & 1248 & 1256 & 1257 & 1258 & 1678 & 2345 \\ 0 & + & - & - & 0 & + & + & - & 0 & - & + \end{array}$$

The orientations $\chi(2,3,4,5) = +$ and $\chi(1,6,7,8) = -$ fulfill the premise: They are antipodal and nonzero. As $\chi(1,2,3,6) = 0$, the first possibility of the conclusion is false. Thus the only remaining possibility must be true, i.e. $\chi(1,2,3,7)$ and $\chi(1,2,4,6)$ must be antipodal and nonzero. Indeed, we can see $\chi(1,2,3,7) = +$ and $\chi(1,2,4,6) = -$.

Note that different binary Grassmann-Plücker relations may lead to the same condition. E.g., the one corresponding to $(3, 4, 1, 2)$ and $(7, 6, 2, 1)$ leads to the same condition as the one discussed above. Test 4 checks all such criteria obtained by binary Grassmann-Plücker relations:

Test 4. Whenever two quadruples (a_1, a_2, a_3, a_4) and (b_1, b_2, b_3, b_2) and all derived quadruples occurring in a binary Grassmann-Plücker relation are either selected directly, or may be derived from a selected quadruple by known minimal Radon partitions as demonstrated above, then ensure that the binary Grassmann-Plücker relation is fulfilled.

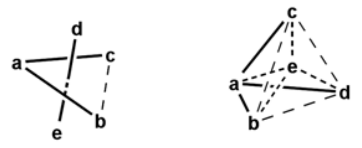
In example **1c** we can check altogether 30 relations of this kind. Though the formulation is quite complicated for humans, the test itself is very efficient in a computer and reduces the number of eligible abstract POFs remarkably. Test 4 in combination with tests 1–3 reduces the number of candidates generated as follows:

- Using tests 1 and 4, we obtain 528 non-isomorphic candidates for orientation functions (instead of 40095 using test 1 alone).
- Using tests 1, 2a, and 4 we still obtain 528 candidates. This means that test 2a used in combination with test 4 did not sharpen the restrictions on realizable POFs.
- Using tests 1, 2b, and 4 we still obtain 528, thus even test 2b does not add any stronger restriction.
- Using tests 1, 2c, and 4 we obtain 18 candidates, i.e the 12 non-realizable candidates from the run with solely tests 1 and 2c were successfully suppressed by the Grassmann-Plücker test 4.
- Using tests 1, 2c, 3, and 4 we obtain again the 9 candidates corresponding to 9 staggered conformers. Here, as expected, the additional test 4 did not change the result.

2.9 Further tests based on minimal Radon Partitions

A conformation cannot have a minimal Radon partition of the form $\{A, \emptyset\}$, as the convex hull of the empty set is empty, and thus, trivially, its intersection with the convex hull of A cannot by nonempty. However, abstract POFs may have abstract minimal Radon partitions of the form $\{A, \emptyset\}$. Such abstract POFs are not realizable because of theorem 1.[39] Thus we can restrict our candidate abstract POFs by the following test:

Test 5. Ensure that χ has no abstract minimal Radon partition of the form $\{A, \emptyset\}$.



$\{\{a,b,c\},\{d,e\}\}$ $\{\{a,b,c,d\},\{e\}\}$

a b

Figure 7: Two chemically forbidden minimal Radon partitions; full lines represent chemical bonds, while broken lines clarify geometrical relations.

Example. Consider the following abstract full orientation function for example **1a**:

$$\chi = \begin{array}{ccccc} 1234 & 1235 & 1245 & 1345 & 2345 \\ + & - & + & - & + \end{array}$$

This candidate passes tests 1 to 4: Test 1: $\chi(2,3,4,5) \neq 0$. Tests 2a, 2b, 2c and 3 are trivial, as there is no relevant quadruple. Test 4 is passed, as any two quadruples must have at least 3 atoms in common (there are only five atoms in the structure) and it is easily shown that the binary Grassmann-Plücker relations belonging to two quadruples (a_1, a_2, a_3, a_4) and (b_1, b_2, b_3, b_4) with at least three atoms in common are trivial, as the premise occurs among the four possibilities of the conclusion.

