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A Generalized Algorithm for the Enumeration of Chiral and Achiral Isomers of Polyheterosubstituted Monocycloalkanes

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Abstract

A common problem in combinatorial and synthetic organic chemistry is the enumeration of the total number of molecules that can be produced in a chemical synthesis due to the large amount of possible products. Here, a generalized algorithm for the enumeration of chiral and achiral isomers of a $m-$ polyheterosubstituted monocycloalcane with ring size n is derived from combinatorial formulae. The formulae are derived for r kind of substituents of k_r carbons each. The algorithm is applied to three test cases as a proof of concept to assess its correctness.

1 Introduction

One of the main challenges in combinatorial and syntethic organic chemistry is the analysis of the synthetic mixture. In order to have a correct interpretation of the outcome of the synthesis, it is required to know the total number of possible molecules that can be produced, as well as their stereochemistry.

In the study of the enumeration of isomers of organic compounds, the contributions made employing Pólya's theorem are numerous.[1–3] However, the direct application of the theorem does not account for stereochemistry which in conjuction with the unwieldiness of the resulting expressions make its direct applications limited for real world cases. The enumeration of isomers of substituted cycloalkanes has been studied extensively by Nemba *et al*,[4–8] including the considerations of non-isomerizable polyheterosubstituents and homomorphic substituents, along with libraries of enumerations for specific values of ring size and alkyl group carbons. Here, we present a generalized algorithm for the enumeration of chiral and achiral isomers of polyheterosubstitued monocycloalcane.

2 Derivation of the Algorithm

Let us consider G_r the molecular stereograph of the polyheterosubstituted monocycloalkane (PHMCA) with molecular formula $\mathrm{C}_n\mathrm{H}_{2n-m}(S_{k_1})_{m_1}(S_{k_2})_{m_2}(S_{k_3})_{m_3}\ldots(S_{k_r})_{m_r}$, with $\sum_{i=1}^{r} m_i = m$, and let the subgraphs T_{k_i} and G_0 be the stereographs of the substituents $S_{k_i} = -C_{k_i}H_{2k_i+1}$ and of the cyclic backbone $\mathrm{C}_n\mathrm{H}_{2n}$, respectively, as shown in Figure 1. Thus, G_r is constructed by attaching the roots of the m rooted steric trees T_{k_i} of order k_i to the m-selected substitution sites selected in G_0. There exists $\binom{2n}{m}$ choices of substitution sites as each carbon has 2 possible sites, one above and one below the ring plane. It is important to stress that due to thermal energy effects, we consider the ring flip fast enough to equilibrate the conformers in a planar configuration on average. Nonetheless, this choice does not account for the stereochemistry of the skeletons or the substituents.

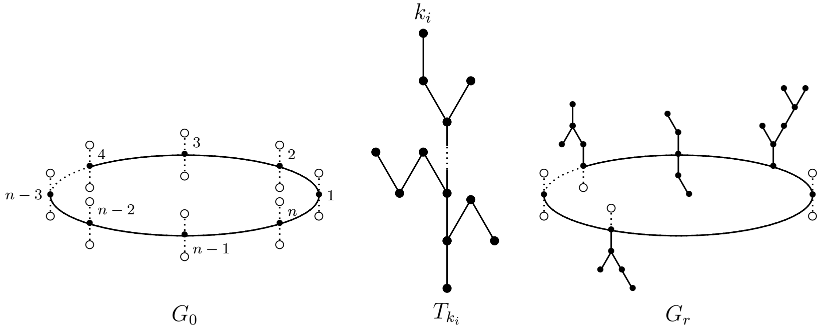

Figure 1. Molecular stereographs G_0, T_{k_i}, and G_r representing a monocycloalkane $\mathrm{C}_n\mathrm{H}_{2n}$, an alkyl group $-\mathrm{C}_{k_i}\mathrm{H}_{2k_i+1}$, and a branched monocyclic cycloalkane $\mathrm{C}_n\mathrm{H}_{2n-m}(S_{k_1})_{m_1}(S_{k_2})_{m_2}(S_{k_3})_{m_3}\ldots(S_{k_r})_{m_r}$, respectively.

Let s_{k_i} and p_{k_i} be the number of total and achiral isomers of the rooted steric tree T_{k_i} of order k_i, therefore, $s_{k_i} - p_{k_i}$ represents the number of chiral isomers of T_{k_i}. Values of s_{k_i}, p_{k_i}, and $s_{k_i} - p_{k_i}$ have been derived by Nemba and Balaban for $0 \leq k_i \leq 18$.

