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Bipartite Enumeration of Chiral and Achiral Skeletons of Substituted Cubane Derivatives and Heteroanalogues. I.

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Abstract

The study presents the determination of: (1)-permutations of 8 substitution sites of cubane submitted to the O_h group action, (2)-the formulation of permutations representations controlling the chirality and the achirality fittingness of cubane skeleton, (3)-the construction of the enumerators of homogeneous and heterogeneous arrangements of substituents among 8 substitution sites of this molecule,(4)-the transformation of permutations representations into generic formulas for bipartite enumeration of A_c chiral and A_{ac} achiral skeletons of homo- and hetero-polysubstituted cubane derivatives ($C_8H_{8-q}X_q$, $C_8H_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$), cubane homohetero-analogues $(CH)_{8-q}X_q$) and cubane hetero hetero-analogues$(CH)_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$ where X,…,Y and Z are achiral substituents.

1 Introduction

The discovery in 1964 by Eaton and Cole [1-4] of cubane a pentacyclo-[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]-octane also called 4-prismane has opened a great deal of interest for the design and synthesis of its derivatives.[5-6] We recall for instance the hepta and octa-nitrocubanes known to be highly explosive[7], the series of cubane dicarboxylic acids[8] and the collection of novel pharmaceutically cubane derivatives reported in the literature.[9] The expansion of such molecular series leads to stereochemical investigations including enumeration problems. Fujita has presented a paper on combinatorial enumeration of cubane derivatives as three-dimensional

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entities [10-11]. This study shows how to construct permutations representations controlling the chirality and the achirality fittingness of cubane submitted to the O_h group action and obtain a bipartite enumeration of enantiomers pairs and achiral skeletons of substituted cubane derivatives and heteroanalogues. The molecule of cubane symbolized by the empirical formulae C_8H_8 or $(CH)_8$ affords the following modes of substitutions:

(1)-Replacement of qH by qX substituents of the same kind yielding homosubstituted cubane derivatives $C_8H_{8-q}X_q$. (2)-Substitution in accord with the obligatory minimum valency (OMV)restrictions [12] of qCH groups by qX trivalent heteroatoms of the same kind giving rise to homogeneous cubane heteroanalogues[13]or cubane homo hetero-analogues$(CH)_{8-q}X_q$;

(3)-Substitution keeping q_0H hydrogen atoms and replacing the remaining others by $q_1X, ..., q_iY, ..., q_kZ$ substituents of different kinds generating polyhetero-substituted cubane derivatives $C_8H_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$;

(4)-Substitution keeping $q_0(CH)$ groups and replacing the remaining CH groups by $q_1X, ..., q_iY, ..., q_kZ$ trivalent heteroatoms of different kinds yielding composite cubane hetero-analogues or cubane hetero hetero-analogues $(CH)_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$.

Throughout this paper we use the following naming approach: (a)- cubane homogeneous heteroanalogue or cubane homo-hetero-analogue for $(CH)_{8-q}X_q$ a molecule of cubane where methine groups (CH) are replaced by trivalent heteroatoms of the same kind and (b)-cubane composite heteroanalogue or cubane hetero hetero-analogue for $(CH)_{q_0}X_{q_1}..Y_{q_i}..Z_{q_k}$ a molecule of cubane where methine groups (CH) are replaced by trivalent heteroatoms of different kinds in accord with the OMV restrictions.

2 Permutations representations controlling the chirality and the achirality fittingness of cubane.

2.1 Permutations of hydrogen and carbon atoms

The architecture of cubane can be described as a succession of 4 edge-fused cyclobutane rings forming 4 vertical faces of a regular 4-gonal prism comprising 4 vertical C-C bonds joined together at right angle and 4 pairs of C-H bonds in eclipsing position. The appropriate representation of such a molecular system is a tridimensional cubic stereograph given in fig.1 where 8 white labeled vertices and 8 alphabetically labeled black vertices representing hydrogen and carbon atoms respectively form a unicage shaped hydrocarbon of octahedral symmetry O_h with 48 symmetry operations detailed in eq.1:

$$O_h = E,\ 8C_3 = 4\left(C_3^1, C_3^2\right),\ 6C_2',\ 6C_4 = 3\left(C_4^1, C_4^3\right),\ 3C_4^2 = 3C_2,\ i,\ 6S_4 = 3\left(S_4^1, S_4^3\right),\ 8S_6 = \left(S_6^1, S_6^5\right),\ 3\sigma_h,\ 6\sigma_d \qquad (1)$$

Let us consider the stereograph of cubane of O_h symmetry shown in fig.1 and note that 8 hydrogen atoms symbolized by 8 labelled white vertices are located in an outer cubic orbit denoted $H_8 = \left(1,2,3,4,1',2',3',4'\right)$ and 8 interconnected and alphabetically labeled black vertices joined to white vertices are located in an inner cubic orbit $C_8 = \left(a,b,c,d,a',b',c',d'\right)$. The O_h group actions on these two concentric cubic orbits are denoted:

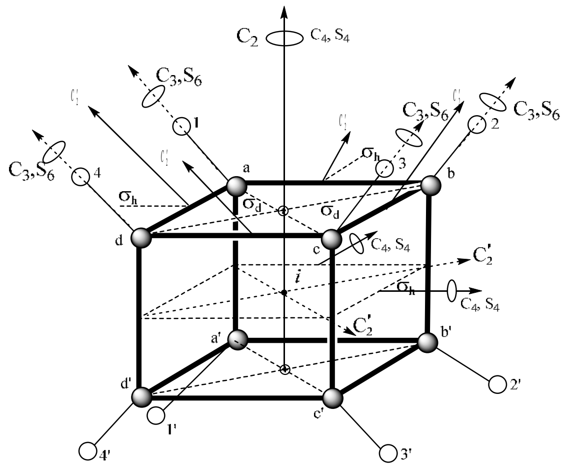

Figure 1. Stereograph of cubane with its O_h symmetry elements.

$$P^{O_h}H_8 = P^{(E)}H_8,\ P^{(C_2')}H_8, P^{(C_2)}H_8, P^{(i)}H_8, P^{(\sigma_h)}H_8, P^{(C_3)}H_8, P^{(C_4)}H_8, P^{(S_4)}H_8,\ P^{(S_6)}H_8, P^{(\sigma_d)}H_8 \qquad (2)$$

$$P^{(O_h)}C_8 = P^{(E)}C_8,\ 8P^{(C_3)}C_8,\ 6P^{(C_2')}C_8, 6P^{(C_4)}C_8, 3P^{(C_2)}C_8, P^{(i)}C_8, 6P^{(S_4)}C_8,\ 8P^{(S_6)}C_8, 3P^{(\sigma_h)}C_8, 6P^{(\sigma_d)}C_8 \qquad (3)$$

