Enumeration, Generation, and Construction of Stereoisomers of High-Valence Stereocenters

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Fundamental tools of molecular structure elucidation are computer programs generating constitutional isomers and configurational isomers. A general disadvantage of the methods of algebraic stereoisomer generation by Nourse, Smith, Carhart, and Djerassi is the restriction of the valences of the stereocenters to four. The present paper discusses an extension of this concept to higher-valence centers. Methods for counting and generating all stereoisomers are provided. Moreover, for some types of isomers algorithms for constructing spatial realizations geometrically are presented. The main mathematical tool is the theory of group actions and double cosets.

1. INTRODUCTION

The automatization of molecular structure elucidation began with the development of generators for molecular graphs[1−3] that produce all connectivity isomers to given conditions. Later also generators were presented[4−6] creating all configurational isomers to each constitutional isomer. For this purpose, the molecule is searched for stereocenters, and the symmetry as well as the environments of these centers are taken into account. A disadvantage of these methods, however, is the restriction of the valence of the stereocenters to four. In some applications and for reasons of mathematical completeness and uniformity an extension to higher valences is desirable. Providing this extension is the main aim of the present paper.

First we will define the necessary notions, followed by an enumeration of possible stereoisomers. Next these isomers will be generated using double coset algorithms. Finally we will discuss the construction of spatial coordinates of some types of isomers by a given reference arrangement.

2. GEOMETRY OF HIGH-VALENCE STEREOCENTERS

The most common elements of organic chemistry C, N, and O bear only valences up to four. Elements with higher valences are mostly inorganic. In general, the geometrical arrangement formed by the ligands of a center is not unique and may depend on the ligands themselves. We will assume that the skeleton of the center is stable under permutations of the ligands—since otherwise symmetry considerations become useless. We will call a pair (G,P) of a set G of points and a subset $P \subseteq$ a *skeleton*. The elements of P are called *skeleton sites*, and $G\backslash P$ is called the *core*. For (G,P) and another set L, the set of ligands, $m \in L^P$ (if $L^P := \{f \mid f: P \rightarrow L\}$), will be called a *protoisomer* which is thus just the preliminary stage to an isomer considering it with regard to one core only. (More information about the geometry of the skeleton of such centers can be found in a number of papers and textbooks.[7−11])

For a concise description of the stereochemistry we shall use the notions of actions and double cosets introduced by Ruch, Hässelbarth, and Richter[12−16] (see also Appendix).

Regarding protoisomers independent of rotations of the skeleton sites we solely have to investigate the orbits of the action of the (induced) rotation group R on L^P. And skeletons with chemically identical ligands are invariant under permutations of those ligands. If there are k sites and $l \leq k$ different sorts of ligands, each sort $i \leq l$ having λ_i elements, we may take S_λ (see Appendix) as the group of permutations without loss of generality. It is therefore sufficient to take only the orbits of the action of S_λ on L^P into account. Combining both we have the following: The essentially different protoisomers of a center of k-coordination correspond to a transversal of the set of double cosets $R\backslash S_{\underline{k}}/S_\lambda$ with $S_{\underline{k}}$ being the symmetric group on $\underline{k} := \{1, ..., k\}$.

3. ENUMERATION OF STEREOISOMERS

Based on these definitions we can immediately state a formula[12,17,18] for the number of all essentially different protoisomers of a center of k-coordination with rotation group R and ligand partition $\lambda \models k$ (cf. Appendix)

$$|R\backslash S_{\underline{k}}/S_\lambda| = \frac{1}{|R|\lambda_1!...\lambda_l!} \sum_{a|-|k} \left(\prod_i i^{a_i} a_i!\right) |\{\varrho \in R \mid {}_a(\varrho) = a\}| \, |\{\sigma \in S_\lambda \mid a(\sigma) = a\}| \quad (1)$$

where λ_i denotes the ith element of the partition λ. As an example, we take a center of eight-coordination with the skeleton of an Archimedean antiprism[19] (see Figure 1). The rotation group is

$$R = \{1, (1234)(5678), (1432)(5876), (13)(24)(57)(68), (15)(28)(37)(46), (16)(25)(38)(47), (17)(26)(35)(48), (18)(27)(36)(45)\} \quad (2)$$

The calculations using eq 1 and the resulting numbers are shown in Table 1.

For obtaining more information about the symmetry of the molecule we have to introduce the automorphism group. Hence again are some definitions: *A labeled m-graph on p vertices* is a mapping $\gamma : p^{[2]} \rightarrow \{0,...,m\}$, where $p^{[2]}$ means the 2-subsets of $\underline{p}$. The value of the mapping at a pair of vertices is the degree of the bond they are connected by.

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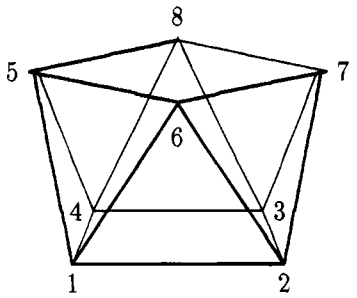


Figure 1. The Archimedean antiprism (thick lines are in front).