Given m substitution sites, the number of possible ways to fill them with the substituents will depend on the number of different substituents and whether they are chiral or achiral. Since there are r different substituents, let us take each kind as a colour and assign each one to a subset of the m substitution sites, thus representing the filling. Let $C(m,r)$ be the number of ways we can do such an operation. Then, $C(m,r)$ is given by

$$C(m,r) = S(m,r)r! \tag{1}$$

where $S(m,r)$ is the Stirling number of the second kind,[9] that represents the number of non-empty partitions of a set of m elements into r subsets, one of each colour. Since each colouring gives different molecules, we multiply these by the $r!$ factor to include each permutation of the colours.

The selection of the r colours is made from a set of $\sum_{i=1}^{r} s_{k_i} = \mathcal{S}$ different colours, therefore, the number of colour choices $D(\mathcal{S},r)$ is given by

$$D(\mathcal{S},r) = \binom{\mathcal{S}}{r} \tag{2}$$

Now, if at least one of the colours correspond to a chiral substituent, the number of choices is given by

$$D(\mathcal{S}-\mathcal{P},r) = \binom{\mathcal{S}}{r} - \binom{\mathcal{P}}{r} \tag{3}$$

Where $\sum_{i=1}^{r} p_{k_i} = \mathcal{P}$

$$D(\mathcal{P},r) = \binom{\mathcal{P}}{r} \tag{4}$$

As the selection of colours and the colourings are two independent operations, the total number of substitutions for any kind, with at least one chiral substituent in the m sites, and with only achiral substituents is given by the product rule, thus,

$$\mathcal{N}(\mathcal{S},m,r) = C(m,r)D(\mathcal{S},r) = S(m,r)r!\binom{\mathcal{S}}{r} \tag{5}$$

$$\mathcal{N}(\mathcal{S}-\mathcal{P},m,r) = C(m,r)D(\mathcal{S}-\mathcal{P},r) = S(m,r)r!\left[\binom{\mathcal{S}}{r} - \binom{\mathcal{P}}{r}\right] \tag{6}$$

$$\mathcal{N}(\mathcal{P},m,r) = C(m,r)D(\mathcal{P},r) = S(m,r)r!\binom{\mathcal{P}}{r} \tag{7}$$

Once counted the number of possible ways to fill the m substitution sites, we consider the molecular skeletons in which they are arranged.

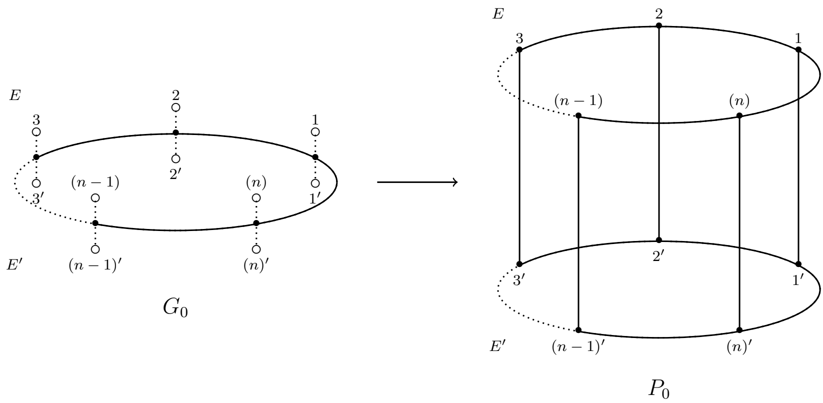

Figure 2. Orthogonal prism P_0 representation of $2n$ substitution sites in the stereograph G_0.

Considering the ring flip fast enough to equilibrate the conformers, G_0 belongs to the symmetry point group D_{nh}, which includes $4n$ symmetry operations. Name $E = \{1, 2, 3, \ldots, n\}$ and $E' = \{1', 2', 3', \ldots, n'\}$ the collections of the substitution sites on opposite sides of the plane containing G_0. We take the action of D_{nh} over the permutations of the vertexes of an orthogonal prism P_0 shown in Figure 2, where P_0 is constructed by taking E and E' as the bases of the prism. Applying the algorithm proposed by Parks and Hendrickson[10] and the considerations given by Nemba and Balaban,[4] the cycle index contributions of each permutation resulting from the action of D_{nh} is summarized in Table 1, with α_i^j representing j permutation cycles of length i.