The terms of types $P^{(g_i)}H_8$ and $P^{(g_i)}C_8$ in eqs.2-3 are permutations of the elements of H_8 and C_8 induced by each symmetry operation g_i of O_h. They satisfy the relations $P^{(g_i)}H_8 \cong P^{(g_i)}C_8$ hence $P^{O_h}H_8 \cong P^{O_h}C_8$. The cycle structure notations [14] of these permutations are as follows:

$$\left.\begin{aligned} &P^{(E)}H_8 = 1^8,\ P^{(C_2')}H_8 = P^{(C_2)}H_8 = P^{(i)}H_8 = P^{(\sigma_h)}H_8 = 2^4, P^{(C_3)}H_8 = 1^2 3^2 \\ &P^{(C_4)}H_8 = P^{(S_4)}H_8 = 4^2,\ P^{(S_6)}H_8 = 2^1 6^1, P^{(\sigma_d)}H_8 = 1^4 2^2 \end{aligned}\right\} \qquad (4)$$

Hence,

$$P^{O_h}H_8 \cong P^{O_h}C_8 = [1^8], 8[1^2 3^2], 6[2^4], 6[4^2], 3[2^4], [2^4], 6[4^2], 8[2^1 6^1], 3[2^4], 6[1^4 2^2] \quad (5)$$

2.2 Permutations representations controlling the chirality and the achirality fittingness of cubane.

Let $\overline{P_{ro}H_8}$ denote in eq.6, the averaged sum of permutations induced by 24 rotations of O_h including $E, 8C_3, 6C_4, 3C_2$ and $6C_2'$:

$$\begin{aligned}\overline{P_{ro}H_8} &= \frac{1}{24}\left(P^{(E)}\Delta_H + 8P^{(C_3)}\Delta_H + 6P^{(C_2')}\Delta_H + 3P^{(C_2)}\Delta_H + 6P^{(C_4)}\Delta_H\right) \\ &= \frac{1}{24}\left([1^8] + 8[1^2 3^2] + 6[2^4] + 3[2^4] + 6[4^2]\right)\end{aligned} \quad (6)$$

and let $\overline{P_{rr}H_8}$ denote in eq.7, the average weight of permutations of the atoms of cubane induced by the other 24 symmetry operations of O_h including the inversion *i,* the rotoreflections $(6S_4, 8S_6)$ and the reflections ($3\sigma_h, 6\sigma_d$) :

$$\begin{aligned}\overline{P_{rr}H_8} &= \frac{1}{24}\left(P^{(i)}\Delta_H + 6P^{(S_4)}\Delta_H + 8P^{(S_6)}\Delta_H + 3P^{(\sigma_h)}\Delta_H + 6P^{(\sigma_d)}\Delta_H\right) \\ &= \frac{1}{24}\left([2^4] + 6[4^2] + 8[2^1 6^1] + 3[2^4] + 6[1^4 2^2]\right)\end{aligned} \quad (7)$$

Definition 1: *The permutations representation controlling the chirality fittingness for cubaneof O_h symmetry denoted $\Delta_c H_8$ is the half value of the positive difference between $\left(\overline{P_{ro}H_8}\right)$ the averaged weight of permutations of equivalent atoms induced by 24 rotations and $\left(\overline{P_{rr}H_8}\right)$ the averaged weight of permutations of equivalent atoms induced by 24 rotoreflections* (*eq.8*).

$$\Delta_c H_8 = \frac{1}{2}\left(\overline{P_{ro}H_8} - \overline{P_{rr}H_8}\right) = \frac{1}{48}\left([1^8] + 5[2^4] + 8[1^2 3^2] - 8[2^1 6^1] - 6[1^4 2^2]\right) \quad (8)$$

Definition 2: *The permutations representation controlling the achirality fittingness for cubane in O_h symmetry denoted $\Delta_{ac} H_8$ is equal to $\left(\overline{P_{rr}H_8}\right)$ the averaged weight of permutations of equivalent atoms induced by 24 rotoreflections including $i, 6S_4, 8S_6$, $3\sigma_h$ and $6\sigma_d$.*

$$\Delta_{ac} H_8 = \overline{P_{rr}H_8} = \frac{1}{24}\left([2^4] + 6[4^2] + 8[2^1 6^1] + 3[2^4] + 6[1^4 2^2]\right) \quad (9)$$

3 Enumeration of distinct homogeneous arrangements of achiral substituents in cubane

Let us consider homosubstituted cubane derivatives $C_8H_{8-q}X_q$ as chemical compounds obtained by putting in distinct ways qX homomorphic achiral substituents among 8 substitution sites submitted to permutations of types $1^8, 2^4, 4^2, 1^4 2^2, 1^2 3^2, 2^1 6^1$ induced by 48 symmetry operations of O_h. Such placements of substituents are in combinatorics homogeneous arrangements [15] of a given sets of q objects of the same kind among 8 positions submitted to permutations. The numbers of such arrangements are calculated as follows:

(a)-*The numbers of distinct ways of putting q elements of the same kind X (homogeneous arrangements) among 8 substitution sites submitted to* l*-cycle permutations of types* $1^8, 2^4, 4^2$ *denoted* $\binom{\frac{8}{l}}{l^l}$ *are obtained from the binomial coefficients*:

$$T\left(\frac{8}{l},\frac{q}{l}\right)=\begin{cases}\binom{8}{q} & \text{for } l=1\\ \binom{4}{\frac{q}{2}} & \text{for } l=2\\ \binom{2}{\frac{q}{4}} & \text{for } l=4\end{cases} \qquad (10)$$

(b)-A composite permutation of type $1^4 2^2$ including 4 unit-cycles and 2 transpositions allows to put in distinct ways $\alpha = 0,1,3,4$ homomorphic substituents X among 4 invariant positions and $(q-\alpha)$ substituents of the same kind X among 4 positions submitted to transpositions.

The number of distinct ways of putting q substituents of the same kind X among 8 positions submitted to a composite permutation of type $1^4 2^2$ *comprising 4 unit cycles and 2 transpositions is obtained from the sum over α=0,1,2,3,4 of the product of binomial coefficients* $T(4,\alpha)$ *and* $T\left(2,\frac{q-\alpha}{2}\right)$ *given in eq.11:*

$$\sum_{\alpha=0}^{4} T(4,\alpha)\, T\left(2,\frac{q-\alpha}{2}\right) = \sum_{\alpha=0}^{4} \binom{4}{\alpha} \binom{2}{\frac{q-\alpha}{2}} \tag{11}$$

(c)-A composite permutation of type $1^2 3^2$ splits 8 substitution sites into 2-3-cycles and 2 invariant positions. This disposition allows to put in distinct ways $\beta = 0,1,2$ substituents X among 2 invariant positions and $(q-\beta)$ substituents X among the 6 remaining positions divided into two 3-cycle permutations

The number of distinct placements of q substituents of the same kind X among 8 positions submitted to permutations of type $1^2 3^2$ *comprising 2 unit cycles and 2 3-cycles is obtained from the sum over* β*=0,1,2 of the product of binomial coefficients* $T(2,\beta)$ *and* $T\left(2,\frac{q-\beta}{3}\right)$ *given in eq.12*:

$$\sum_{\beta=0}^{2} T(2,\beta)\, T\left(2,\frac{q-\beta}{3}\right) = \sum_{\beta=0}^{2} \binom{2}{\beta} \binom{2}{\frac{q-\beta}{3}} \tag{12}$$

(d)-The permutation $2^1 6^1$ induced by S_6 includes one transposition and one 6-cycle which allow to put $\lambda = 0,1$ pair of substituents of the same kind X among 2 positions submitted to a transposition and $(q-2\lambda)$ substituents of the same kind X among 6 remaining positions submitted to one 6-cycle permutation.