However, we will show that χ has an abstract minimal Radon partition of the form $\{A, \emptyset\}$. Consider quintuple $(a_1, a_2, a_3, a_4, a_5) = (1,2,3,4,5)$:

atom a_i	$\chi(a_1, \ldots, a_{i-1}, a_{i+1}, \ldots, a_5)$	β_i
$a_1 = 1$	$\chi(2,3,4,5) = +$	$+$
$a_2 = 2$	$\chi(1,3,4,5) = -$	$-$
$a_3 = 3$	$\chi(1,2,4,5) = +$	$+$
$a_4 = 4$	$\chi(1,2,3,5) = -$	$-$
$a_5 = 5$	$\chi(1,2,3,4) = +$	$+$

Comparing the signs in the table, we obtain the abstract minimal Radon partition $\{\{1,2,3,4,5\},\emptyset\}$. Thus the orientation function χ is not realizable.

A further test is based on chemical experience: We can exclude some kinds of abstract minimal Radon partitions that would result in conformations of high steric energy. Examples of such “forbidden minimal Radon partitions” are shown in Figure 7. Figure 7a illustrates the rule that a bond (de) must not cross the triangle formed by two consecutive bonds (bac). Thus we can exclude any abstract POF containing an abstract minimal Radon partition $\{A, B\} = \{\{a,b,c\},\{d,e\}\}$ with this bond pattern. Figure 7b illustrates

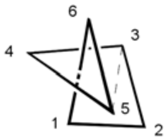


Figure 8: A non-chemical arrangement of atoms for structure **1b**.

the rule that the space inside a tripod formed by three bonds emanating from one atom (ab, ac, ad) must not be occupied by another atom (e). Thus we can exclude any abstract POF containing an abstract minimal Radon partition $\{A, B\} = \{\{a, b, c, d\}, \{e\}\}$ with this bond pattern.

Test 6. Ensure that in abstract POFs no abstract minimal Radon partition of the forms shown in Figure 7 will occur.

Example. Consider the abstract full orientation function χ of constitution **1b**

$$\begin{array}{cccccccccccccccc} & 1234 & 1235 & 1236 & 1245 & 1246 & 1256 & 1345 & 1346 & 1356 & 1456 & 2345 & 2346 & 2356 & 2456 & 3456 \\ \chi = & + & + & + & + & + & - & + & + & - & + & + & + & + & + & + \end{array}$$

that was already examined in the first example of section 2.7. There we demonstrated that χ has the abstract minimal Radon partition $\{\{1, 6\}, \{3, 4, 5\}\}$. In Figure 8 an arrangement of six atoms having this orientation function is shown. Thus this function is realizable. However, since in **1b** there are chemical bonds 3-4, 4-5, and 1-6, this arrangement contains the chemically forbidden minimal Radon partition drawn in Figure 7a, whence this realization of χ is not a chemical realization. Moreover, as any realization of the abstract POF has the minimal Radon partition $\{\{1, 6\}, \{3, 4, 5\}\}$ according to theorem 1, any realization has a forbidden minimal Radon partition and thus the abstract POF is not chemically realizable.

We here applied the test to an abstract full orientation function and successfully excluded a non-chemically realizable one. The test is applicable only in situations where five quadruples (a, b, c, d), (a, b, c, e), (a, b, d, e), (a, c, d, e) and (b, c, d, e) are all either selected or their function values can be obtained by known minimal Radon partitions. Only in such a case can we determine the abstract Radon partition corresponding to the 5-set $\{a, b, c, d, e\}$ and decide whether or not it is a forbidden one. However, if we select quadruples of type i and ii, then as a rule no such cluster of five quadruples is available, and test 5 and test 6 do not exclude any candidate abstract POF.