Table 1. Symmetry operations of D_{nh} and cycle index contributions of its action over P_0.

n odd		n even	
Symmetry operation	Cycle index	Symmetry operation	Cycle index
E, $(n-1)C_n^r$, $(n-1)S_n^r$	$\sum_{\substack{d\mid 2n \\ d\neq 2}} \varphi(d)\alpha_d^{2n/d}$	E, $(n-2)C_n^r$, $(n-2)S_n^r$	$\sum_{\substack{d\mid 2n \\ d\neq 2}} \varphi(d)\alpha_d^{2n/d}$
nC_2, σ_h	$(n+1)\alpha_2^n$	$C_2, \frac{n}{2}C_2' \frac{n}{2}C_2''$, $\frac{n}{2}\sigma_d, \sigma_h$	$\left(\frac{3n}{2}+2\right)\alpha_2^n$
σ_v	$n\alpha_1^2\alpha_2^{n-1}$	$\frac{n}{2}\sigma_v$	$\frac{n}{2}\alpha_1^4\alpha_2^{n-2}$

Applying Pólya's theorem,[11] we obtain the figure inventories $Y_T(n_\pm)$ for the total different geometrical isomers of G_0, which is given by

$$Y_T(n_-) = \frac{1}{4n}\left[\sum_{(d\neq 2)|2n} \rho(d)\alpha_d^{\frac{2n}{d}} + (n+1)\alpha_2^n + n\alpha_1^2\alpha_2^{n-1}\right] \tag{8}$$

$$Y_T(n_+) = \frac{1}{4n}\left[\sum_{(d\neq 2)|2n} \rho(d)2\alpha_d^{\frac{2n}{d}} + \left(\frac{3n}{2}+2\right)\alpha_2^n + \frac{n}{2}\alpha_1^4\alpha_2^{n-2}\right] \tag{9}$$

Excluding the contributions of reflections and rotoflections, we get the figure inventories $Y_E(n_\pm)$ for the total different enantiomeric isomers of G_0, given by

$$Y_E(n_-) = \frac{1}{2n}\left[\sum_{(d\neq 2)|2n} \rho'(d)\alpha_d^{\frac{2n}{d}} + n\alpha_2^n\right] \tag{10}$$

$$Y_E(n_-) = \frac{1}{2n}\left[\sum_{(d\neq 2)|2n} \rho'(d)\alpha_d^{\frac{2n}{d}} + (n+1)\alpha_2^n\right] \tag{11}$$

Through this work, the nomenclature n_+, n_-, and $n_\pm$ represent integer values of n even, n odd and n even or odd, respectively. The values of $\rho(d)$ and $\rho'(d)$ are obtained from equations (12)–(15), where $\varphi(d)_{pr}$ and $\varphi(d)_{ir}$ are the Euler totient function for the integer d in which the subindices *pr* and *ir* refer to proper and improper rotations induced by the $d-$fold rotation axis.[4]

$$\rho(d) = \varphi(d)_{pr} \text{ if } d \text{ is odd} \tag{12}$$

$$\rho(d) = \varphi(d)_{pr} + \varphi(d)_{ir} + \varphi(P_i)_{pr} \text{ if } d \text{ is even and } d = 2P_i;\ P_i \text{ odd prime integer} \tag{13}$$

$$\rho(d) = \varphi(d)_{pr} + \varphi(d)_{ir} \text{ if } d \text{ is even and } d \neq 2P_i;\ P_i \text{ odd prime integer} \tag{14}$$

$$\rho'(d) = \varphi(d)_{pr} \tag{15}$$

By substituting $\alpha_a^b = (x^0 + x^a)^b = (1 + x^a)^b$ as the polynomial representation of the cycle α_a^b in equations (8)–(11), we get the geometrical and enantiomerical polynomials for G_0, say $P_T(n_\pm)$ and $P_E(n_\pm)$

$$P_T(n_-) = \frac{1}{4n}\left[\sum_{(d\neq 2)|2n} \rho(d)(1+x^d)^{\frac{2n}{d}} + (n+1)(1+x^2)^n + n(1+x)^2(1+x^2)^{n-1}\right] \quad (16)$$

$$P_T(n_+) = \frac{1}{4n}\left[\sum_{(d\neq 2)|n} \rho(d)(1+x^d)^{\frac{2n}{d}} + \left(\frac{3n}{2}+2\right)(1+x^2)^n + \frac{n}{2}(1+x)^4(1+x^2)^{n-2}\right] \quad (17)$$

$$P_E(n_-) = \frac{1}{4n}\left[\sum_{(d\neq 2)|2n} \rho'(d)(1+x^d)^{\frac{2n}{d}} + n(1+x^2)^n\right] \quad (18)$$

$$P_E(n_+) = \frac{1}{4n}\left[\sum_{(d\neq 2)|2n} \rho'(d)(1+x^d)^{\frac{2n}{d}} + (n+1)(1+x^2)^n\right] \quad (19)$$