Table 1. Numbers of Possible Protoisomers of a Center of Eight-Coordination

λ		$\lvert R\backslash S_8/S_\lambda\rvert$
(8)	$(8! + 2\cdot8! + 5\cdot8!)/(8\cdot8!) =$	1
(1,7)	$8!/(8\cdot7!) =$	1
(2,6)	$(8! + 5\cdot8\cdot6!)/(8\cdot2!\cdot6!) =$	6
(1,1,6)	$8!/(8\cdot6!) =$	7
(3,5)	$8!/(8\cdot3!\cdot5!) =$	7
(1,2,5)	$8!/(8\cdot2!\cdot5!) =$	21
(1,1,1,5)	$8!/(8\cdot5!) =$	42
(4,4)	$(8! + 2\cdot4^2\cdot2!\cdot36 + 5\cdot2^4\cdot4!\cdot9)/(8\cdot4!^2) =$	13
(1,3,4)	$8!/(8\cdot3!\cdot4!) =$	35
(2,2,4)	$(8! + 5\cdot2^4\cdot4!\cdot3)/(8\cdot2!^2\cdot4!) =$	60
(1,1,2,4)	$8!/(8\cdot2!\cdot4!) =$	105
(1,1,1,1,4)	$8!/(8\cdot4!) =$	210
(2,3,3)	$8!/(8\cdot2!\cdot3!^2) =$	70
(1,1,3,3)	$8!/(8\cdot3!^2) =$	140
(1,2,2,3)	$8!/(8\cdot2!^2\cdot3!) =$	210
(1,1,1,2,3)	$8!/(8\cdot2!\cdot3!) =$	420
(1,1,1,1,1,3)	$8!/(8\cdot3!) =$	840
(2,2,2,2)	$(8! + 5\cdot2^4\cdot4!)/(8\cdot2!^4) =$	330
(1,1,2,2,2)	$8!/(8\cdot2!^3) =$	630
(1,1,1,1,2,2)	$8!/(8\cdot2!^2) =$	1260
(1,1,1,1,1,1,2)	$8!/(8\cdot2!) =$	2520
(1,1,1,1,1,1,1,1)	$8!/8 =$	5040

But a molecule does not consist of connectivity alone. The types of the atoms are expressed in terms of *labeling* $\beta \in \{E_1,...,E_n\}^{\underline{p}}$, where E_i are the different elements occurring in the molecule. Without loss of generality we can put $E_i := i$. Since the symmetric group $S_{\underline{p}}$ acts on the graph as well as on the labelings, the *automorphism group of the molecular graph* (γ,β) is defined as $A(\gamma,\beta) := \{\pi \in S_{\underline{p}} \mid \pi\beta = \beta, \pi\gamma = \gamma\}$.

Working with stereocenters, the consideration of the mere automorphism group does not suffice;[20] we will now discuss the necessary extension. If a molecule has s stereocenters, they can be numbered according to the initial numbering of the whole molecule. Let the corresponding mapping be ν. (If the vertex i is the jth stereocenter, it will yield $\nu(i) = j$.) Moreover, ν induces a mapping $\bar{\nu} : A(\gamma,\beta) \rightarrow S_{\underline{s}}$. The image of $\bar{\nu}$ are thus the permutations of the stereocenters.

For each $\pi \in A(\gamma,\beta)$ we now define additional functions. For ordinary stereocenters (max. valence 4) the functions $\epsilon_\pi(i)$ are equivalent to Nourse's concept of superscripts ($\epsilon_\pi(i) = (0, 1)$ if there is a superscript and identity otherwise).[20] For high-valence stereocenters $\epsilon_\pi(i)$ is always the identity if $\bar{\nu}(i) = i$. If this is not the case, it must be checked into which double coset of the ligand arrangement the configuration of the center is changed by the application of π on the ligands, and $\epsilon_\pi(i)$ must be set accordingly. So the *extended configuration symmetry group* (ECSG) can now be defined as

$$C(\gamma,\beta) := \{(\epsilon_\pi,\bar{\nu}(\pi)) \mid \pi \in A(\gamma,\beta)\} \tag{3}$$

and turns out to be a subgroup of the wreath product[21] $S_t \int_{\underline{s}} \bar{\nu}(A(\gamma,\beta))$ (cf. Appendix), where t is the maximal number of double cosets of ligand arrangements of all centers [In fact, $C(\gamma,\beta)$ is just isomorphic to a subgroup of $S_t \int_{\underline{s}} \bar{\nu}(A(\gamma,\beta))$.]. While the ECSG emerges in the generation process quite naturally, it is the key to theoretic enumeration.