3 Discussion

Organic chemists traditionally distinguish stereoisomers and conformers, where the former are fully characterized by their configuration, the latter by their conformation. Since this distinction is artificial, mathematics should be able to treat stereoisomerism in a unified manner. A step in this direction is presented here.

There are $\binom{N}{4}$ quadruples of atoms in a molecule. This number scales with N^4 and thus seems to render the approach impractical. However, by selection of only few relevant quadruples the complexity of algorithms could be kept within manageable limits. Selection of neighbors of stereocenters only would result in an analogon to Nourse's algorithm which has proven to be efficient even for large molecules. By selecting further quadruples, we have the possibility to generate conformers and (nonclassical) stereoisomers in addition to classical stereoisomers. By the number of selected quadruples, we may generate sets of conformations that cover the conformational space more or less thoroughly.

Stereogenic double bonds are expected not to cause major problems to our approach, since a double bond was shown by Nourse already to be treatable as a special kind of stereocenter.[3] The suggested selection of quadruples of types i and ii is not able to distinguish 60° and 90° torsion angles. An open question is whether these are distinguished by selecting another few quadruples.

Generation of all possible patterns of orientations, i.e. of abstract partial orientation functions (POFs), has been demonstrated here for small examples and is effective also for larger molecules, as long as the amount of selected quadruples remains moderate. By using various combinatorial tests, the number of generated abstract POFs is kept manageable. As a demonstration, we present the number of abstract POFs generated for cyclohexane through cyclotetradecane when selecting all quadruples of type ii, both all abstract POFs and abstract POFs without zero function values.

structure	C_6H_{12}	C_7H_{14}	C_8H_{16}	C_9H_{18}	$C_{10}H_{20}$	$C_{11}H_{22}$	$C_{12}H_{24}$	$C_{13}H_{26}$	$C_{14}H_{28}$
abstract POFs	92	198	498	1219	3210	8418	22913	62415	173088
without zeros	13	18	30	46	78	126	224	380	687

The computation times (sec) on a Dual Core AMD Opteron Processor 265 were as follows:

structure	C_6H_{12}	C_7H_{14}	C_8H_{16}	C_9H_{18}	$C_{10}H_{20}$	$C_{11}H_{22}$	$C_{12}H_{24}$	$C_{13}H_{26}$	$C_{14}H_{28}$
abstract POFs	0s	0s	0s	0.2s	0.4s	1s	4s	16s	74s
without zeros	0s	0s	0s	0s	0s	0s	0.2s	0.4s	0.5s

Note that for the cycloalkane examples, tests 1-6 do not exclude any candidate abstract POFs. By developing further combinatorial tests, it should be possible to reduce the number of candidates generated in this case also.

The main missing part necessary for investigations on larger examples is an efficient tool for constructing reasonable embeddings of atoms in space for a given abstract POF. For the small examples treated here we used as a workaround constrained conformation optimization of random atom placements. More sophisticated methods are desirable. As a starting point the work of Richter-Gebert[40] and Shor[41] could serve. Also the Gröbner base approach by Hazebroek and Oosterhoff[42] could be combined with the orientation functions approach, as suggested in an earlier paper.[20b]

The question has often been raised how completely a particular conformer generation algorithm covers the total conformational space.[12-14] The exhaustiveness of our method is controlled by the selection of quadruples. When selecting all quadruples, we expect that in principle no conformer sufficiently different in structure from others will be missed. However, complexity increases heavily with increasing number of selected quadruples. We demonstrated for small examples that a small selection of quadruples can suffice to provide an exhaustive overview over the conformation space.

We cannot exclude the possibility that there might be distinct conformers not differing in the orientation of any quadruple. Thus even selecting all quadruples does not guarantee to find each conformer. One would expect such hypothetical unresolved twin conformers to be of very similar structure, whence missing one would not be too bad. However, the situation is worse, since it turned out that the realization spaces of orientation functions could be arbitrarily complicated, as Mnëv pointed out.[43] Thus, theoretically, there could even exist two conformers not differing in any quadruple orientation, but having considerably different geometric structures. Still, the hope is that such orientation functions with “strange” realization space will not be of chemical relevance.