By expanding $P_T(n_\pm)$ and $P_E(n_\pm)$, we get the generating functions, equations (20) and (21), for the geometrical and enantiomerical isomers of G_0.

$$P_T(n_\pm, m_\pm) = \sum_{m=0}^{2n} A_T(n_\pm, m_\pm)x^m \quad (20)$$

$$P_E(n_\pm, m_\pm) = \sum_{m=0}^{2n} A_E(n_\pm, m_\pm)x^m \quad (21)$$

The coefficients $A_T(n_\pm, m_\pm)$ and $A_E(n_\pm, m_\pm)$ satisfy the relations in equations (22) and (23), where $A_c(n_\pm, m_\pm)$ and $A_{ac}(n_\pm, m_\pm)$ represent the number of chiral and achiral skeletons of a homopolysubstituted monocyclic alkane with formula $C_nH_{2n-m}X_m$

$$A_T(n_\pm, m_\pm) = A_c(n_\pm, m_\pm) + A_{ac}(n_\pm, m_\pm) \quad (22)$$

$$A_E(n_\pm, m_\pm) = 2A_c(n_\pm, m_\pm) + A_{ac}(n_\pm, m_\pm) \quad (23)$$

The solution to the problem of finding values of $A_c(n_\pm, m_\pm)$ and $A_{ac}(n_\pm, m_\pm)$ and general recurrence formulae for them has been derived by Nemba *et al.*[4, 5, 7, 8] The algorithm to determine its values is given by equations (24)–(31), where $D_{n_\pm}$, $D_{2n_\pm}$, and $D_{m_\pm}$ represent the sets of divisors of $n_\pm$, $2n_\pm$, and $m_\pm$ respectively.

If $(d \neq 2) \in D_{2n_-} \cap D_{m_-}$, then

$$A_c(n_-, m_-) = \frac{1}{4n}\left[\sum_{d\neq 2}(2\rho'(d) - \rho(d))\binom{\frac{2n}{d}}{\frac{m}{d}} - 2n\binom{n-1}{\frac{m-1}{2}}\right] \tag{24}$$

$$A_{ac}(n_-, m_-) = \frac{1}{2n}\left[\sum_{d\neq 2}(\rho(d) - \rho'(d))\binom{\frac{2n}{d}}{\frac{m}{d}} + 2n\binom{n-1}{\frac{m-1}{2}}\right] \tag{25}$$

If $(d \neq 2) \in D_{2n_-} \cap D_{m_+}$, then

$$A_c(n_-, m_+) = \frac{1}{4n}\left[\sum_{d\neq 2}(2\rho'(d) - \rho(d))\binom{\frac{2n}{d}}{\frac{m}{d}} - \binom{n}{\frac{m}{2}}\right] \tag{26}$$

$$A_{ac}(n_-, m_+) = \frac{1}{2n}\left[\sum_{d\neq 2}(\rho(d) - \rho'(d))\binom{\frac{2n}{d}}{\frac{m}{d}} + (n+1)\binom{n}{\frac{m}{2}}\right] \tag{27}$$

If $(d \neq 2) \in D_{n_+} \cap D_{m_-}$, then

$$A_c(n_+, m_-) = \frac{1}{4n}\left[\sum_{d\neq 2}(2\rho'(d) - \rho(d))\binom{\frac{2n}{d}}{\frac{m}{d}} - 2n\binom{n-1}{\frac{m-1}{2}}\right] \tag{28}$$

$$A_{ac}(n_+, m_-) = \frac{1}{2n}\left[\sum_{d\neq 2}(\rho(d) - \rho'(d))\binom{\frac{2n}{d}}{\frac{m}{d}} + 2n\binom{n-1}{\frac{m-1}{2}}\right] \tag{29}$$

