Combinatorial Enumeration of Chemical Isomers

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The stereoisomers of symmetric polyenes and the isomers of polysubstituted peri-condensed compounds are counted and enumerated via a well-known combinatorial theorem of Polya. The method gives generating functions in general, from which the number of isomers of many types of molecules can just be read-off.

Even though there were earlier works on the problem of enumeration of chemical isomers, a powerful and elegant method is that of Polya, now well known as Polya’s theorem. In spite of this technique for isomer enumeration, chemists, in general, have been using the so-called ‘intuitive’ methods which sometimes lead to erroneous results. Blackman, in his attempt to point out the textbook errors on the isomers of porphyrins obtained erroneous results. Pilgrim corrected this, however, again with no organized method like Polya’s theorem. Balaban applied Polya’s theorem to porphyrins in particular and obtained a generating function for the isomers of porphyrin. Ron Har-Zvi and Wittes have counted the geometric isomers of a symmetric polyene in a rather tedious way. This counting is a simple application of Polya’s theorem as we will be shown in this paper. Moreover, they have not obtained a configuration-inventory wherein the coefficient of a given term specifies the number of stereoisomers with a given type of configuration. We shall not go into a historical survey of the topic, since this can be found in review articles. In this paper the mathematical concepts related to Polya’s theorem have been introduced in a considerably simplified manner. However, the theorem has been applied to situations that have not been discussed elsewhere in the same manner.

Theory

In order to abstract the problem of counting isomers in the language of mathematics, initially attempt has been made to find the geometric isomers of a symmetric polyene. A symmetric polyene by definition is invariant when rotated by an angle of 180° about an axis passing through the centre as shown in Figs. 1-2. In order to count the geometric isomers, around a double bond the possible configurations have been assigned to see if such configurations are distinct. Therefore, let us look at all the maps from a set D to a set R, where D is the set of double bonds and R is the set \{c, t\} representing the configuration cis or trans. Each map from the set D to the set R represents a configuration of a symmetric polyene. By definition

\[ W(f) = \prod_{d \in D} w(f(d)) \]

To illustrate, a ‘stereo-map’ that takes \( n \) double bonds of a symmetric polyene into \( n \)-cis and the
rest being trans will have a weight C^t_r (n-k) in the above set up.

We are now ready to give a formula for isomers and a generating function for configurations. Let F be the set of all stereo-maps from the set D to R. Two functions f_1, f_2 in F are equivalent if one is transformable to the other by a rotation. In the mathematical language we look at the group G of rotations and two functions f_1, f_2 in F are equivalent if there exists a π in G such that f_1(d) = f_2(πd) for every d in D. In this sense the maps that are non-equivalent go into different equivalence classes and the G-equivalence classes of F are the isomers of the symmetric polyene. Polya's theorem gives a formula for the G-equivalence classes of F in terms of what is known as the cycle index of a permutation group. A typical permutation π in G is said to have the cycle representation x_1^{b_1} x_2^{b_2} \ldots if it has b_1 cycles of length one, b_2 cycles of length two and so on.

Then the cycle index is defined by Eq. (2)

\[ P_G(x_1, x_2, \ldots) = \frac{1}{|G|} \sum_{\pi \in G} \prod_{i=1}^{k} x_i^{b_i} \ldots \]  \hspace{1cm} (2)

where |G| denotes the number of elements in G.

Polya's Theorem

The number of G-equivalence classes of F is given by expression (3)

\[ P_G(|R_1|, |R_2|, \ldots) \]  \hspace{1cm} (3)

The pattern-inventory is given by expression (4)

\[ P_G(\Sigma \mu(\gamma), \Sigma \nu(\gamma)^2, \ldots) \]  \hspace{1cm} (4)

It can be seen that since a symmetric polyene is symmetric about a C_2 axis, the group G is C_2. Therefore, if there are m double bonds the cycle index is \(\frac{1}{2}(x_1^m + x_2^{m-1})^a\) if m is even or \(\frac{1}{2}(x_1^m + x_2^{m-1})^a\) if m is odd.

It can be immediately seen from expression (3) that the number of geometric isomers of a symmetric polyene is \(\frac{1}{2}(2^m - 2^{m/2})\) if m is even or \(\frac{1}{2}(2^m + 2^{m-1/2})\) if m is odd. (Note: |R| = 2.)