The number of distinct placements of q substituents of the same kind X among 8 positions submitted to a permutation of type $2^1 6^1$ *comprising one transposition and one 6-cycle is obtained from the sum over* $\lambda = 0,1$ *of the product of binomial coefficients* $T(1,\lambda)$ *and* $T\left(1,\frac{q-2\lambda}{6}\right)$ *given in eq. 13:*

$$\sum_{\lambda=0}^{1} T(1,\lambda)\, T\left(1,\frac{q-2\lambda}{6}\right) = \sum_{\lambda=0}^{1} \binom{1}{\lambda} \binom{1}{\frac{q-2\lambda}{6}} \tag{13}$$

4 Bipartite combinatorial enumeration of chiral and achiral skeletons of homopolysubstituted cubane derivatives and cubane homo hetero-analogues

4.1 Generic formulas for bipartite enumeration of homopolysubstituted cubane derivatives and cubane homo hetero-analogues

By replacing the right-hand side terms of $\Delta_c H_8$ and $\Delta_{ac} H_8$ with equivalent algebraic expressions given in eqs.10-13 one obtains respectively a pair of associated generic functions $A_c(8, q)$ and $A_{ac}(8, q)$ given in eqs.14-15 for a bipartite enumeration of chiral and achiral homopolysubstituted cubane derivatives $C_8H_{8\text{-}q}X_q$ and cubane homo hetero-analogues $(CH)_{8\text{-}q}X_q$.

$$A_c(8,q)=\frac{1}{48}\left[\binom{8}{q}+5\binom{4}{\frac{q}{2}}+8\sum_{\beta=0}^{2}\binom{2}{\beta}\binom{2}{\frac{q-\beta}{3}}-6\left(\sum_{\alpha=0}^{4}\binom{4}{\alpha}\binom{2}{\frac{q-\alpha}{2}}\right)-8\left(\sum_{\lambda=0}^{1}\binom{1}{\lambda}\binom{1}{\frac{q-2\lambda}{6}}\right)\right] \quad (14)$$

and

$$A_{ac}(8,q)=\frac{1}{24}\left[6\binom{2}{\frac{q}{4}}+4\binom{4}{\frac{q}{2}}+6\left(\sum_{\alpha=0}^{4}\binom{4}{\alpha}\binom{2}{\frac{q-\alpha}{2}}\right)+8\left(\sum_{\lambda=0}^{2}\binom{1}{\lambda}\binom{1}{\frac{q-2\lambda}{6}}\right)\right] \quad (15)$$

4.2 Applications

Example 1: A bipartite enumeration of chiral and achiral skeletons for the series of homosubstituted cubane derivatives $C_8H_{8\text{-}q}X_q$ and their corresponding cubane homo hetero-analogues $(CH)_{8\text{-}q}X_q$ where $0 \le q \le 8$ are calculated as follows:

$$A_c(8,0)=\frac{1}{48}\left[\binom{8}{0}+5\binom{4}{0}+8\binom{2}{0}\binom{2}{0}-8\binom{1}{0}\binom{1}{0}-6\binom{4}{0}\binom{2}{0}\right]=0$$

$$A_{ac}(8,0)=\frac{1}{24}\left[6\binom{2}{0}+4\binom{4}{0}+8\binom{1}{0}\binom{1}{0}+6\binom{4}{0}\binom{2}{0}\right]=1$$

$$A_c(8,1)=\frac{1}{48}\left[\binom{8}{1}+8\binom{2}{1}\binom{2}{0}-6\binom{4}{1}\binom{2}{0}\right]=0$$

$$A_{ac}(8,1)=\frac{1}{24}\left[6\binom{4}{1}\binom{2}{0}\right]=1$$

$$A_c(8,2)=\frac{1}{48}\left[\binom{8}{2}+8\binom{2}{2}\binom{2}{0}+5\binom{4}{1}-8\binom{1}{1}\binom{1}{0}-6\binom{4}{0}\binom{2}{1}-6\binom{4}{2}\binom{2}{0}\right]=0$$

$$A_{ac}(8,2)=\frac{1}{24}\left[4\binom{4}{1}+8\binom{1}{1}\binom{1}{0}+6\binom{4}{0}\binom{2}{1}+6\binom{4}{2}\binom{2}{0}\right]=3$$

$$A_c(8,3)=\frac{1}{48}\left[\binom{8}{3}+8\binom{2}{0}\binom{2}{1}-6\binom{4}{1}\binom{2}{1}-6\binom{4}{3}\binom{2}{0}\right]=0$$

$$A_{ac}(8,3)=\frac{1}{24}\left[6\binom{4}{1}\binom{2}{1}+6\binom{4}{3}\binom{2}{0}\right]=3$$

$$A_c(8,4)=\frac{1}{48}\left[\binom{8}{4}+8\binom{2}{1}\binom{2}{1}+5\binom{4}{2}-6\binom{4}{0}\binom{2}{2}-6\binom{4}{4}\binom{2}{0}-6\binom{4}{2}\binom{2}{1}\right]=1$$

$$A_{ac}(8,4)=\frac{1}{24}\left[4\binom{4}{2}+6\binom{2}{1}+6\binom{4}{0}\binom{2}{2}+6\binom{4}{4}\binom{2}{0}+6\binom{4}{2}\binom{2}{1}\right]=5$$

The integer sequences $A_c(8,q)$ and $A_{ac}(8,q)$ of chiral and achiral skeletons of homopolysubstituted cubane derivatives $C_8H_{8-q}X_q$ and cubane homo hetero-analogues $(CH)_{8-q}X_q$ calculated for $0 \le q \le 8$ are reported in table 1 where columns 6 and 7 indicate the corresponding numbers of diastereoisomers $C_{ho}(8,q)=A_c(8,q)+A_{ac}(8,q)$ and the occurring symmetries respectively. The results summarized in table 1 predict for *q*=8, one octa-substituted cubane derivative of O_h-symmetry. For q=1, 7 mono and hepta substituted cubane derivatives C_8H_7X, C_8HX_7 and their corresponding mono and hepta homo hetero-analogues $(CH)_7X$ and $(CH)X_7$ exhibit a C_{3v}-symmetry. For *q*=2,6 di or hexa substituted cubanes $C_8H_6X_2, C_8H_2X_6$ and their di and hexa-homo hetero-analogues $(CH)_6X_2$, $(CH)_2X_6$ exhibit 3 achiral diastereoisomers skeletons partitioned into $D_{3d}+2C_{2v}$ symmetries. For *q*=3,5 tri or penta-homosubstituted cubane $C_8H_5X_3, C_8H_3X_5$ and their tri- and penta-homo hetero-analogues $\left(CH\right)_5 X_3$ and $\left(CH\right)_3 X_5$ are reduced to 3 achiral diastereoisomers partitioned into $2C_s$+C_{3v}-symmetries. For q=4 one obtains in the series of tetra homosubstituted cubane derivatives $C_8H_4X_4$ and cubane tetra-homo hetero-analogues $\left(CH\right)_4 X_4$,6 diastereoisomers partitioned into one C_2-chiral and C_s+C_{3v}+C_{4v}+D_{2h} +T_d achiral skeletons. Thus, if the degrees of substitution vary in the range $1 \le q \le 8$ one obtains a total of 21 distinct stereoisomers predicted respectively for the series of homosubstituted cubanes $C_8H_{8-q}X_q$ and cubane homo hetero-analogues $\left(CH\right)_{8-q} X_q$ illustrated in fig.1 of part II of this study.