If $(d \neq 2) \in D_{n_+} \cap D_{m_+}$, then

$$A_c(n_+, m_+) = \frac{1}{4n}\left[\sum_{d\neq 2}(2\rho'(d) - \rho(d))\binom{\frac{2n}{d}}{\frac{m}{d}} - \frac{1}{n-1}\left(\frac{m^2}{2} - n(m+1) + 1\right)\binom{n}{\frac{m}{2}}\right] \tag{30}$$

$$A_{ac}(n_+, m_+) = \frac{1}{4n}\left[\sum_{d\neq 2}(2\rho'(d) - \rho(d))\binom{\frac{2n}{d}}{\frac{m}{d}} + \frac{1}{n-1}\left(n^2 - n(m+1) - \frac{m^2}{2} - 2\right)\binom{n}{\frac{m}{2}}\right] \tag{31}$$

The chirality of a PHMCA can be derived from having at least one chiral substituent or having a subtituent in chiral positions. As these two operations are independent, the total number of possible arranges is given by the product rule. Thus, the number of isomers of G_r can be classified in four groups:

$A^{ac}_{ac}(n_\pm, m_\pm)$: the number of isomers with achiral skeletons with only achiral substituents.

$A^{c}_{ac}(n_\pm, m_\pm)$: the number of isomers with achiral skeletons with at least one chiral substituent.

$A_c^{ac}(n_\pm, m_\pm)$: the number of isomers with chiral skeletons with only achiral substituents.

$A_c^{c}(n_\pm, m_\pm)$: the number of isomers with chiral skeletons with at least one chiral substituent.

Hence, according to equations (5)–(7) and (24)–(31), the total number of each kind of isomers is given by equations (32)–(35).

$$A_{ac}^{ac}(n_\pm, m_\pm) = A_{ac}(n_\pm, m_\pm)\mathcal{N}(\mathcal{P}, m_\pm, r) = A_{ac}(n_\pm, m_\pm)\mathcal{S}(m_\pm, r)r!\binom{\mathcal{P}}{r} \tag{32}$$

$$A_{ac}^{c}(n_\pm, m_\pm) = A_{ac}(n_\pm, m_\pm)\mathcal{N}(\mathcal{S}-\mathcal{P}, m_\pm, r) = A_{ac}(n_\pm, m_\pm)\mathcal{S}(m_\pm, r)r!\left[\binom{\mathcal{S}}{r} - \binom{\mathcal{P}}{r}\right] \tag{33}$$

$$A_{c}^{ac}(n_\pm, m_\pm) = A_{c}(n_\pm, m_\pm)\mathcal{N}(\mathcal{P}, m_\pm, r) = A_{c}(n_\pm, m_\pm)\mathcal{S}(m_\pm, r)r!\binom{\mathcal{P}}{r} \tag{34}$$

$$A_{c}^{c}(n_\pm, m_\pm) = A_{c}(n_\pm, m_\pm)\mathcal{N}(\mathcal{S}-\mathcal{P}, m_\pm, r) = A_{c}(n_\pm, m_\pm)\mathcal{S}(m_\pm, r)r!\left[\binom{\mathcal{S}}{r} - \binom{\mathcal{P}}{r}\right] \tag{35}$$

3 Proof-of-concept

3.1 One substituent case ($n = 3$) for $C_3H_5(C_3H_7)$

1. Number of permutations of the substituents

$$\begin{aligned}
\mathcal{N}(\mathcal{P}, m, r) &= S(m, r)r!\binom{\mathcal{P}}{r} \\
&= S(1,1)1!\binom{2}{1} \\
\mathcal{N}(\mathcal{P}, m, r) &= 2
\end{aligned}$$

$$\begin{aligned}
\mathcal{N}(\mathcal{S}-\mathcal{P}, m, r) &= S(m, r)r!\left[\binom{\mathcal{S}}{r} - \binom{\mathcal{P}}{r}\right] \\
&= S(1,1)1!\left[\binom{2}{1} - \binom{2}{1}\right] \\
\mathcal{N}(\mathcal{S}-\mathcal{P}, m, r) &= 0
\end{aligned}$$

