

On the Theoretical Number of some Inositol-Tetramers

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Abstract

The numbers of possible tetramers of a selected subset of the nine known inositols have been calculated by manual as well as computer assisted approaches using the *MATHEMATICA* application program package ISOMERS. The evaluation of the number of possible achiral (*meso*-) forms of these tetramers is included.

Introduction

A rather simple sounding question was the starting point for this work: How many "tetramers" of four specific inositols, namely *neo*-, *muco*- *D-chiro* and *L-chiro* are there? Prof. Tomas Hudlicky of the Univ. of Florida, engaged in the synthesis of such compounds¹ posed this question to one of us (H.H.). The reason for this was the fact, that we had already published some sample applications², including some oligomers of inositols calculated with the help of the package ISOMERS³. From another point of view, the answer to such questions of course is interesting in connection with the increasing knowledge in the field of structural biology, where sugars and pseudosugars gain status as information - bearing macromolecules⁴. Doing combinatorial chemistry without the knowledge of just how many combinations are to be expected seems rather impractical.

Theoretically, there are nine inositols (1,2,3,4,5,6-hexahydroxy-cyclohexans), which are all known. They are depicted in Figure 1, along with their symmetry elements.

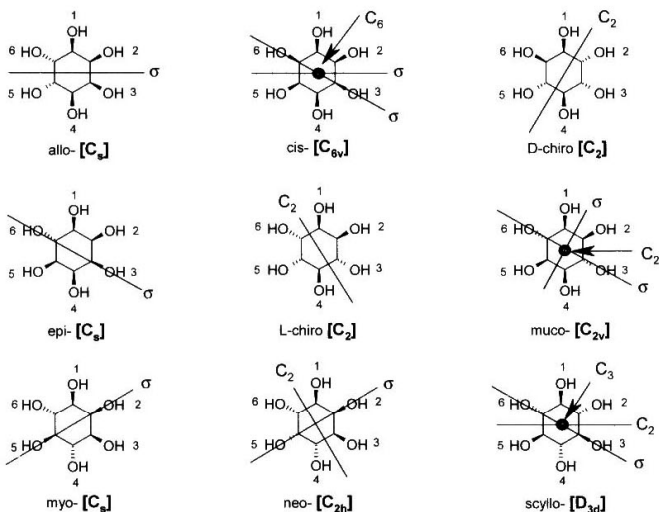


Figure 1: All nine inositols and their elements of symmetry including numbering for ISOMERS - input

Oligomers of inositols are formed by an ether linkage of two hydroxy functions. For the sake of simplification, we will use the terms "dimer", "trimer", "tetramer" and "oligomer" also for compounds formed by different inositols, although formally this is incorrect, since oligomers should be formed from identical units. For tetramers, there are two general forms possible, either by "linear" or by branched assembly resp. (Figure 2):

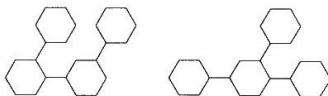


Figure 2: Examples for possible arrangements of tetramers (OHs omitted, ether linkage = single bond)

All possible substitutional patterns (1,2-; 1,3-; 1,4- as well as 1,5- and 1,6-, if applicable) at the inositols will be allowed, while cyclic oligomers, because of factual and practical reasons, will not be considered. Although cyclic analogs in principle are possible, e.g. the well known cyclodextrins, the cyclic assembly of such structures needs more than four units: The smallest cyclodextrin known, the α -form, starts with 6 units⁵.

By using the package ISOMERS, one can determine the general substitutional possibilities at the inositols mentioned above. We will limit this to three substituents, since this is the highest substitution necessary in our context (for branched tetramers). So the figures below give the numbers of isomers (including stereoisomers) in principle of the respective inositols with one, two or three different substituents, e.g. **A**, **B** and **C**. The results are summarized in Table 1⁶:







Substituents	1	2		3		
<i>Inositol</i>						
<i>allo-</i>	6	15	30	20	60	120
<i>cis-</i>	1	3	5	4	10	20
<i>D-chiro-</i>	3	9	15	10	30	60
<i>epi-</i>	6	15	30	20	60	120
<i>L-chiro-</i>	3	9	15	10	30	60
<i>muco-</i>	3	9	15	10	30	60
<i>myo-</i>	6	15	30	20	60	120
<i>neo-</i>	3	9	15	10	30	60
<i>scyllo-</i>	1	4	5	4	10	20