Table 1. Numbers A_c of chiral, A_{ac} of achiral and $C_{he} = A_c + A_{ac}$ of diastereoisomers predicted for homosubstituted cubanes $C_8H_{8-q}X_q$ and cubane homo-hetero-analogues $\left(CH\right)_{8-q} X_q$ where $0 \le q \le 8$.

q	$C_8H_{8-q}X_q$	$(CH)_{8-q}X_q$	A_c	A_{ac}	C_{ho}	*Occurring Symmetries*
0	C_8H_8	$(CH)_8$	0	1	1	O_h
1	C_8H_7X	$(CH)_7X$	0	1	1	C_{3V}
2	$C_8H_6X_2$	$(CH)_6X_2$	0	3	3	D_{3d}+$2C_{2v}$
3	$C_8H_5X_3$	$(CH)_5X_3$	0	3	3	$2C_s$+C_{3v}
4	$C_8H_4X_4$	$(CH)_4X_4$	1	5	6	C_2+C_s+C_{3v}+C_{4v} +D_{2h}+T_d
5	$C_8H_3X_5$	$(CH)_3X_5$	0	3	3	$2C_s$+C_{3v}
6	$C_8H_2X_6$	$(CH)_2X_6$	0	3	3	D_{3d}+$2C_{2v}$
7	C_8HX_7	$(CH)X_7$	0	1	1	C_{3V}
8	C_8X_8	X_8	0	1	1	O_h

5 Bipartite combinatorial enumeration of chiral and achiral hetero-polysubstituted cubane derivatives and cubane hetero-hetero-analogues.

Two chemical transformations applicable to cubane skeleton are : (a*)* the outer heteropolysubstitution of rank k yielding heterosubstituted cubane derivatives $C_8H_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$ is an operation of putting in distinct ways q_0H and k distinct sets of $q_1X, ...,q_iY,...,q_kZ$ achiral substituents among 8 positions occupied by hydrogen atoms submitted to permutations induced by 48 symmetry operations of the O_h point group and (b) the inner heteropolysubstitution of rang k yielding cubane hetero hetero-analogues $\left(CH\right)_{q_0} X_{q_1}....Y_{q_i}...Z_{q_k}$ consists to put in distinct ways in accord with the obligatory minimum valency (OMV) restrictions $q_0\left(CH\right)$ and $q_1X, ...,q_iY,...,q_kZ$ trivalent atoms among 8 positions occupied by methine groups submitted to permutations induced by *48* symmetry operations of

O_h. In these 2 series of cubane derivatives the integer sequences $q_0, q_1, \ldots, q_i, \ldots, q_k$ satisfy the restriction:

$$\sum_{i=0}^{k} q_i = 8. \qquad (16)$$

5.1 Enumeration of heterogeneous arrangements of substituents in cubane

The numbers of heterogeneous arrangements[15] of achiral substituents in a cubane skeleton are numbers of stereoisomers $C_8H_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$ or $(CH)_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$ obtained by putting in distinct ways $q_0H,\ q_1X,\ \ldots, q_iY, \ldots, q_kZ$ among 8 substitution sites submitted to permutations of types $1^8, 2^4, 4^2$, $1^4 2^2$, $1^2 3^2$, $2^1 6^1$ induced by 48 symmetry operations of O_h. Such placements of substituents are called in combinatorics heterogeneous arrangements of given sets of $q_0, q_1, \ldots, q_i, \ldots, q_k$ objects of different kinds among 8 positions submitted to permutations previously indicated. The numbers of such arrangements are calculated as follows:

(a)-The number of heterogeneous arrangements of achiral substituents in a cubane skeleton submitted to permutations of types 1^8, 2^4 and 4^2.

The number of heterosubstituted permutomers of types $C_8H_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$ *or* $(CH)_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$ *issued from heterogeneous arrangements of* $q_0H,\ q_1X,\ \ldots, q_iY, \ldots, q_kZ$ *achiral substituents among 8 substitution sites of cubane submitted to 8 unit-cycles* (1^8)*, 4 transpositions* (2^4) *and 2-4-cycles permutations* (4^2) *are obtained from multinomial coefficients summarized by the general formula*:

$$T\left(8; \frac{q_0}{l}, \ldots, \frac{q_i}{l}, \ldots, \frac{q_k}{l}\right) = \begin{pmatrix} 8 \\ \frac{q_0}{l}, \ldots, \frac{q_i}{l}, \ldots, \frac{q_k}{l} \end{pmatrix} \text{ where } l=1,2,4. \qquad (17)$$

(b)-The number of heterogeneous arrangements of substituents in a cubane skeleton submitted to permutations of type $1^4.2^2$ induced by the reflection σ_d.

The composite permutation $1^4.2^2$ comprising 4 invariant positions and 2 transpositions allows to put $\alpha_0 H$ and $\alpha_1 X, \ldots, \alpha_i Y, \ldots, \alpha_k Z$ achiral substituents among 4 invariant positions and simultaneously to display $q''_0 H$ and $q''_1 Y,...,q''_i Y,...,q''_k Z$ pairs of remaining others among 2 boxes for transpositions. Such arrangements of substituents require solving the partition eqs.18-19

$$\alpha_0 + \ldots + \alpha_i + \ldots + \alpha_k = 4 \quad (18)$$

$$q''_0 + \ldots + q''_i + \ldots + q''_k = 2 \quad (19)$$

to derive the integer sequences $(\alpha_0,\ldots,\alpha_i,\ldots,\alpha_k)$ and $(q''_0,\ldots,q''_i,\ldots,q''_k)$ indicating the numbers

of H atoms and achiral substituents of kinds X, Y, ..., Z to be put among 4 invariant positions and the numbers of pairs of H atoms and achiral substituents of kinds X, Y … Z to display among 2 boxes for transpositions. The λ_1 solutions to retain are associated pairs of integer sequences $(\alpha_0,\ldots,\alpha_i,\ldots,\alpha_k)$ and $(q''_0,\ldots,q''_i,\ldots,q''_k)$ where α_i and q''_i satisfy the condition:

$$q''_i = \frac{q_i - \alpha_i}{2} \quad (20)$$

Let $T(4;\ \alpha_0,\ldots,\alpha_i,\ldots,\alpha_k)$ be the number of distinct ways of putting $(\alpha_0,\ldots,\alpha_i,\ldots,\alpha_k)$ atoms H, and achiral substituents of kinds X,…, Y,…, Z among 4 invariant positions and let $T(2;\ q''_0,\ldots,q''_i,\ldots,q''_k)$ denote the number of placements of $q''_0,\ldots,q''_i,\ldots,q''_k$ pairs of H, X, Y, …,Z among 2 boxes for transpositions.