2. Chiral and achiral coefficients

As n and m are both odd, we apply equations (24) and (25). Thus, $D_{2n-} = \{1,2,3,6\}$ and $D_{m-} = \{1\}$, which implies that $D_{2n-} \cap D_{m-} = \{1\}$. Therefore,

$$\begin{aligned}
A_c(n_-, m_-) &= \frac{1}{4n}\left[\sum_{d\neq 2} [2\rho'(d) - \rho(d)] \binom{\frac{2n}{d}}{\frac{m}{d}} - 2n\binom{n-1}{\frac{m-1}{2}}\right] \\
&= \frac{1}{4\cdot 3}\left[[2\rho'(1) - \rho(1)] \binom{\frac{2\cdot 3}{1}}{\frac{1}{1}} - 2\cdot 3\binom{3-1}{\frac{1-1}{2}}\right] \\
&= \frac{1}{12}\left[(2-1)\binom{6}{1} - 6\binom{2}{0}\right] \\
A_c(n_-, m_-) &= 0
\end{aligned}$$

$$\begin{aligned}
A_{ac}(n_-, m_-) &= \frac{1}{2n}\left[\sum_{d\neq 2} [\rho(d) - \rho'(d)] \binom{\frac{2n}{d}}{\frac{m}{d}} + 2n\binom{n-1}{\frac{m-1}{2}}\right] \\
&= \frac{1}{2\cdot 3}\left[[\rho(1) - \rho'(1)] \binom{\frac{2\cdot 3}{1}}{\frac{1}{1}} + 2\cdot 3\binom{3-1}{\frac{1-1}{2}}\right] \\
&= \frac{1}{6}\left[(1-1)\binom{6}{1} + 6\binom{2}{0}\right] \\
A_{ac}(n_-, m_-) &= 1
\end{aligned}$$

3. Total number of isomers counted by substituent and skeleton type

$$\begin{aligned}
A_{ac}^{ac} &= A_{ac}(n,m)\mathcal{N}(\mathcal{P}, m, r) && = 1\cdot 2 = 2 \\
A_{ac}^{c} &= A_{ac}(n,m)\mathcal{N}(\mathcal{S} - \mathcal{P}, m, r) && = 1\cdot 0 = 0 \\
A_{c}^{ac} &= A_{c}(n,m)\mathcal{N}(\mathcal{P}, m, r) && = 0\cdot 2 = 0 \\
A_{c}^{c} &= A_{c}(n,m)\mathcal{N}(\mathcal{S} - \mathcal{P}, m, r) && = 0\cdot 0 = 0
\end{aligned}$$

which gives a total number of isomers of 2, depicted in Figure 3.

4. Structures

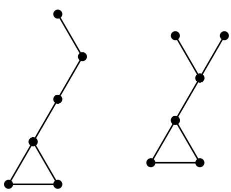

Figure 3. Stereographs of the 2 A_{ac}^{ac} isomers obtained by having a single C_3H_7 substituent in a C_3H_5 ring.

3.2 Homomorphic case ($n = 3$) for $C_3H_4(C_3H_7)_2$

1. Number of permutations of the substituents

$$\begin{aligned}\mathcal{N}(\mathcal{P}, m, r) &= S(m, r) r! \binom{\mathcal{P}}{r} \\ &= S(2,1)1! \binom{2}{1} \\ \mathcal{N}(\mathcal{P}, m, r) &= 2\end{aligned}$$

$$\begin{aligned}\mathcal{N}(\mathcal{S}-\mathcal{P}, m, r) &= S(m, r) r! \left[\binom{\mathcal{S}}{r} - \binom{\mathcal{P}}{r}\right] \\ &= S(2,1)1! \left[\binom{2}{1} - \binom{2}{1}\right] \\ \mathcal{N}(\mathcal{S}-\mathcal{P}, m, r) &= 0\end{aligned}$$

2. Chiral and achiral coefficients

As n is odd and m is even, we apply equations (26) and (27). Thus, $D_{2n-} = \{1, 2, 3, 6\}$ and $D_{m+} = \{1, 2\}$, which implies that $D_{2n-} \cap D_{m+} = \{1, 2\}$. Therefore,

$$\begin{aligned}A_c(n_-, m_+) &= \frac{1}{4n}\left[\sum_{d \neq 2} [2\rho'(d) - \rho(d)] \binom{\frac{2n}{d}}{\frac{m}{d}} - \binom{n}{\frac{m}{2}}\right] \\ &= \frac{1}{4 \cdot 3}\left[[2\rho'(1) - \rho(1)] \binom{\frac{2 \cdot 3}{1}}{\frac{2}{1}} - \binom{3}{\frac{2}{2}}\right] \\ &= \frac{1}{12}\left[(2-1)\binom{6}{2} - \binom{3}{1}\right] \\ A_c(n_-, m_+) &= 1\end{aligned}$$