This result, of course, agrees with that of Ron Har-Zvi and Wittes but this follows immediately from Polya's theorem! We can also obtain what may be called the configuration-inventory using the formula (4)

\[ \text{Cl} = \frac{1}{2} \sum_{k=0}^{m} \sum_{l=0}^{k} \left( \binom{m}{l} - \binom{(m-1)/2}{l-1} \right) C^{m-k} t^k \ldots \text{if m is odd} \]  \hspace{1cm} (5)

(where l = k/2 if k is even and l = (k-1)/2 if k is odd).

\[ \text{Cl} = \sum_{k=0}^{m} \sum_{l=0}^{k} \left( \binom{m}{l} - \binom{(m-2)/2}{l-1} \right) C^{m-k} t^k \ldots \text{if m is even} \]  \hspace{1cm} (6)

(where l = k/2 if k is even and l = -1 if k is odd).

For example, let us apply this to 2,4,6-octatriene (m = 3). The number of geometric isomers would be 12. The configuration inventory is \(C^3 + 2C^1 + 6C^2 + 2C^0\). Thus we get the following distributions of c's and t's:

- CCC \ldots C^3
- CCt \ldots 2C^1
- Ctt \ldots 2C^2
- ttt \ldots t^3

Isomers of Polysubstituted Peri-condensed Compounds

We shall now apply Polya's theorem to polysubstituted peri-condensed compounds containing any number of rings either odd or even. In either case the point group of the molecule is D_{m} and the group for isomer enumeration is D_{m}. In this set up the set D is the set of 'chemically unlabelled' vertices of the graph where we may attach the substituents. R is the set of atoms or functional groups. Since in this situation we are interested in only molecules with the same formula, we shall look at only those maps that have the same weight. Hence, if the molecule has b_i functional groups of the type F_i, b_a of the type F_a etc., we shall look at those maps with the weight \(f_1 f_2 \ldots\) where \(f_1, f_2, \ldots\) are the weights corresponding to \(F_1, F_2, \ldots\). Such non-equivalent maps are given by the coefficient of \(f_1 f_2 \ldots\) in the pattern inventory. Next attempt is made to obtain the cycle index and hence the pattern inventory for a peri-condensed compound containing any number of rings.

Let h be the number of carbon atoms to which substituents can be attached. It can be easily seen that for a peri-condensed compound h must be a multiple of 6 and so let h = 6l where l is an integer. Two cases arise, namely l is even or odd. (Typical structure of each of these is shown in Figs. 3 and 4 respectively.) The cycle index is given by expressions (7) and (8)

\[ 1 + \frac{1}{12} (x_1^h + 7x_2^h + 2x_3^h + 2x_4^h) \text{ if l is even} \]  \hspace{1cm} (7)

\[ 1 + \frac{1}{12} (x_1^h + 2x_2^h + 4x_3^h + 3x_4^h + 4x_5^h) \text{ if l is odd} \]  \hspace{1cm} (8)

The pattern inventory is given by the equations (9) or (10)

\[ 1 \left[ (f_1 + f_2 + \ldots + f_6)^{h/6} + 7(f_1^2 + f_2^2 + \ldots + f_6^2)^{h/6} + 2(f_1^3 + f_2^3 + \ldots + f_6^3)^{h/6} \right] \text{ if l is even} \]  \hspace{1cm} (9)

\[ 1 \left[ (f_1 + f_2 + \ldots + f_6)^{h/6} + 2(f_1^2 + f_2^2 + \ldots + f_6^2)^{h/6} + 4(f_1^3 + f_2^3 + \ldots + f_6^3)^{h/6} + \ldots \right] \text{ if l is odd} \]  \hspace{1cm} (10)

For example, on applying the Eq. (10) to the case l = 3 with one functional group we get 1 + 2 + 18f^2 + 73f^3 + 276f^4 + 728f^5 + 1599f^6 + 2680f^7 + 3270f^8 + 4090f^9 + 3270f^{10} + 2680f^{11} + 1599f^{12} + 728f^{13} + 276f^{14} + 73f^{15} + 18f^2 + 2f^3 + f^4 \ldots \]  \hspace{1cm} (11)

Thus there are 2680 such heptasubstituted compounds!
Conclusion

Muttertities\textsuperscript{11} used a formula for obtaining the number of different configurations of a labelled polytopal form. He has not given any proof for this formula. It follows immediately from Polya's theorem. The problem is one of finding the number of different polytopal forms with labelled vertices. This is just the coefficient of $f_1$, $f_2$, \ldots, $f_k$ in the pattern-inventory if there are $k$ vertices in the polytopal form. It is

$$\frac{1}{|G|} \left[ \binom{k}{11, \ldots, 11} \right] = \frac{k!}{|G|}$$

where $|G|$ denotes the number of elements in the rotational subgroup of the polytopal form.

Applications of the theorem to many situations including NMR spectroscopy can be found\textsuperscript{10,12}. A good introduction to Polya's work is available\textsuperscript{6}. The author\textsuperscript{12} recently enumerated the stable stereo and position isomers of polysubstituted alcohols by incorporating the principle of inclusion and exclusion in the generalized Wreath product method\textsuperscript{18}.

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