The number of permutomers for heterosubstituted cubane derivatives $C_8H_{q_0}X_{q_1}\ldots Y_{q_i}\ldots Z_{q_k}$ *and the number of cubane hetero hetero-analogues* $(CH)_{q_0}X_{q_1}\ldots Y_{q_i}\ldots Z_{q_k}$ *resulting from heterogeneous arrangements of* $q_0H, q_1X,\ldots,q_kZ$ *among 8 substitution sites of cubane submitted to a composite permutation of type* $1^4 2^2$ *are calculated from the sum total of* λ_1 *products of multinomial coefficients given hereafter*:

$$\sum_{\lambda_1} T(4;\ \alpha_0,\ldots,\alpha_i,\ldots,\alpha_k)\,T(2;\ q''_0,\ldots,q''_i,\ldots,q''_k) = \sum_{\lambda_1} \binom{4}{\alpha_0,\ldots,\alpha_i,\ldots,\alpha_k} \binom{2}{q''_0,\ldots,q''_i,\ldots,q''_k} \quad (21)$$

(c)-The number of heterogeneous arrangements of achiral substituents in a cubane skeleton submitted to permutations of type $1^2 3^2$ induced by 3-fold rotations C_3.

The composite permutation $1^2 3^2$ allows to put β_0H atoms and $\beta_1 X,\ldots,\beta_i Y,\ldots,\beta_k Z$ achiral substituents among 2 invariant positions and simultaneously to distribute $q'_0,q'_1,\ldots,q'_i,\ldots,q'_k$ 3-tuples of remaining substituents H, X, …, Y, …Z among 2 boxes for 3-cycle permutations. These 2 choices require solving the partition eqs.22-23 and obtaining the integer sequences $\left(\beta_0,\beta_1,\ldots,\beta_i,\ldots,\beta_k\right)$ of substituents to put among 2 invariant positions and $\left(q'_0,q'_1,\ldots,q'_i,\ldots,q'_k\right)$ 3-tuples of substituents to display among 2 boxes for 3-cycle permutations. The λ_2 pairs of integer sequences $\left(\beta_0,\beta_1,\ldots,\beta_i,\ldots,\beta_k\right)\leftrightarrow\left(q'_0,q'_1,\ldots,q'_i,\ldots,q'_k\right)$ to retain satisfy the conditions:

$$\beta_0+\ldots+\beta_i+\ldots+\beta_k=2 \qquad (22)$$

$$q'_0+\ldots+q'_i+\ldots+q'_k=2 \qquad (23)$$

$$q'_i=\frac{q_i-\beta_i}{3} \qquad (24)$$

Let $T\left(2;\, q'_0,\ldots,q'_i,\ldots,q'_k\right)$ be the number of distinct ways of putting $\left(q'_0,\ldots,q'_i,\ldots,q'_k\right)$ 3-tuples of objects of kinds H, X,Y,…, Z among 2 boxes having each 3 positions and let $T\left(2;\beta_0,\ldots,\beta_i,\ldots,\beta_k\right)$ denote the number of placements of $\left(\beta_0,\ldots,\beta_i,\ldots,\beta_k\right)$ remaining objects of the same kinds among 2 invariant positions.

The number of permutomers for polyheterosubstituted cubane $C_8H_{q_0}X_{q_1}\ldots Y_{q_i}\ldots Z_{q_k}$ and the number of cubane hetero hetero-analogues $(CH)_{q_0}X_{q_1}\ldots Y_{q_i}\ldots Z_{q_k}$ resulting from heterogeneous arrangements of q_0H and $q_1X,\ldots,q_iY,\ldots,q_kZ$ achiral substituents among 8 substitution sites of cubane submitted to composite permutations of type $1^2 3^2$ is the sum total of λ_2 products of multinomial coefficients $T\left(2;\beta_0,\ldots,\beta_i,\ldots,\beta_k\right)$ and $T\left(2;\, q'_0,\ldots,q'_i,\ldots,q'_k\right)$ given in eq. 25 :

$$\sum_{\lambda_2} T\left(2;\beta_0,\ldots,\beta_i,\ldots,\beta_k\right) T\left(2;\, q'_0,\ldots,q'_i,\ldots,q'_k\right)=\sum_{\lambda_2}\binom{2}{\beta_0,\ldots,\beta_i,\ldots,\beta_k}\binom{2}{q'_0,\ldots,q'_i,\ldots,q'_k} \qquad (25)$$

(d)-The number of heterogeneous arrangements of achiral substituents in a cubane skeleton submitted to permutations of type $2^1.6^1$ induced by 6-fold rotoreflections S_6.

The composite permutation $2^1.6^1$ including one 6-cycle permutation and 1 transposition allows to put $\lambda_0,...,\lambda_i,...,\lambda_k$ pairs of H, X, …, Y, Z in the box of transposition and $q_0''',...,q_i''',...,q_k'''$ 6-tuples of H, X, Y …Z in one box of 6-cycle permutations. These 2 arrangements require solving the partition eqs.26-27:

$$\lambda_0 + \ldots + \lambda_i + \ldots + \lambda_k = 1 \quad (26)$$

$$q_0''' + \ldots + q_i''' + \ldots + q_k''' = 1 \quad (27)$$

and obtain λ3 pairs of integer sequences $(\lambda_0,...,\lambda_i,...,\lambda_k) \leftrightarrow (q_0''',...,q_i''',...,q_k''')$ which satisfy the condition:

$$q_i''' = \frac{q_i - 2\lambda_i}{6} \quad (28)$$

Let $T(2;\lambda_0,...,\lambda_i,...,\lambda_k)$ be the number of distinct ways of putting $(\lambda_0,...,\lambda_i,...,\lambda_k)$ pairs of substituents of types H,X,…,Y,…,Z inside one box of 2 equivalent positions and let $T(1;q_0''',...,q_i''',...,q_k''')$ denote the number of placements of $(q_0''',...,q_i''',...,q_k''')$ 6-tuples of substituents of types H, X,…,Y,…,Z in one box of 6 equivalent positions.

The number of permutomers $C_8H_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$ *or* $(CH)_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$ *resulting from heterogeneous arrangements of* $q_0H, q_1X, ...,q_iY,...,q_kZ$ *among 8 substitution sites of cubane submitted to a composite permutations of type* $2^1.6^1$ *is the sum total of* γ_3 *products of multinomial coefficients given in eq.29:*

$$\sum_{\gamma_3} T(2;\lambda_0,...,\lambda_i,...,\lambda_k)T(1;q_0''',...,q_i''',...,q_k''') = \sum_{\gamma_3}^{1} \binom{1}{\lambda_0,...,\lambda_i,...,\lambda_k}\binom{1}{q_0''',...,q_i''',...,q_k'''} \quad (29)$$

5.2 Generic formulas for bipartite enumeration of chiral and achiral hetero-polysubstituted cubane derivatives and cubane hetero hetero-analogues.