$$\begin{aligned}A_{ac}(n_-, m_+) &= \frac{1}{2n}\left[\sum_{d \neq 2} [\rho(d) - \rho'(d)] \binom{\frac{2n}{d}}{\frac{m}{d}} + (n+1)\binom{n}{\frac{m}{2}}\right] \\ &= \frac{1}{2 \cdot 3}\left[[\rho(1) - \rho'(1)] \binom{\frac{2 \cdot 3}{1}}{\frac{2}{1}} + (3+1)\binom{3}{\frac{2}{2}}\right] \\ &= \frac{1}{6}\left[(1-1)\binom{6}{2} + 4\binom{3}{1}\right] \\ A_{ac}(n_-, m_+) &= 2\end{aligned}$$

3. Total number of isomers counted by substituent and skeleton type

$$\begin{aligned}A_{ac}^{ac} &= A_{ac}(n, m)\mathcal{N}(\mathcal{P}, m, r) && = 2 \cdot 2 = 4 \\ A_{ac}^{c} &= A_{ac}(n, m)\mathcal{N}(\mathcal{S}-\mathcal{P}, m, r) && = 2 \cdot 0 = 0 \\ A_{c}^{ac} &= A_{c}(n, m)\mathcal{N}(\mathcal{P}, m, r) && = 1 \cdot 2 = 2 \\ A_{c}^{c} &= A_{c}(n, m)\mathcal{N}(\mathcal{S}-\mathcal{P}, m, r) && = 1 \cdot 0 = 0\end{aligned}$$

which gives a total number of isomers of 6, depicted in Figure 4.

4. Structures

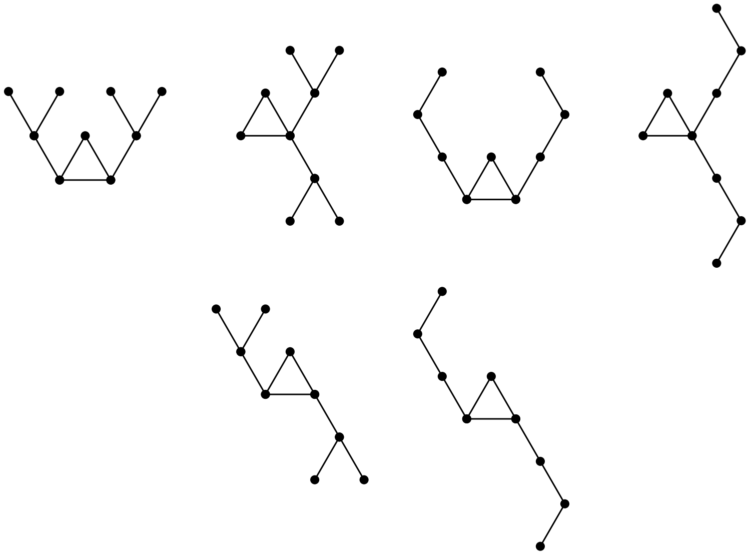

Figure 4. Homomorphic stereographs of the 6 isomers, 4 A_{ac}^{ac} (upper row) and 2 A_{c}^{ac} (lower row), obtained by having 2 C_3H_7 substituents in a C_3H_4 ring.

3.3 Heteromorphic case ($n = 3$) for $C_3H_4(C_3H_7)_2$

1. Number of permutations of the substituents

$$\begin{aligned}\mathcal{N}(\mathcal{P}, m, r) &= S(m, r)r!\binom{\mathcal{P}}{r} \\ &= S(2, 2)2!\binom{2}{2} \\ \mathcal{N}(\mathcal{P}, m, r) &= 2\end{aligned}$$

$$\begin{aligned}\mathcal{N}(\mathcal{S} - \mathcal{P}, m, r) &= S(m, r)r!\left[\binom{\mathcal{S}}{r} - \binom{\mathcal{P}}{r}\right] \\ &= S(2, 2)2!\left[\binom{2}{2} - \binom{2}{2}\right] \\ \mathcal{N}(\mathcal{S} - \mathcal{P}, m, r) &= 0\end{aligned}$$