Table 1: Basic substitutional possibilities at inositols with up to three substituents

As can be easily seen, there is a clustering into three different substitutional patterns:

- (i) *allo-*, *epi-* and *myo-*inositols
- (ii) *cis-* and *scyllo-*inositols
- (iii) *D-* and *L-chiro-*, *muco-* and *neo-*inositols

This is due to their similar symmetry elements, although some of the inositols in a group differ in their structure and/or their elements of symmetry. These differences are only reflected in the number of stereoisomers, if one calculates the number of possible chiral and achiral forms upon substitution, a feature also included within ISOMERS⁷. The respective numbers then read as follows (Table II):







Substituents	1	2		3		
Inositol						
<i>allo-</i>	6 [0]	12 [3]	30 [0]	20 [0]	60 [0]	120 [0]
<i>cis-</i>	0 [1]	0 [3]	4 [1]	2 [2]	8 [2]	20 [0]
<i>D-chiro-</i>	3 [0]	9 [0]	15 [0]	10 [0]	30 [0]	60 [0]
<i>epi-</i>	4 [2]	12 [3]	28 [2]	16 [4]	56 [4]	120 [0]
<i>L-chiro-</i>	3 [0]	9 [0]	15 [0]	10 [0]	30 [0]	60 [0]
<i>muco-</i>	2 [1]	6 [3]	14 [1]	8 [2]	28 [2]	60 [0]
<i>myo-</i>	4 [2]	12 [3]	28 [2]	16 [4]	56 [4]	120 [0]
<i>neo-</i>	2 [1]	6 [3]	14 [1]	8 [2]	28 [2]	60 [0]
<i>scyllo-</i>	0 [1]	2 [2]	4 [1]	2 [2]	8 [2]	20 [0]

Table II: Chiral [achiral] stereoisomers on substitution of inositols with up to three substituents

Already at this stage it can easily be seen, that manual construction of all possibilities is virtually impossible. Now *allo-* differs from *epi-* and *myo* [σ in *allo-* goes through edges (bonds), while in *epi-* and *myo-*, σ goes through corners (atoms) of the graph]. Similarly to the "identity" with respect to symmetry of *epi-* and *myo*-inositol, *muco-* and *neo*-inositol show still the same pattern (C_2 plus σ).

Calculations

1. Tetramers made of the four different inositols *D-chiro-*, *L-chiro-*, *muco-* and *neo-*:

1.a. Linear tetramers:

There are 12 linear "tetramers" of the general form **A-B-C-D** (ref. 8, line 15). From table I it can be easily depicted, that all four inositols show the same pattern for mono- and disubstitution if all substituents are different: Three different positions for mono- and 15 for disubstitution. The monosubstitution applies for the outer "monomers" (**A** and **D**), while for the inner inositols (**B** and **C**), the disubstitutional pattern can be applied. Thus any pattern of a linear tetramer made of these four inositols would have $3 * 15 * 15 * 3 = 2,025$ isomers. So there are $12 * 2,025 = \underline{24,300}$ linear tetramers possible.

1.b. Branched tetramers:

There are 4 different "stars" possible made of four different inositols of the general form



(ref. 9, line 2). Again from table I we learn, that for all four inositols under consideration, there are 60 substitutional patterns possible with three different inositols located on a central fourth one. All these "substituents" exhibit three possibilities for their attachment (table I). Thus there are: $4 * 60 * 3 * 3 * 3 = \underline{6,480}$ branched tetramers of this particular kind of tetramer.

So in summary, there are $24,300 + 6,480 = \underline{30,780}$ tetramers in total made of the four specific and different inositols *D-chiro-*, *L-chiro-*, *muco-* and *neo-*.