For deriving the final formula, we have to define a last notion: Let $G \leq S_{\underline{n}}$ and $(\psi;\pi) \in H \int_{\underline{n}} G$, where π is given in standard notation, i.e., $\pi = \prod_\kappa^{c(\pi)}(j_\kappa...\pi^{j_\kappa-1}j_\kappa)$ with $j_\kappa \leq \pi^m j_\kappa$ $\forall m \in \mathbf{N}$ and $j_\kappa < j_{\kappa+1}$ for $\kappa < c(\pi)$, which means just an increasing order among and within the cycles. (The number $c(\pi)$ denotes the number of cycles of π.) Then $h_\kappa(\psi;\pi) := \psi(j_\kappa)\psi(\pi^{-1}j_\kappa) \cdot ... \cdot \psi(\pi^{-l_\kappa+1}j_\kappa)$ is called the *kth cycle product of* $(\psi;\pi)$. Using this concept the orbits of $H \int_{\underline{n}} G$ can be counted:

$$|H \int_{\underline{n}} G \backslash\backslash Y^{\underline{n}}| = \frac{1}{|H \int_{\underline{n}} G|} \sum_{(\psi;\pi)\in H \int G} \prod_{\kappa=1}^{c(\pi)} |Y_{h_\kappa(\psi;\pi)}| \tag{4}$$

If $\bar{\pi} := \bar{\nu}(\pi)$ is in the ith conjugacy class $C^S(\bar{\pi}) \in \mathcal{C}$, then n_{ik} is defined to be the number of inversions corresponding to the kth cycle of representatives of this class. So applying the above result to the enumeration of stereocenters yields for molecules with ordinary centers only:[4]

$$\frac{1}{|C(\gamma,\beta)|} \sum_{\bar{\pi}\in\mathcal{C}} |C^S(\bar{\pi})| \cdot 2^{c(\bar{\pi})} \prod_{\kappa=1}^{c(\bar{\pi})} ((n_{ik} + 1) \bmod 2) \tag{5}$$

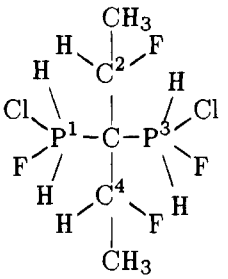
For molecules with high-valence stereocenters the formula must be extended, because the centers do not have a common image set Y which in fact now corresponds to the number of protoisomers. The set $\underline{s}$ of stereocenters is split by the automorphism group $A(\gamma,\beta)$ into orbits $X_1,...,X_n$. The elements of each of these orbits have the same atom types, the same valences, and even the same ligand partition. To each X_i there corresponds an image set $Y_i := \{1,...,|R\backslash S_k/S_\lambda|\}$ if the centers in X_i are of k-coordination and have ligand partition λ. So the orbits to be counted are of the type of an action of a $H \int_{\underline{s}} G$ on $Y_1^{X_1} \times ... \times Y_n^{X_n}$. Since no permutation from $A(\gamma,\beta)$ with cycles composed by elements of different orbits exists, the same $h_\kappa(\psi;\pi)$ as above can be applied. So the number of all stereoisomers is

$$|C(\gamma,\beta)\backslash\backslash Y_1^{X_1} \times ... \times Y_n^{X_n}| =$$
$$\frac{1}{|C(\gamma,\beta)|} \sum_{(\epsilon_\pi;\bar{\pi})\in C(\gamma,\beta)} \prod_i^n \prod_\kappa^{c_i(\bar{\pi})} |(Y_i)_{h_\kappa(\epsilon_\pi;\bar{\pi})}| =$$
$$\frac{1}{|C(\gamma,\beta)|} \sum_{(\epsilon_\pi;\bar{\pi})\in C(\gamma,\beta)} \prod_i^n (\prod_\kappa^{c_i(\bar{\pi})} |\{1,...,|R\backslash S_{\underline{k}^{(i)}}/S_{\lambda^{(i)}}|\}_{h_\kappa(\epsilon_\pi;\bar{\pi})}|) \tag{6}$$

Here by $k^{(i)}$ we mean the coordination of the ith center, and $\lambda^{(i)}$ denotes the ligand partition of the ith center. Note that due to the different impact of each cycle the summation over the conjugacy classes is no longer possible.

We now want to take a look at an example and consider the following structure [The examples in this paper were composed artificially for explanational reasons and may not

exist in reality.]



The ECSG of this molecule is

$$\begin{array}{ll} \{(\mathrm{id}_\psi; & (1)(2)(3)(4)), \\ ((\mathrm{id},(0,1),\mathrm{id},(0,1)); & (1)(2,4)(3)), \\ (\mathrm{id}_\psi; & (1,3)(2)(4)), \\ ((\mathrm{id},(0,1),\mathrm{id},(0,1)); & (1,3)(2,4))\} \end{array} \quad (7)$$

where the left column denotes the ϵ_π part of the pair and the right column of $\bar{\pi}$. For the trigonal-bipyramidal skeleton of phosphorus, 10 different arrangements correspond to the ligand partition (1,1,1,2), so applying formula 6 we obtain

$$\frac{1}{4}(10\cdot2\cdot10\cdot2 + 10\cdot2\cdot10 + 10\cdot2\cdot2 + 10\cdot2) = 165 \quad (8)$$

as the total number of stereoisomers.