By replacing the right hand side terms of $\Delta_c H_8$ and $\Delta_{ac} H_8$ (eqs.6-7) with equivalent terms given in eqs.17, 21, 25, 29 one obtains eqs.30-31 which are generic formulae giving a bipartite inventory of $A_c(8;q_0,...,q_i,...,q_k)$ chiral and $A_{ac}(8;q_0,...,q_i,...,q_k)$ achiral skeletons of both hetero-polysubstituted cubanes $C_8H_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$ and cubane hetero hetero-analogues $(CH)_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$.

$$A_c(8;q_0,..q_i,...,q_k)=\frac{1}{48}\left[\begin{array}{l}\binom{8}{q_0,...,q_i,...,q_k}+5\binom{4}{\frac{q_0}{2},...,\frac{q_i}{2},...,\frac{q_k}{2}}+8\sum_{\gamma_1}\binom{2}{\beta_0,...,\beta_i,...,\beta_k}\binom{2}{q'_0,...,q'_i,...,q'_k}\\ -6\sum_{\gamma_2}\binom{4}{\alpha_0,...,\alpha_i,...,\alpha_k}\binom{2}{q''_0,...,q''_i,...,q''_k}-8\left(\sum_{\gamma_3}^{1}\binom{1}{\lambda_0,...,\lambda_i,...,\lambda_k}\binom{1}{q'''_0,...,q'''_i,...,q'''_k}\right)\end{array}\right] \quad (30)$$

and

$$A_{ac}(8;q_0,..q_i,...,q_k)=\frac{1}{24}\left[\begin{array}{l}4\binom{4}{\frac{q_0}{2},...,\frac{q_i}{2},...,\frac{q_k}{2}}+6\binom{2}{\frac{q_0}{4},...,\frac{q_i}{4},...,\frac{q_k}{4}}+6\sum_{\gamma_2}\binom{4}{\alpha_0,...,\alpha_i,...,\alpha_k}\binom{2}{q''_0,...,q''_i,...,q''_k}\\ +8\left(\sum_{\gamma_3}^{1}\binom{1}{\lambda_0,...,\lambda_i,...,\lambda_k}\binom{1}{q'''_0,...,q'''_i,...,q'''_k}\right)\end{array}\right] \quad (31)$$

5.3 Applications

Example **2**: Bipartite enumeration of di, tri, tetra, penta, hexa and hepta-heteropolysubstituted cubane derivatives and their corresponding hetero hetero-analogues given in table 2 where the subscript *k* represents the number of distinct types of achiral substituents.

Table 2. Molecular formula of di, tri, tetra, penta, hexa and hepta hetero-polysubstituted cubane derivatives $C_8H_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$ and cubane hetero hetero-analogues $(CH)_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$

*k	$C_8H_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}/(CH)_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$	k	$C_8H_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}/(CH)_{q_0}X_{q_1}....Y_{q_i}...Z_{q_k}$
2	C_8H_6XY / $(CH)_6XY$	4	$C_8H_2X_2W_2YZ$ / $(CH)_2X_2W_2YZ$
	$C_8H_5X_2Y$ / $CH)_5X_2Y$		C_8H_4XWYZ / $(CH)_4XWYZ$
	$C_8H_4X_2Y_2$ / $(CH)_4X_2Y_2$		$C_8H_3X_2WYZ$ / $(CH)_3X_2WYZ$
3	$C_8H_3X_2Y_2Z$ / $(CH)_3X_2Y_2Z$	5	$C_8H_2X_2UWYZ$ / $(CH)_2X_2UWYZ$
	C_8H_5XYZ / $CH)_5XYZ$	6	$C_8H_2XPUWYZ$ / $(CH)_2XPUWYZ$
		7	$C_8HXSPUWYZ$ / $(CH)XSPUWYZ$

**k=number of achiral substituents of different kinds.*

To solve this problem for each compound aforementioned we list the appropriate values $q_0,..q_i,...,q_k$ reported in column 1 of table 3 then we compute from couples of partition eqs.(18-19), (22-23) and (26-27) satisfying the restrictions 20, 24 and 28, pairs of integer sequences $(\beta_0,...,\beta_i,...,\beta_k)\leftrightarrow(q'_0,...,q'_i,...,q'_k)$, $(\alpha_0,...,\alpha_i,...,\alpha_k)\leftrightarrow(q''_0,...,q''_i,...,q''_k)$ and

$(\lambda_0,\ldots,\lambda_i,\ldots,\lambda_k) \leftrightarrow (q'''_0,\ldots,q'''_i,\ldots,q'''_k)$. The data collected from such calculations are reported in table 3 and used in eqs.30-31 to derive the numbers of enantiomers pairs and achiral skeletons required. We note for these series that non-occurring compatible pairs of integer sequences are indicated by empty cells with dashed lines.

Table 3. Compatible pairs of integer sequences ($\beta_0,\ldots,\beta_i,\ldots,\beta_k$)$\leftrightarrow$($q'_0,\ldots,q'_i,\ldots,q'_k$),($\alpha_0,\ldots,\alpha_i,\ldots,\alpha_k$)$\leftrightarrow$ ($q''_0,\ldots,q''_i,\ldots,q''_k$),($\lambda_0,\ldots,\lambda_i,\ldots,\lambda_k$)$\leftrightarrow$($q'''_0,\ldots,q'''_i,\ldots,q'''_k$) for heteropolysubstituted cubane derivatives $C_8H_{q_0}X_{q_1}\ldots Y_{q_i}\ldots Z_{q_k}$ and cubane hetero hetero-analogues $(CH)_{q_0}X_{q_1}\ldots Y_{q_i}\ldots Z_{q_k}$ having distinct types of achiral substituents.

$q_0,..q_i,...,q_k$	$\beta_0,\ldots,\beta_i,\ldots,\beta_k$	$q'_0,\ldots,q'_i,\ldots,q'_k$	$\alpha_0,\ldots,\alpha_i,\ldots,\alpha_k$	$q''_0,\ldots,q''_i,\ldots,q''_k$	$\lambda_0,\ldots,\lambda_i,\ldots,\lambda_k$	$q'''_0,\ldots,q'''_i,\ldots,q'''_k$
6,1,1	0,1 ,1	2,0,0	2,1,1	2,0,0	-------	--------
5,2,1	---	---	1,2,1	2,0,0	-------	--------
			3,0,1	1,1,0	-------	--------
4,2,2	---	---	4,0,0	0,1,1	-------	--------
			2,2,0	1,0,1	-------	--------
			2,0,2	1,1,0	-------	--------
			0,2,2	2,0,0	-------	--------
5,1,1,1	-------	--------	1,1,1,1	2,0,0,0	-------	--------
3,2,2,1	-------	--------	3,0,0,1	0,1,1,0		
			1,2,0,1	1,0,1,0		
			1,0,2,1	1,1,0,0		
4,1,1,1,1			0,1,1,1,1	2,0,0,0,0		
3,2,1,1,1	-------	--------	1,0,1,1,1	1,1,0,0,0	-------	--------
2,2,2,1,1	-------	--------	2,0,0,1,1	0,1,1,0,0	-------	--------
	-------	--------	0,2,0,1,1	1,0,1,0,0	-------	--------
	-------	--------	0,0,2,1,1	1,1,0,0,0		
2,2,1,1,1,1,	-------	--------	------------	--------	-------	--------
2,1,1,1,1,1,1	-------	--------	------------	--------	-------	--------
1,1,1,1,1,1,1,1	-------	--------	------------	--------	-------	--------