1.c. Stereochemical considerations

As can be seen from Table II, naturally all possible substitutional patterns in the *chiro*-inositols are chiral, while for the disubstitution of *muco*- and *neo*-inositols, there should be just one *meso*-form. So there should be a single *meso*-dimer that can only be of the following form:

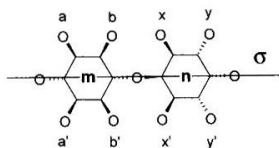


Figure 3: The only achiral (= *meso*) form of the dimer *muco* (*m*) - *neo* (*n*)

One could argue though, that there should be three more forms of such dimers by different orientations (up and down) at the ether linkage, as e.g. depicted in Figure 4:

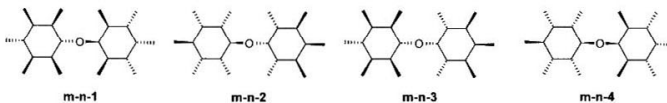
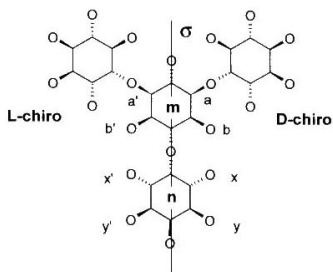


Figure 4: Possible *m-n*-dimers which are all identical

For readers not so familiar with stereochemical views and rotations of molecules, the use of molecular models (e.g. DreidingTM or MinitTM) is recommended. Imagine a kind of an axis through the ether linkage, then **m-n-2** is derived from **m-n-1** by a simple 180° rotation around this axis, while in **m-n-3** only the right ring has been rotated. Structure **m-n-4** again is derived from **m-n-3** by a rotation of the whole molecule. Also ring-flips, which are quite common in cyclohexane derivatives, would do the job. Within the dimer shown in Figure 3, there are four positions linked by the plane of symmetry: a, b, x and y together with their prime- equivalents. Since the remaining inositols for the construction of the tetramers are of the enantiomeric *chiro*-type, there exists the possibility to produce *meso* forms of the type depicted in Figure 5:

Figure 5:
Example for *meso*-forms in
branched tetramers



Within this general structure, there are 3 positions each in the respective *chiro*-inositols leading to such branched *meso* compounds, thus there are 4 (positions a , b , x and y) $\cdot 3$ (positional possibilities on *chiro*-inositols) = 12 achiral meso forms to be expected.

Within the linear series of tetramers, due to the presence of the chiral *chiro*-inositols and the different nature of all four individual inositols, there are only chiral isomers.

2. Tetramers made of the four different inositols *D-chiro*-, *L-chiro*-, *muco*- and *neo*-, allowing all possible combinations:

In order to tackle this problem we will start with dimers and trimers to show the principle of our approach. Substituting inositols by inositols means they function as central unit as well as a ligand. With the information of *Table 1* we know, that each inositol considered here has the possibility to render three different monosubstituted products. Taken the other way round, this means that each inositol provides three different ligands. Therefore we have to consider the set of ligands (*muco*1, *muco*2, ... up to ... *L-chiro*3) which has $n = 12$ elements. The different disubstitutional possibilities will be presented in chapter 2.b.

2.a. Dimers:

From ISOMERS we learn, that in general, there are n symmetrical **A-A**-dimers (ref. 8, line 2), that is (with n being 12) 12 symmetrical dimers. Similarly there are $n \cdot (n - 1) / 2$ asymmetrical **A-B**-dimers (ref. 8, line 3) and the equation for $n = 12$ thus yields 66

asymmetrical dimers. In summary there are $n*(n + 1) / 2 = 78$ dimers in total (ref. 8, line 4).

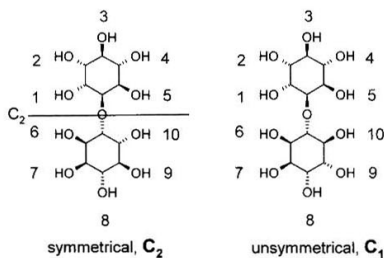


Figure 6: Examples for symmetrical and asymmetrical chiro-dimers

At such inositol dimers, there are the following general substitutional possibilities¹⁰ (see Table III):

Substituents	X	X,X	X,Y	Sum for 2 substituents
Inositol Dimer				
symmetrical	$5n$	$25n$	$45n*(n - 1) / 2$	$5n*(9n + 1) / 2$
asymmetrical	$10n$	$45n$	$45n*(n - 1)$	$45n^2$