So the approach via double cosets has proved to be very effective in this situation. It should be mentioned, however, that there are more methods for the enumeration of chemical objects. The pioneer work of G. Pólya,[22,23] which even discussed aspects of stereochemistry, but required much information about the skeleton of the whole molecule, gave rise to numerous papers based on the concepts described there. (More references can be found elsewhere.[24,25]) Moreover, there are approaches using representation theory[26,27] and Redfield's counting theory.[28-30]

4. GENERATION OF STEREOISOMERS

As announced we will proceed with an extension of the generation algorithm by Nourse et al.[4] All atoms with five or larger coordination are taken as potential stereocenters. As a first step, the ligand partitions of the stereocenters are determined using a simple node partitioning algorithm. By this method the atoms of the molecule are divided into equivalence classes with respect to their atom type, valence, hydrogen number, and connectivity such that any automorphism of the molecular graph just permutes the atoms within their classes.

For computing a transversal of the double cosets $R\backslash S_k/S_\lambda$ an algorithm basing on the classical method[31] is used. The output are vectors $\hat{\gamma}$ assigning class numbers to each site of the skeleton. No chemical information is involved in this process; so all possible solutions are provided, and the task of checking their plausibility is left to the chemist, in contrast to other authors.[32]

We now want to compute the stereoisomers to s stereocenters. Let the coordination numbers be $k_1,...,k_s$, the ligand partitions $\lambda^{(1)},...,\lambda^{(s)}$, and the number of double cosets, i.e., of protoisomers, $\omega_1,...,\omega_s$. The stereoisomers will be represented by vectors of the form $f = (f_1,...,f_s)$ where we have $f_i \in \{0,...,\omega_i - 1\}$ for $i \in \underline{s}$. The inversions of Nourse's algorithm were not based on the knowledge of the double cosets; they were actually used to recognize whether different cosets coincide. And it was sufficient to consider inversions only because the possible cases were limited to two. For centers of higher valence this way is no longer valid.

The knowledge of the double cosets bears nevertheless an advantage: If a center is a fixed point, there will be no permutation of the ligands in the automorphism group that could change the protoisomer type of the center. If the center is not fixed, however, a check becomes necessary in which double coset corresponds to the arrangement of the neighbors after the permutation.

For computing orbits, as we are now going to do, it is always important to avoid comparing each new candidate with all the already known representatives. One way is to compute only those orbit representatives which are minimal in their orbits with respect to some order. In our case we consider the lexicographical order of the vectors f. So while running through all vectors each f must be tested on minimality and saved if necessary. [More sophisticated methods even allow the skipping of some candidates.[33]]

So we can now sum up our discussion to the following algorithm. Again we will consider mappings $\bar{\pi}$ (see eq 5).

4.1. Minimality Test for High-Valence Centers. Let f be the current test candidate.

(i) Run through all $\pi \in A(\gamma,\beta)$ and compute $\tilde{f}(i) = f(\bar{\pi}^{-1}i)$.

(ii) For each π run through all $i \in \underline{s}$. If $\bar{\pi} \neq i$, execute:

(a) Let $\hat{\eta}$ be the representative of the symmetry class for $\tilde{f}(\bar{\pi}i)$. Compose an environment vector v increasingly from the elements of the ligand classes of the center i, according to the block numbers in $\hat{\eta}$.

(b) Compute $\tilde{v}$ with $\tilde{v}_\kappa := \pi(v_\kappa)$ for $\kappa \in \underline{k_i}$.

(c) Check whether $\tilde{v}_\kappa$ is in the ligand class corresponding to $\hat{\eta}_\kappa$ for each $\kappa \in \underline{k_i}$. If this is true, continue with the next i at (a); else go to (d).

(d) Compute a representative $\hat{\chi}$ from $\tilde{v}$ by entering the class number of $\tilde{v}_\kappa$ at $\tilde{\chi}_\kappa$ for each κ.

(e) Run through all double cosets with their canonical representatives $\hat{\xi}$, where $\hat{\xi} \neq \hat{\eta}$. If $\hat{\chi} < \hat{\xi}$, they cannot belong to the same orbit; so continue with the next $\hat{\xi}$. Else: For each representative run through all $\varrho \in R$. If $\varrho\hat{\xi} = \hat{\chi}$, and $\hat{\xi}$ is in the μth coset, set $\tilde{f}(\bar{\pi}i) := \mu$.

(iii) Determine the smallest $j \in \underline{s}$ with $\tilde{f}(j) \neq f(j)$.

(iv) If $\tilde{f}(j) < f(j)$ holds, stop the iteration and return 0 (f is not minimal); else go to (i).

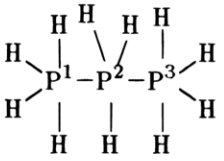
(v) Return 1 (f is minimal).

Note that only due to the use of the node partition we got a unique order of the classes making the environment vectors of a center and of the image of the center comparable at all.

Now we start the generation. Begin with $f = (0,...,0)$. If the minimal test returns 1, the current representative is minimal and can be saved. Now increase f according to the following rule: Set $\kappa := s$. If $f(\kappa) < \omega_\kappa$, set $f(\kappa) \leftarrow f(\kappa) + 1$ and continue with the next minimal test provided $\kappa > 0$. In the other case set $f(\kappa) := 0$, $\kappa \leftarrow \kappa - 1$ and test again.