The numbers $A_c(8;q_0,..q_i,...,q_k)$ and $A_{ac}(8;q_0,..q_i,...,q_k)$ of enantiomer pairs and achiral skeletons for these heteropolysubstituted cubane derivatives and cubane hetero hetero-analogues are derived as follows:

For C_8H_6XY and $(CH)_6XY$

$$A_c(8,6,1,1)=\frac{1}{48}\left[\binom{8}{6,1,1}+8\left[\binom{2}{0,1,1}\binom{2}{2,0,0}\right]-6\left[\binom{4}{2,1,1}\binom{2}{2,0,0}\right]\right]=0$$

$$A_{ac}(8,6,1,1)=\frac{1}{24}\,6\left[\binom{4}{2,1,1}\binom{2}{2,0,0}\right]=3$$

For $C_8H_5X_2Y$ and $CH)_5X_2Y$

$$A_c(8,5,2,1)=\frac{1}{48}\left[\binom{8}{5,2,1}-6\left[\binom{4}{1,2,1}\binom{2}{2,0,0}+\binom{4}{3,0,1}\binom{2}{1,1,0}\right]\right]=1$$

$$A_c(8,5,2,1)=\frac{1}{24}\left[6\left[\binom{4}{1,2,1}\binom{2}{2,0,0}+\binom{4}{3,0,1}\binom{2}{1,1,0}\right]\right]=5$$

For C_8H_5XYZ and $CH)_5XYZ$

$$A_c(8,5,1,1,1)=\frac{1}{48}\left[\binom{8}{5,1,1,1}-6\binom{4}{1,1,1,1}\binom{2}{2,0,0,0}\right]=4$$

$$A_{ac}(8,5,1,1,1)=\frac{1}{24}\left[6\binom{4}{1,1,1,1}\binom{2}{2,0,0,0}\right]=6$$

For $C_8H_4X_2Y_2$ and $(CH)_4X_2Y_2$

$$A_c(8,4,2,2)=\frac{1}{48}\left[\binom{8}{4,2,2}+5\binom{4}{2,1,1}-6\left[\begin{array}{l}\binom{4}{4,0,0}\binom{2}{0,1,1}+\binom{4}{2,2,0}\binom{2}{1,0,1}\\+\binom{4}{2,0,2}\binom{2}{1,1,0}+\binom{4}{0,2,2}\binom{2}{2,0,0}\end{array}\right]\right]=6$$

$$A_{ac}(8,4,2,2)=\frac{1}{24}\left[4\binom{4}{2,1,1}+6\left[\begin{array}{l}\binom{4}{4,0,0}\binom{2}{0,1,1}+\binom{4}{2,2,0}\binom{2}{1,0,1}\\+\binom{4}{2,0,2}\binom{2}{1,1,0}+\binom{4}{0,2,2}\binom{2}{2,0,0}\end{array}\right]\right]=10$$

For $C_8H_3X_2Y_2Z$ and $(CH)_3X_2Y_2Z$

$$A_c(8,3,2,2,1)=\frac{1}{48}\left[\binom{8}{3,2,2,1}-6\left[\binom{4}{3,0,0,1}\binom{2}{0,1,1,0}+\binom{4}{1,2,0,1}\binom{2}{1,0,1,0}+\binom{4}{1,0,2,1}\binom{2}{1,1,0,0}\right]\right]=28$$

$$A_{ac}(8,3,2,2,1)=\frac{6}{24}\left[\binom{4}{3,0,0,1}\binom{2}{0,1,1,0}+\binom{4}{1,2,0,1}\binom{2}{1,0,1,0}+\binom{4}{1,0,2,1}\binom{2}{1,1,0,0}\right]=14$$

For C_8H_4XWYZ and $(CH)_4XWYZ$

$$A_c(8,4,1,1,1,1)=\frac{1}{48}\left[\binom{8}{4,1,1,1,1}-6\binom{4}{0,1,1,1,1}\binom{2}{2,0,0,0,0}\right]=32$$

$$A_{ac}(8,4,1,1,1,1)=\frac{1}{24}\left[6\binom{4}{0,1,1,1,1}\binom{2}{2,0,0,0,0}\right]=6$$

For $C_8H_3X_2WYZ$ and $(CH)_3\,X_2WYZ$

$$A_c(8,3,2,1,1,1)=\frac{1}{48}\left[\binom{8}{3,2,1,1,1}-6\binom{4}{1,0,1,1,1}\binom{2}{1,1,0,0,0}\right]=64$$

$$A_{ac}(8,3,2,1,1,1)=\frac{1}{24}\left[6\binom{4}{1,0,1,1,1}\binom{2}{1,1,0,0,0}\right]=12$$

For $C_8H_2X_2W_2YZ$ and $(CH)_2\,X_2\,W_2YZ$

$$A_c(8,2,2,2,1,1)=\frac{1}{48}\left[\binom{8}{2,2,2,1,1}-6\left[\binom{4}{2,0,0,1,1}\binom{2}{0,1,1,0,0}+\binom{4}{0,2,0,1,1}\binom{2}{1,0,1,0,0}+\binom{4}{0,0,2,1,1}\binom{2}{1,1,0,0,0}\right]\right]=96$$

$$A_{ac}(8,2,2,2,1,1)=\frac{1}{24}\left(6\left[\binom{4}{2,0,0,1,1}\binom{2}{0,1,1,0,0}+\binom{4}{0,2,0,1,1}\binom{2}{1,0,1,0,0}+\binom{4}{0,0,2,1,1}\binom{2}{1,1,0,0,0}\right]\right)=18$$

For $C_8H_2X_2UWYZ$ and $(CH)_2X_2UWYZ$

$$A_c(8,2,2,1,1,1,1)=\frac{1}{48}\left[\binom{8}{2,2,1,1,1,1}\right]=210$$

$$A_{ac}(8,2,2,1,1,1,1)=0$$

For $C_8H_2XPUWYZ$ and $(CH)_2XPUWYZ$

$$A_c(8,2,1,1,1,1,1,1)=\frac{1}{48}\left[\binom{8}{2,1,1,1,1,1,1}\right]=420$$

$$A_c(8,2,1,1,1,1,1,1)=0$$

For $C_8HXSPUWYZ$ and $(CH)XSPUWYZ$

$$A_c(8,1,1,1,1,1,1,1,1)=\frac{1}{48}\left[\binom{8}{1,1,1,1,1,1,1,1}\right]=840$$