Acknowledgement

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References and Notes

[1] Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*, Wiley, New York, 1994, page 1208.
Consider also the following definitions given there (pp. 1195-1196):
"**Constitution**. The description of the nature of the atoms and the connectivity (including bond multiplicity) between them in a molecule, disregarding their spatial array.

Configuration. The spatial array of atoms that distinguishes stereoisomers ... other than distinction due to differences in conformation.

Conformation. The spatial array of atoms in a molecule of given constitution and configuration. Conformation of such molecules can be changed by (rapid) rotation around single bonds ... without, in general, affecting the constitution and configuration."

For a discussion of the problematic and "somewhat fuzzy" (page 49) distinction between configuration and conformation see sections 2-3 and 2-4 therein. A **conformer** is a conformation that is a (global or local) potential energy minimum.

”**Stereogenic element**. A focus of stereoisomerism ... in a molecule such that interchange of two ligands attached to an atom in such a molecule ... leads to a stereoisomer." (p 1208)

Definitions almost identical to those above are given by IUPAC, see reference 2.

[2] International Union of Pure and Applied Chemistry, Basic Terminology of Stereochemistry (IUPAC Recommendations 1996). *Pure Appl. Chem.* **1996**, *68*, 2193-2222.

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[21] Orientations are sensitive to the handedness of the coordinate system, but not to its translation or rotation in space. Thus, changing the handedness of a coordinate system (e.g. by exchanging x and y axes) will exchange positive and negative orientations, see Gerlach, H. Handedness and Chirality. *MATCH Commun. Math. Comput. Chem.* **2009**, *61*, 5-10.

[22] In the examples treated here we used a tolerance value of 0.1Å^3. Instead of a fixed threshold value, a tolerance depending on the magnitude of the tetrahedron considered

may be preferable. Alternatively, one could develop a measure independent of scaling, e.g. the tetrahedron's volume relative to the volume of the circumscribed sphere.

[23] Note that in previous articles[20a,b] the quadruples were listed in a different order: There, the *reverse lexicographical order* for the quadruples was used, i.e. the reverse quadruples (a_4, a_3, a_2, a_1) were ordered lexicographically. We decided to use the lexicographical order here, because we assume it is more easily understood.

[24] Note that on the other hand an orientational automorphism – though fixing the orientation function – may change the conformation of the molecule. The *geometric automorphism group,* i.e. the set of all renumberings keeping the conformation fixed, is a subgroup of the orientational automorphism group.

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A short definition of the canonic form used here as well as a sketch of the generation algorithm is given in reference 20b also.

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[28] The energy function, a simplified version of Allinger's MM2, is taken from the MOLGEN system (`http://www.molgen.de`). For the original MM2 energy function see:
Allinger, N. L. MM2. A Hydrocarbon Force Field Utilizing V_1 and V_2 Torsional Terms. *J. Am. Chem. Soc.* **1977**, *99*, 8127-8134.

[29] Additional restrictions discussed in reference 20b are described in the following sections. For the example of cyclohexane, they reduce the number of abstract full orientation functions as reported there. However, when considering abstract POFs with respect to the given selection S, the restrictions do not reduce the number of candidates.

[30] There are exceptions even to this rule, e.g. the four bonds of the so-called pyramidalized carbon all point into the same half-sphere. Thus, such a carbon is outside the tetrahedron formed by its neighbors.