Table III: Positional possibilities at Inositol - dimers on mono- and disubstitution

2.b. Trimers:

From ISOMERS (ref. 11, lines 1-3) we know, that the following disubstitutional possibilities at our 4 inositols are given:

A-z-A :	$9n$	therefrom $3n$ are C_2 - symmetrical ($= 1 / 3$), see Figure 7
A-z-B :	$15n*(n - 1) / 2$	all C_1
Sum :	$3n*(5n + 1) / 2$	

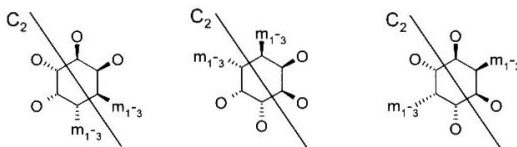


Figure 7: Examples for symmetrical **m-n-m**-trimers

As the number of substituents (n) we take the monosubstitutional possibilities of our four inositols under consideration (3 for each inositol), that is $4 * 3 = 12$, and thus we get:

A-z-A: $n = 12$, 4 different z; $9n = 108$; $* 4 = 432$, 144 thereof C_2 -symm

A-z-B: $n = 12$; $15n(n - 1) / 2 = 990$; $* 4 = 3,960$,

Sum: $n = 12$; $3n*(5n + 1) / 2 = 1,098$; $* 4 = 4,392$

Thus there are 4,392 trimers possible for all combinations of the four inositols under consideration.

Another approach would be:

Let us consider a trimer made of a central *neo*- and two *muco*- inositols, the latter having 3 monosubstitutional possibilities each: **m1**, **m2** and **m3**. Then obviously for the **AA**-pattern, which will each have 9 possibilities, there are three basic forms possible: **m1-n-m1**, **m2-n-m2** and **m3-n-m3**. Thus, there are $9 \times 3 = 27$ trimers of this type. For the **AB**-pattern, which is present 15 times at n , there are likewise three basic forms possible: **m1-n-m2**, **m1-n-m3** and **m2-n-m3**. Thus there are 3 times 15 trimers of this type (= 45) and in summary 72 *neo(muco)*₂- trimers. This number we also get by putting in $n = 3$ in the general formula for a disubstituted *neo*-inositol with all combinations (ref. 11, line 3): $3n*(5n + 1) / 2$ is exactly 72 for $n = 3$.

Thus there are the following 40 combinations possible for general trimers (ref. 8, line 9)

Type	possible inositol combinations for each type	isomers
4 * AAA	72 [3 * 9 (sym) + 3 * 15 (asym)]	288
12 * AAB [*]	135 [3 * 15 * 3]	1,620
12 * ABA [*]	72 [3 * 9 (sym) + 3 * 15 (asym)]	864
12 * ABC	135	1,620
<u>Sum of trimers</u>		<u>4,392</u>

[*] The 24 types **AAB** (ref. 8, line 7: {2,1}) have to be split in 12 **AAB** and 12 **ABA** because of different symmetry!

2.c. Branched tetramers:

This is straightforward: In inositol structures like



the sum of trisubstitution is given by ISOMERS (ref. 11, line 4) as follows: $10n^3$. For $n = 12$ and 4 different central **z** this then amounts to $10 \cdot 12^3 \cdot 4 = 4 \cdot 17,280 = \underline{69,120}$ branched tetramers.

2.d. Linear tetramers:

Now, we will consider all possible combinations of the four inositols under consideration, i.e. also isomers of the form **A-A-A-A**, **A-A-A-B** etc. up to **D-D-D-D**. From ISOMERS we learn, that there are $(n^4 + n^2) / 2$ possible combinations (ref. 8, line 16), which results in 136 for $n = 4$. The considerations regarding the individual substitutional positions given in chapter 1.a. are still valid, but we have to use all patterns (**AA**, **AB**, **BB**) of table I, like $9 + 15 + 9 = 33$. The coefficient 15 we already used in chapter 1. Thus it would be appropriate to simply calculate, that there are $136 \cdot 3 \cdot 3 \cdot 33 \cdot 33 \cdot 3 = 1,332,936$ linear tetramers of the multiple occurrence forms possible. But caution is warranted, since our different substituents are taken from a sample of sometimes identical structures. So the provision of chapter 1, that all four inositols forming the tetramer are different, is no longer valid. Thus, we use two different approaches:

2.d.1. Combining two dimers

From chapter 2.a. we know, that there are 12 symmetrical dimers (S) with 5 monosubstitutional positions (s1) as well as 66 asymmetrical dimers (U) with 10 monosubstitutional positions (s2).