$$A_{ac}(8,1,1,1,1,1,1,1,1)=0$$

These results predict the occurrence of $A_c(8,6,1,1)=0$ chiral and $A_{ac}(8,6,1,1)=$ 3 achiral isomers partitioned into $C_{3v}+2C_s'$ isomers for di-hetero-substituted cubane derivatives C_8H_6XY and its cubane di-hetero hetero-analogues $(CH)_6XY$. The tri-heterosubstituted cubane $C_8H_5X_2Y$ and cubane tri-hetero hetero-analogues $(CH)_5X_2Y$ give rise to $A_c(8,5,2,1)=$ 1C$_1$ chiral and $A_{ac}(8,5,2,1)=5\,C_s'$ achiral isomers. The series of tri-heterosubstituted cubane derivatives C_8H_5XYZ and cubane tri-hetero hetero-analogues $(CH)_5XYZ$ exhibit $A_c(8,5,1,1,1)=4$C$_1$ chiral and $A_{ac}(8,5,1,1,1)=6C_s'$ achiral skeletons. In the series of tetra-hetero-substituted cubane derivatives $C_8H_4X_2Y_2$ and their corresponding cubane tetra-hetero hetero-analogues$(CH)_4X_2Y_2$ the pattern inventory predicts the occurrence of $A_c(8,4,2,2)=6$, $A_{ac}(8,4,2,2)=10$chiral isomers partitioned into $4C_1+2C_2'$ and $C_s+4C_s'++3C_{2v}'+C_{2v}''+C_{2h}'$ then for the series C_8H_4XWYZ and $(CH)_4XWYZ$, $A_c(8,4,1,1,1,1)=32C_1$ chiral and $A_{ac}(8,4,1,1,1,1)=6C_s'$ achiral isomers skeletons respectively. The series of penta-heterosubstituted cubane derivatives $C_8H_3X_2Y_2Z$ and cubane penta-hetero hetero-analogues $(CH)_3X_2Y_2Z$ exhibit $A_C(8,3,2,2,1)=28C_1$ chiral and $14C_S'$-achiral skeletons. For the hexa-heterosubstituted cubane derivatives $C_8H_2X_2W_2YZ$ and their cubane hexa-hetero hetero-analogues $(CH)_2X_2W_2YZ$ the pattern inventory predicts the occurrence of $A_c(8,2,2,2,1,1)=96$ C_1-chiral and $A_{ac}(8,2,2,2,1,1)=18\ C'_s$-achiral isomers skeletons. The hexa-heterosubstituted cubane derivatives $C_8H_2X_2UWYZ$, $C_8H_2XPUWYZ$ and their related hexa-hetero hetero-analogues $(CH)_2X_2UWYZ$, $(CH)_2XPUWYZ$ exhibit $A_c(8,2,2,1,1,1,1)=210\,C_1$, $A_c(8,2,1,1,1,1,1,1)=420$ C_1-chiral isomers and $A_{ac}(8,2,2,1,1,1,1)=0$, $A_{ac}(8,2,1,1,1,1,1,1)=0$-achiral isomers skeletons respectively. The hepta-hetero substituted cubane derivatives $C_8HXSPUWYZ$ and their hepta hetero hetero-analogues $(CH)XSPUWYZ$ exhibit $A_c(8,1,1,1,1,1,1,1,1)=840$ C_1-chiral and $A_{ac}(8,1,1,1,1,1,1,1,1)=0$ achiral isomers. These results are summarized in table 4 and some illustrations given in fig.2 part II of this study.

Table 4. Numbers A_c of chiral, A_{ac} of achiral and $C_{he}=A_c+A_{ac}$ of diastereoisomers predicted for some series of di, tri, tetra, penta, hexa, hepta-heterosubstituted cubanes and cubane di,tri,tetra, penta, hexa,hepta,-hetero hetero-analogues.

$q_0,\ldots q_i,\ldots,q_k$	Heterosubstituted cubanes	Cubane hetero-hetero-analogues	A_c	A_{ac}	C_{he}	Occurring Symmetries
6,1,1	C_8H_6XY	$(CH)_6XY$	0	3	3	$C_{3v}+2C'_s$
5,2,1	$C_8H_5X_2Y$	$(CH)_5X_2Y$	1	5	6	$C_1+5C'_s$
5,1,1,1	C_8H_5XYZ	$(CH)_5XYZ$	4	6	10	$4C_1+6C'_s$
4,2,2	$C_8H_4X_2Y_2$	$(CH)_4X_2Y_2$	6	10	16	$4C_1+2C_2+4C'_s+C_s+3C_{2v}+C''_{2v}+C_{2h}$
3,2,2,1	$C_8H_4X_2Y_2Z$	$(CH)_3X_2Y_2Z_1$	28	14	42	$28C_1+14C'_s$
4,1,1,1,1	C_8H_4XWYZ	$(CH)_4XWYZ$	32	6	38	$32C_1+6C'_s$
3,2,1,1,1	$C_8H_3X_2WYZ$	$(CH)_3X_2WYZ$	64	12	76	$64C_1+12C'_s$
2,2,2,1,1	$C_8H_2X_2W_2YZ$	$(CH)_2X_2W_2YZ$	96	18	114	$96C_1+18C'_s$
2,2,1,1,1,1	$C_8H_2X_2UWYZ$	$(CH)_2X_2UWYZ$	210	0	210	$210C_1$
2,1,1,1,1,1,1	$C_8H_2XPUWYZ$	$(CH)_2XPUWYZ$	420	0	420	$420C_1$
1,1,1,1,1,1,1,1	$C_8HXSPUWYZ$	$(CH)XSPUWYZ$	840	0	840	$840C_1$

6 Concluding remarks

The procedure of bipartite combinatorial enumeration of substituted cubane derivatives and cubane homo hetero-analogues and cubane hetero hetero-analogues contains the following steps:

1-Determination of $\overline{P_{ro}H_8}$ and $\overline{P_{rr}H_8}$ the averaged weight of permutations generated respectively by 24 rotations and 24 rotoreflections of O_h acting on the substitutions sites.

2-Determination of permutations representations $\Delta_c H_8$ and $\Delta_{ac} H_8$ controlling the chirality and the achirality fittingness of the substitution sites of cubane.

3- Formulation of algebraic expressions (eqs.10-14 and eqs.17-29) for counting homogeneous and heterogeneous arrangements of substituents.

4- For cubane heteropolysubstituted cubane derivatives and cubane hetero hetero-analogues the solution of partition eqs. (18-19), (22-23), (26-27) is required to obtain pairs of integer sequences compatible with the sequences of partial degrees of heteropolysubstitution $q_0, q_1, \ldots, q_i, \ldots, q_k$.

5- Replacement of the right-hand side terms of $\Delta_c H_8$ and $\Delta_{ac} H_8$ by equivalent algebraic expressions obtained in step 3 to derive pairs of generic counting formulae (eqs.14-15 or 30-31).

6- Introduction in eqs. (14) - (15) or in eqs. (30) - (31) of appropriate data and computation of chiral and achiral isomers numbers A_c and A_{ac} for the series.

The applications of this algorithm yield congruent isomers figures [15] inventories for both substituted cubane derivatives and their corresponding cubane homo-heteroanalogues or hetero hetero-analogues. For the sake of comparison, the sum $A_c + A_{ac}$ obtained in each series matches up with Pólya's coefficients C_{ho} and C_{he} derived from cycle indices.[16] From these results at hand it remains to solve the problem of partition of A_c and A_{ac} stereoisomers among the sequence of subgroups of O_h. Part II of this work provides the methodology of the partition of such bulk stereoisomers numbers as sum of symmetry adapted isomers numbers (column 7 table 4) and presents their detailed illustrations by the graphs of fig.1 and 2.

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