This way we get a transversal with all representatives being minimal in their orbit. For an implementation this method may be improved by more subtle techniques.[33,34] In the following example, the phosphorus atoms are again assumed

to be stereochemically stable:



The centers 1 and 3 have two protoisomers, while no. 2 has three ones; the full automorphism group is of order 6912, and there is a total of nine stereoisomers with the configurations:

0,0,0	0,1,1	1,0,1
0,0,1	0,2,0	1,1,1
0,1,0	0,2,1	1,2,1

5. CONSTRUCTION OF SPATIAL REPRESENTATIONS

The output as a configuration vector is not very feasible. Since stereoisomers refer to spatial properties, a three-dimensional representation is desirable. One way to obtain this is using a referene placement, e.g., computed via an energy model.[35] The actual isomers are then constructed geometrically. This approach has already proven to be useful for conventional stereoisomerism.[6,36,37] For applying it to molecules with high-valence centers there are some obstacles. On the one hand, there is no universal possibility to identify the configuration of a given placement—a situation which gets even worse if distorted skeletons should be allowed. On the other hand, there is no way to construct stereoisomers of cyclic compounds containing centers in a ring.

We will, however, now present an algorithm for noncyclic molecules with unidentate ligands. From the variety of skeletons we shall discuss the identification of the trigonal bipyramid. First we assume that a reference placement of the structure in question is available and attempt to characterize it.

5.1. Identification of the Configuration at a Stereocenter.

(i) Take every triple combination out of the five neighbors of the center and compute the planes they span. The plane having the least distance to the center and having at least one other neighbor almost perpendicular to it is identified as the equatorial plane.

(ii) The two atoms not belonging to the equatorial plane are arranged in a way such that the atoms in the plane are in clockwise orientation (seen from the top).

(iii) Identify the corresponding double coset as in 4.1.

After the identification of the given placement, the family of the stereoisomers can be constructed. This is carried out by means of reflections and rotations.

Two ligands are reflected by the following method: First compute the plane through the center and the middle of the two atoms, perpendicular to the interchanging line of both. Then reflect recursively all atoms contained in the two ligands on the plane; if an atom is a stereocenter itself, check and note possible changes of its configuration as in 4.1.

The rotations are done according to classical methods.[38] For taking possible distortions of the structure into account an atom *A* which shall be sent to the place of an atom *B* is rotated around the axis going through the center and the middle of the line *AB*. Again the other members of the ligands are mapped recursively, but configurational changes need not be considered here.

Switching between different protoisomers is expressed in terms of permutations of the skeleton sites. These permutations are then processed cycle-wise where even cycles give rise to rotations and odd cycles to reflections. So the complete algorithm reads:

5.2. Construction of Coordinate Representations of a Family of Stereoisomers.

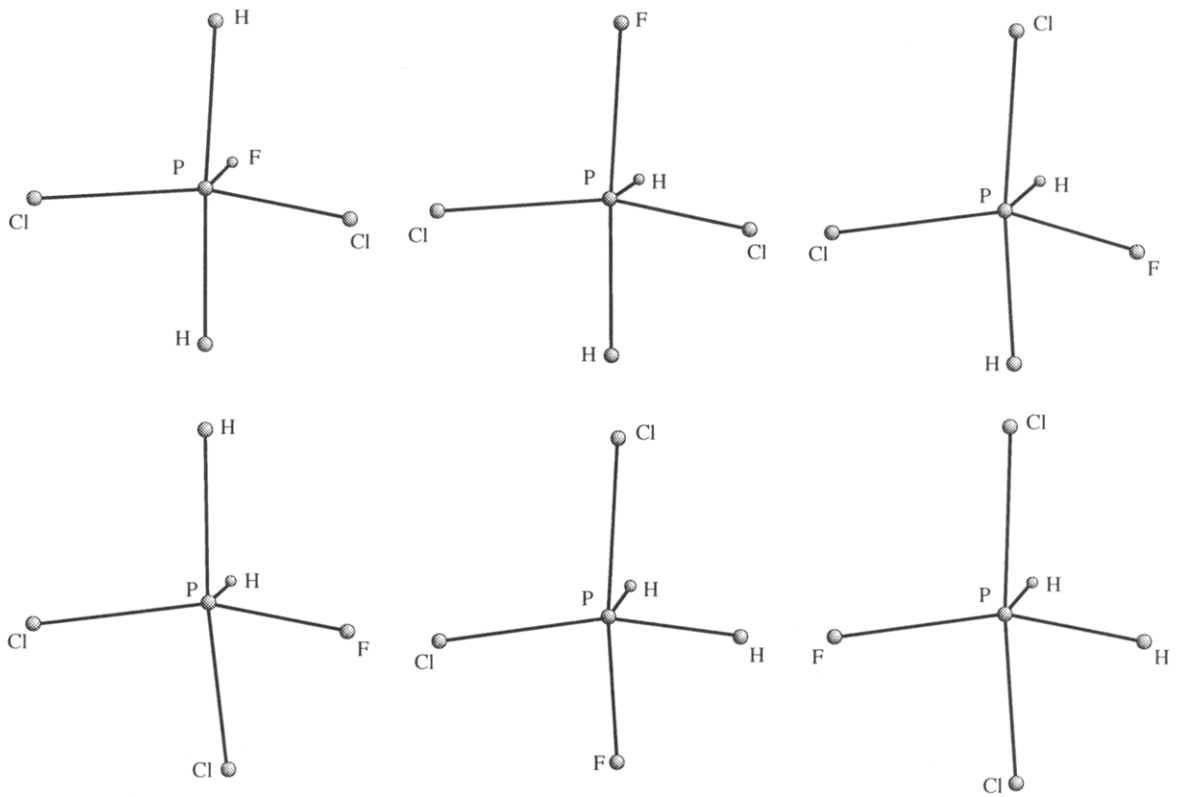


Figure 2. Stereoisomers of dichlorofluorophosphorane.

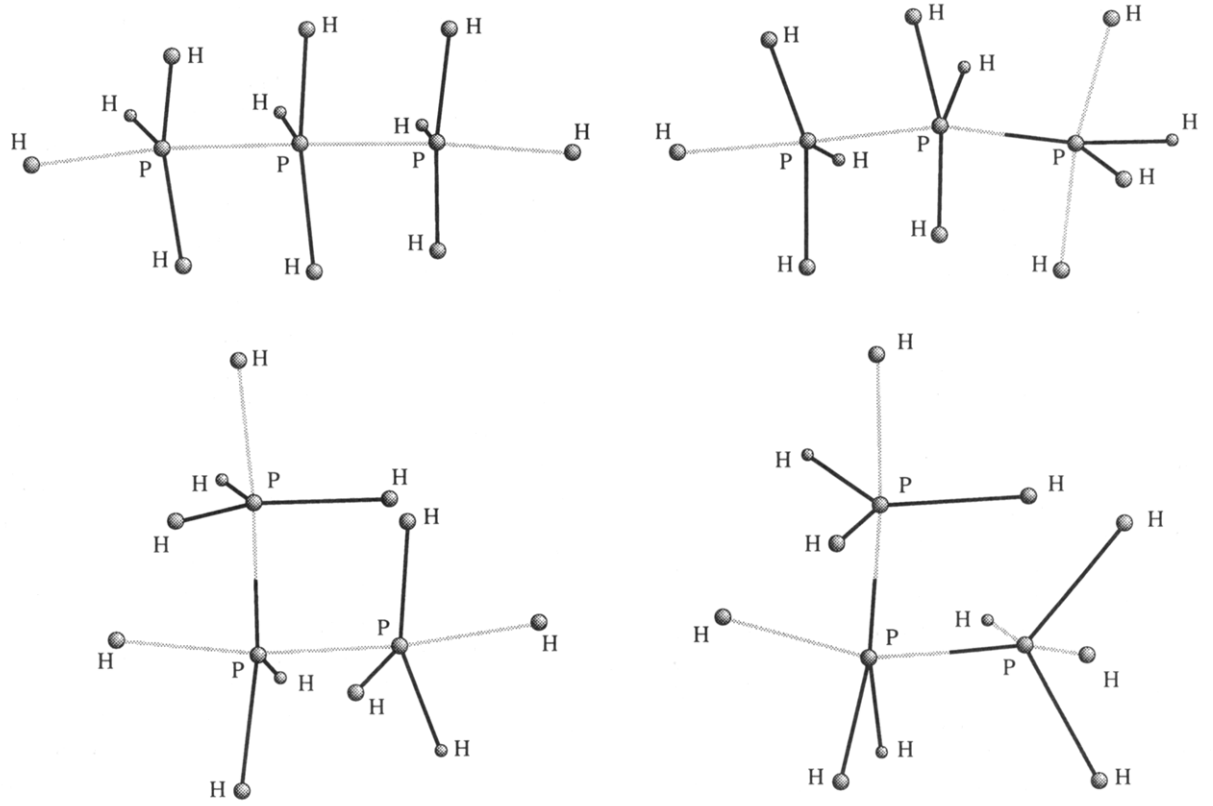


Figure 3. Four stereoisomers of the triphosphorus compound.

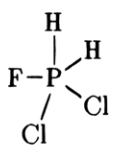
(i) Run through the list of configuration vectors as generated by the above algorithm.

(ii) Set the reference configuration vector to values determined as in 5.1.

(iii) If the entry for the current stereocenter in the configuration vector is equal to the one in the list, go to (iv). Else: Determine the double coset representative corresponding to the value from the list and change the protoisomer by means of the methods discussed above. Enter the new value in the vector. If configurations of other centers were changed during the reflections, restart with the first center; else continue with the next center.

(iv) While not all centers are processed, go to (iii).

As an easy example we will consider



There are six stereoisomers the computed placements of which are shown in Figure 2. Figure 3 shows four of the nine isomers of the compound from section 4. For a better visualization of the skeletons the main axes (perpendicular to the equatorial plane) are highlighted.