Simple combinatorics thus yields: isomers

$$S + S: \quad S * s1 * (S * s1 + 1) / 2 \text{ [§]} \quad 1,830$$

$$S + U: \quad S * s1 * U * s2 \quad 39,600$$

$$U + U: \quad U * s2 * (U * s2 + 1) / 2 \text{ [§]} \quad 218,130$$

$$\text{Sum of linear tetramers} \quad 259,560$$

[§] half matrix including diagonal

2.d.2. From the general patterns of linear tetramers:

In analogy to the second approach in chapter 2.b. let us consider tetramers made from two *neo*- (**n** or **N**) and two *muco*-inositols (**m** or **M**), e.g. of the form: **m-N-M-n**. If they are located at the outside (**n** or **m**), they will exhibit three monosubstitutional positions each. As "inner" monomers (**M** or **N**) they will invariably exhibit 15 disubstitutional possibilities, because there are no symmetrical disubstitutions possible at those: such **N** or **M** invariably will have a monomer and a dimer as substituents. So simple combinatorics will give $3 * 15 * 15 * 3 = 2,025$ tetramers for e.g. **m(1-3)-N(1-15)-M(1-15)-n(1-3)**. But for symmetrical tetramers of the form **n-M-M-n** or **m-M-M-m**, there obviously are some identical forms, e.g. **n2-M7-M7-n2**. Thus for those, we use the already known approach of the dimers (chapter 2.d.1.): The $3 * 15 = 45$ "halves" of these symmetrical tetramers can be combined like the S + S dimers there: $45 * (45 + 1) / 2 = 1,035$ (half matrix including diagonal).

Thus, for general linear tetramers with 4 units we found (ref. 8, line 11-15)

Type	possible combinations for each type	isomers
4 * AAAA	1,035 [45 * 46 / 2 = half matrix including diagonal]	4,140
24 * AAAB	2,025 [3 * 15 * 15 * 3]	48,600
12 * AABB [§]	2,025 [3 * 15 * 15 * 3]	24,300
12 * ABBA [§]	1,035 [as for AAAA]	12,420
72 * AABC	2,025 [3 * 15 * 15 * 3]	145,800
12 * ABCD	2,025 [3 * 15 * 15 * 3]	24,300
<u>Sum of linear tetramers</u>		<u>259,560</u>

[§] The term of the 24 **AABB** [{2,2}] has to be split into 12 **AABB** and 12 **ABBA** because of symmetry reasons in analogy to chapter 2.b.

Thus there are 69,120 (branched) and 259,560 (linear) = 328,680 tetramers in total made of the four inositols mentioned above.

2.e. Stereochemical considerations

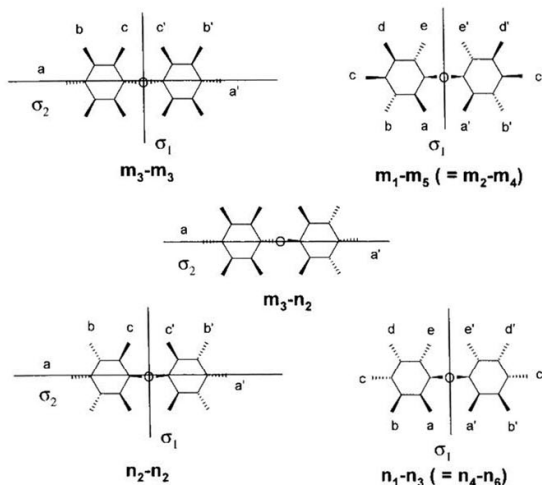
In the context of all possible combinations of the four inositols under consideration, the estimation of all chiral/achiral isomers is much more tedious than given under chapter 1. The first principle valid in this respect is: Whenever one chiro-inositol is involved, the final combination will be chiral. But there exists the possibility to build *meso*-structures from two (or powers of two) enantiomeric chiral molecules, as already mentioned in chapter 1.c. So achiral combinations to be considered will be made of *neo* and/or *muco*-inositol alone or in combination with the two enantiomeric *chiro*-inositols as a D/L-pair (some special cases have been discussed already in chapter 1.c.) or from two D/L- pairs of *chiro*-inositols.