2. Chiral and achiral coefficients

As n is odd and m is even, we apply equations (26) and (27). Thus, $D_{2n-} = \{1,2,3,6\}$ and $D_{m+} = \{1,2\}$, which implies that $D_{2n-} \cap D_{m+} = \{1,2\}$. Therefore,

$$\begin{aligned} A_c(n_-,m_+) &= \frac{1}{4n}\left[\sum_{d\neq 2}[2\rho'(d)-\rho(d)]\binom{\frac{2n}{d}}{\frac{m}{d}} - \binom{n}{\frac{m}{2}}\right] \\ &= \frac{1}{4\cdot 3}\left[[2\rho'(1)-\rho(1)]\binom{\frac{2\cdot 3}{1}}{\frac{2}{1}} - \binom{3}{\frac{2}{2}}\right] \\ &= \frac{1}{12}\left[(2-1)\binom{6}{2} - \binom{3}{1}\right] \\ A_c(n_-,m_+) &= 1 \end{aligned}$$

$$\begin{aligned} A_{ac}(n_-,m_+) &= \frac{1}{2n}\left[\sum_{d\neq 2}[\rho(d)-\rho'(d)]\binom{\frac{2n}{d}}{\frac{m}{d}} + (n+1)\binom{n}{\frac{m}{2}}\right] \\ &= \frac{1}{2\cdot 3}\left[[\rho(1)-\rho'(1)]\binom{\frac{2\cdot 3}{1}}{\frac{2}{1}} + (3+1)\binom{3}{\frac{2}{2}}\right] \\ &= \frac{1}{6}\left[(1-1)\binom{6}{2} + 4\binom{3}{1}\right] \\ A_{ac}(n_-,m_+) &= 2 \end{aligned}$$

3. Total number of isomers counted by substituent and skeleton type

$$\begin{aligned} A_{ac}^{ac} &= A_{ac}(n,m)\mathcal{N}(\mathcal{P},m,r) && = 2\cdot 2 = 4 \\ A_{ac}^{c} &= A_{ac}(n,m)\mathcal{N}(\mathcal{S}-\mathcal{P},m,r) && = 2\cdot 0 = 0 \\ A_{c}^{ac} &= A_{c}(n,m)\mathcal{N}(\mathcal{P},m,r) && = 1\cdot 2 = 2 \\ A_{c}^{c} &= A_{c}(n,m)\mathcal{N}(\mathcal{S}-\mathcal{P},m,r) && = 1\cdot 0 = 0 \end{aligned}$$

which gives a total number of isomers of 6, depicted in Figure 5.

4. Structures

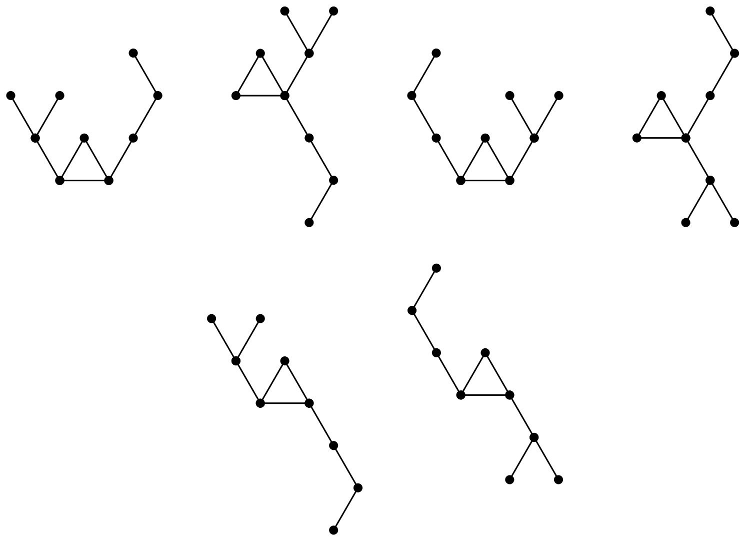

Figure 5. Heteromorphic stereographs of the 6 isomers, 4 A^{ac}_{ac} (upper row) and 2 A^{ac}_{c} (lower row), obtained by having 2 C_3H_7 substituents in a C_3H_4 ring.

4 Conclusions

We have developed a generalized algorithm for the enumeration of chiral and achiral isomers of polyheterosubstituted monocycloalkanes. As a proof-of-concept, the algorithm has been employed for three test cases, namely, a one substituent case ($n = 3$) for $C_3H_5(C_3H_7)$, a homomorphic case ($n = 3$) for $C_3H_4(C_3H_7)_2$, and a heteromorphic case ($n = 3$) for $C_3H_4(C_3H_7)_2$.

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