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APPENDIX: GROUP ACTIONS

An *action of a finite group G on a finite set X* is defined to be a mapping $G \times X \rightarrow X$, $(g,x) \mapsto gx$ with $g(g'x) = (gg')x$ and $1x = x$. The set $G(x) := \{gx \mid g \in G\}$ is called the *orbit of x*; $G\backslash\backslash X$ denotes the set of all orbits, and $X_g := \{x \mid gx = x\}$ means the set of fixed points. The fundamental tool for enumeration is the lemma of Cauchy–Frobenius: $|G\backslash\backslash X| = 1/|G| \sum_{g \in G} |X_g|$. The sets $C^G(x) := \{gxg^{-1} \mid g \in G\}$ are called *conjugacy classes*. Regarding the symmetric group on $\underline{n} := \{1,...,n\}$ and one of its elements π we define the ordered lengths $\alpha_i(\pi)$ of the cyclic factors of π as the *cycle partition*. Furthermore we shall call $a(\pi) := (a_1(\pi),...,a_n(\pi))$ with $a_i(\pi) := |\{j|\alpha_j(\pi) = i\}|$ the *cycle type of* π. Here we have $\sum i \cdot a_i = n$ and denote the situation by $a \mid\!-\!\mid n$. Note that $C^S(\pi) = C^S(\sigma)$ *iff* $a(\pi) = a(\sigma)$ holds for any $\pi, \sigma, \in S_{\underline{n}}$. The cardinalities are $|C^S(\pi)| = n!/\sum_i i^{a_i(\pi)} a_i(\pi)!$.

If G and H are finite groups and X is a finite set on which G acts, we define the *wreath product of G and H (with respect to X)* as

$$H \int_X G := H^X \times G = \{(\psi;g) | \psi : X \rightarrow H, g \in G\} \quad (9)$$

where the multiplication is defined as

$$(\psi;g)(\psi';g') = (\psi\psi';gg') \quad \text{with}$$
$$(\psi\psi'_g)(x) := \psi(x)\psi'(g^{-1}x) \quad (10)$$

The wreath product $H \int_X G$ acts on Y^X as follows: $H \int_X G \times Y^X \rightarrow Y^X$, $((\psi;g),f) \mapsto \tilde{f}$, where $\tilde{f}(x) := \psi(x) f(g^{-1}x)$.

If A and B are subgroups of a group G, the orbits of the action of $A \times B$ on G: $A\backslash G/B := \{AgB \mid g \in G\}$ are called *double cosets*. An application of the Cauchy–Frobenius lemma yields

$$|A\backslash G/B| = \frac{|G|}{|A||B|}\sum_{g\in\mathcal{C}}\frac{|C^G(g)\cap A||C^G(g)\cap B|}{|C^G(g)|} \quad (11)$$

where $\mathcal{C}$ is a transversal of the conjugacy classes.

An *improper partition* $\lambda \models n$ is defined as an m-tuple of natural numbers λ_i with $\sum_{i=1}^{m}\lambda_i = n$. Additionally defining $\underline{n}_i^\lambda := \{\sum_{j=1}^{i-1}\lambda_j + 1,\ldots,\sum_{j=1}^{i}\lambda_j\}$ we can introduce the *canonical Young group*

$$S_\lambda := S_{\underline{n}_1^\lambda} \otimes S_{\underline{n}_2^\lambda} \otimes \ldots \otimes S_{\underline{n}m^\lambda} = \{\pi \in S_{\underline{n}} | \pi\underline{n}_i^\lambda = \underline{n}_i^\lambda \; \forall i \in \underline{m}\} \quad (12)$$

REFERENCES AND NOTES

(1) Carhart, R. E.; Smith, D. H.; Brown, H.; Djerassi, C. An approach to computer-assisted elucidation of molecular structure. *J. Am. Chem. Soc.* **1975**, *97*, 5755−5762.

(2) Lindsay, R. K.; Buchanan, B. G.; Feigenbaum, E. A.; Lederberg, J. *Applications of artificial intelligence for organic chemistry: The Dendral Project*; McGraw-Hill: New York, 1980.

(3) *MATCH (Vol. 27): Generators for molecular graphs, nomenclatorial questions*; Kerber, A., Ed.; 1992.

(4) Nourse, J. G.; Smith, D. H.; Carhart, R. E.; Djerassi, C. Exhaustive generation of stereoisomers for structure elucidation. *J. Am. Chem. Soc.* **1970**, *101*, 1216−1223.

(5) Abe, H.; Hayasaka, H.; Miyashita, Y.; Sasaki, S. Generation of stereoisomeric structures using topological information alone. *J. Chem. Inf. Comput. Sci.* **1984**, *24*, 216−219.

(6) Zlatina, L. A.; Elyashberg, M. E. Generation of stereoisomers and their spatial models corresponding to the given molecular structure. *MATCH* **1992**, *27*, 191−207.

(7) Huheey, J. E. *Inorganic Chemistry*, 2nd ed.; Harper and Row: New York, 1978.

(8) Shriver, D. F.; Atkins, P. W.; Langford, C. H. *Inorganic Chemistry*; Oxford University Press: Oxford, 1990.