[31] An alternative way to see that χ_3 is a POF for **3** is to apply the graph automorphism (1,2)(3,6)(4,7)(5,8) on χ_3, obtaining an isomorphic POF χ'_3:
$\chi'_3(1,2,3,6) = \chi_3(2,1,6,3) = \chi_3(1,2,3,6) = +$;
$\chi'_3(1,2,3,7) = \chi_3(2,1,6,4) = \chi_3(1,2,4,6) = -$;
...

$$\begin{array}{rccccccccccc} & 1236 & 1237 & 1238 & 1246 & 1247 & 1248 & 1256 & 1257 & 1258 & 1678 & 2345 \\ \chi'_3 = & + & - & 0 & 0 & + & - & - & 0 & + & - & + \end{array}$$

The result χ'_3 describes conformer **3**.

[32] Named after Johann Radon, Austrian mathematician (1887–1956).

[33] Line here is meant to include the endpoints, triangle includes the edges and vertices, tetrahedron includes the faces, edges, and vertices. Of course, all three expressions include the interior parts. Triangles and tetrahedra may be degenerate.

[34] Eckhoff, J. Helly, Radon, and Carathéodory Type Theorems. Chapter 2.1 in Gruber, P. M.; Wills, J. M., Eds. Handbook of Convex Geometry. North-Holland, **1993**, 389-448.

[35] Note that, strictly speaking, this theorem is valid only in the case of no zero-orientation tolerance. If we use a tolerance as suggested here, a more detailed examination on the validity of the theorem is necessary.
The implication abstract minimal Radon partition to minimal Radon partition is still true as long as the abstract minimal Radon partition consists of exactly five atoms. For abstract minimal Radon partitions with fewer than five atoms, a quadruple of atoms with assigned zero-orientation may not lie exactly in a plane. However, as the convex hulls "nearly intersect", we can interprete this as some kind of tolerance for Radon partitions.

[36] For a proof of the theorem refer to theorem 3.5.5 on page 128 in reference 19a. However, relevance of the statement given there is not obvious at a first glance.
First, an alternating, nontrivial (i.e. not constantly zero) function $\chi : \{1, \ldots, N\}^4 \to \{+, -, 0\}$ fulfilling the binary Grassmann-Plücker relations (see section 2.8 here) is called a *chirotope* (of rank 4) over $\{1, \ldots, N\}$, according to definition 3.5.3 in the reference. Thus the orientation function of any sequence of atoms (not all in one plane) is a chirotope. *Oriented matroids* are introduced in the reference on page 103 using the structure of *(signed) circuits,* here named abstract minimal Radon partitions. On pages 104f in the reference (example "The CUBE"), it is demonstrated that minimal

Radon partitions of a sequence of points correspond to the circuits of an oriented matroid. Theorem 3.5.5 in the reference finally states that the pairs of functions consisting of a chirotope χ and its negative $-\chi$ are in one-to-one correspondence to oriented matroids. Lemma 3.5.7 explains how to obtain the signed circuits (i.e. the abstract minimal Radon partitions) from the chirotope. See also remark 3.7.3 in the same reference.
The established nomenclature of the theory of oriented matroids is misleading in the context of chemical conformation analysis and is therefore avoided in this work. Besides *circuits*, we avoided the following concepts: Chirotopes having no circuit of the form $(A, \emptyset)$ are called *acyclic*. Abstract (not necessarily minimal) Radon partitions are called *signed vectors*.

[37] Named after Herrmann Grassmann, German mathematician (1809–1877) and Julius Plücker, German mathematician and physicist (1801–1868).

[38] For a proof refer to theorem 2.12 and corollary 2.13 on page 38ff in reference 16.
Again, this is valid only in the case of no zero-orientation tolerance. Otherwise, the same nonzero orientation of two quadruples of atoms (a_1, a_2, a_3, a_4) and (b_1, b_2, b_3, b_4) could be explained by a pair of quadruples of atoms (b_i, a_2, a_3, a_4) and $(b_1, ..., a_1, ..., b_4)$ whose tetrahedra have a volume below the tolerance threshold. If one is interested especially in conformations having almost coplanar atoms, as e.g. in structure **B** from the introductory section, then, perhaps one should not use test 4.

[39] Here, reasoning is correct even for zero-tolerances.

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