(9) Testa, B. The geometry of molecules: Basic principles and nomenclatures. In *Stereochemistry. New comprehensive biochemistry*; Tamm, Chr., Ed.; Elsevier Biomedical Press: Amsterdam, New York, Oxford, 1982; Vol. 3.

(10) Favas, M. C.; Kepert, D. L. Aspects of the stereochemistry of nine-coordination, ten-coordination and twelve-coordination. *Prog. Inorg. Chem.* **1981**, *28*, 310−367.

(11) Kepert, D. L. Aspects of the stereochemistry of eight-coordination. *Prog. Inorg. Chem.* **1978**, *24*, 179−249.

(12) Ruch, E.; Hässelbarth, W.; Richter, B. Double cosets as class notion and principle of nomenclature for isomers and their enumeration. *Theor. Chim. Acta* **1970**, *19*, 288−300.

(13) Klein, D. J.; Cowley, A. H. Permutational isomerism. *J. Am. Chem. Soc.* **1975**, *97*, 1633−1640.

(14) Nourse, J. G. Generalized stereoisomerization modes. *J. Am. Chem. Soc.* **1977**, *99*, 2063−2069.

(15) Brocas, J.; Gielen, M.; Willem, R. *The permutational approach to dynamic stereochemistry*; McGraw-Hill: New York, 1983.

(16) Brocas, J. Double cosets and enumeration of permutational isomers of fixed symmetry. *J. Am. Chem. Soc.* **1986**, *108*, 1135−1145.

(17) Hässelbarth, W.; Ruchs, E. Classifications of rearrangement mechanisms by means of double cosets and counting formulas for the number of classes. *Theor. Chim. Acta* **1973**, *29*, 259−268.

(18) Ruch, E.; Klein, D. J. Double Cosets in Chemistry and Physics. *Theoret. Chim. Acta* **1983**, *63*, 447−472.

(19) Cotton, F.; Wilkinson, G. *Advanced inorganic chemistry*, 5th ed.; J. Wiley: New York, 1988.

(20) Nourse, J. G. The configuration symmetry group and its application to stereoisomer generation, specification and enumeration. *J. Am. Chem. Soc.* **1979**, *101*, 1210−1216.

(21) Kerber, A. Characteristics of wreath products and some applications to representation theory and combinatorics. *Discr. Math.* **1975**, *13*, 13−30.

(22) Pólya, G. Combinatorial enumeration of groups, graphs, and chemical compounds. *Acta math.* **1937**, *68*, 145−253.

(23) Pólya, G.; Read, R. C. *Combinatorial enumeration of groups, graphs, and chemical compounds*; Springer: Berlin, 1987.

(24) *Chemical applications of graph theory*; Balaban, A. T., Ed.; Academic Press: London, 1976.

(25) Robinson, R. W.; Harary, F.; Balaban, A. T. The number of chiral and achiral alkanes and mono-substituted alkanes. *Tetrahedron* **1976**, *32*, 355−361.

(26) Fujita, S. *Symmetry and combinatorial enumeration in chemistry*; Springer: Berlin, 1991.

(27) Fujita, S. A group-theoretical formalism for stereochemistry. In *Chemical group theory. Introduction and fundamentals*; Bonchev, D., Rouvray, D. H., Eds.; Gordon & Breach: Yverdon, 1994; pp 81−132.

(28) Redfield, H. J. The theory of group-reduced distributions. *Am. J. Math.* **1927**, *49*, 433−455.

(29) Davidson, R. A. Isomers and isomerization: elements of Redfield's combinatorial theory. *J. Am. Chem. Soc.* **1981**, *103*, 312−314.

(30) Lloyd, E. K. Redfield's papers and their relevance to counting isomers and isomerizations. *Discr. Appl. Math.* **1988**, *19*, 289−304.

(31) Brown, H.; Hjelmeland, L.; Masinter, L. Constructive graph labeling using double cosets. *Discr. Math.* **1974**, *7*, 1−30.

(32) Hutchings, M. G.; Johnson, J. B.; Klemperer, W. G.; Knight, R. R., III. The steric courses of chemical reactions. 3. Computer generation of product distributions, steric courses, and permutational isomers. *J. Am. Chem. Soc.* **1977**, *99*, 7126−7132.

(33) Grund, R. Symmetry clases of mappings and the construction of discrete structures. *Bayreuther Mathematische Schriften* **1990**, *31*, 19−54.

(34) Grund, R. Construction of molecular graphs with given hybridizations and non-overlapping fragments. *Bayreuther Mathematische Schriften*, in press.

(35) Allinger, N. L. MM2. A hydrocarbon force field utilizing V_1 and V_2 torsional terms. *J. Am. Chem. Soc.* **1977**, *99*, 8127−8134.

(36) Zlatina, L. A. *Mathematical models of generation of stereoisomers and building space models of molecules*. Ph.D. Thesis, All-Union Research Institute of Organic Synthesis, Moscow, 1991 (in Russian).

(37) Wieland, Th. Generation, enumeration, and construction of stereoisomers. *MATCH* **1994**, *31*, 153−203.

(38) Harrington, S. *Computer Graphics*. McGraw-Hill: New York, 1983.

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