2.e.1. *muco*- and *neo*-inositols exclusively:

2.e.1.1. Linear tetramers from **m** and **n**:

The achiral positions at these inositols are aligned along the plane of symmetry σ . As "chiral positions" we define all those at achiral molecules (like seven of the nine inositols), which are rendered chiral upon substitution. Likewise, "achiral positions" are those, which do not yield chiral products upon substitution (with achiral substituents). But, as can be seen from *Table II*, for *muco* and *neo*-inositols there exist three (and not just only one) achiral symmetrical

disubstituted products. Thus, e.g. for *neo*-inositol, there exist not only the achiral disubstituted product at positions 2 and 5 (*Figure 1*) but also at positions 1 and 3 as well as at 2 and 4. The latter positions (1/3 and 2/4) we will call enantiotopic.



*Figure 8: Achiral Dimers **m-m**, **m-n** and **n-n** Including Substitutional Sites for Achiral Connections of Identical or Enantiomeric Substituents to form Linear Tetramers*

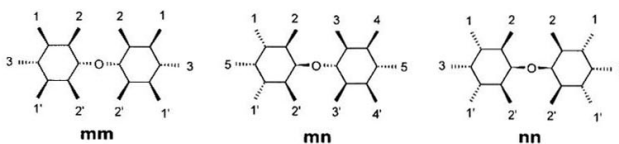
In *Figure 8*, the subscripts (e.g. **m₅** or **n₂**) denominate the respective numbering of positions at the inositols from *Figure 1*. As can be seen from *Figure 8* there exist the following achiral dimers from *muco*- and *neo*-inositols: Two **m-m**, two **n-n** and one **m-n**. For achiral linear tetramers, σ_1 is important, while σ_2 will play the prominent role in the case of achiral branched tetramers (chapter 2.e.1.2.). Through the connecting oxygen, perpendicular to the plane of this paper, there goes a C_2 for all symmetrical dimers (**m-m** and **n-n**), thus reducing the possible number of three forms to just two. *Figure 8* exemplifies the following facts: There are three positions (a, b and c) in the number symmetrical dimers **m₃-m₃** and **n₂-n₂** and five positions in the number - asymmetrical dimers **m₁-m₅** and **n₁-n₃** which - together with their prime equivalents - can yield achiral linear tetramers on disubstitution. For tetramers

made solely from the two inositols **m** and **n**, with three monosubstitutional possibilities each (one achiral, two enantiotopic) this gives the following numbers of tetramers:

m-m₁-m₅-m:	15	m-m₃-m₃-m:	8	m-m₃-m₃-n:	1
m-m₃-n₂-m:	1	m-m₃-n₂-n:	1	m-n₁-n₃-m:	15
m-n₂-n₂-m:	8	m-n₂-n₂-n:	1	n-m₁-m₅-n:	15
n-m₃-m₃-n:	8	n-m₃-n₂-m:	1	n-m₃-n₂-n:	1
n-n₁-n₃-n:	15	n-n₂-n₂-n:	8		

Thus in total, there are 98 achiral linear tetramers made from *muco*- and/or *neo*-inositols solely.

2.e.1.2. Branched tetramers from **m** and **n**:



*Figure 9: Achiral Dimers **mm**, **mn** and **nn** Including Substitutional Sites for Achiral Connections of Identical or Enantiomeric Substituents to form Branched Tetramers*

As can be seen from *Figure 9*, there are two positional pairs for connecting identical substituents in an achiral manner to **n-n**-dimers as well as to **m-m**-dimers (positions 1 and 2 together with their prime equivalents) to build branched tetramers. Positions 3 yield linear tetramers (chapter 2.e.1.1.). Similarly, for **m-n**-dimers, there are 4 pairs (positions 1 to 4 together with their prime equivalents), positions 5 already included in chapter 2.e.1.1. (linear case). Thus there are 2 possibilities x 3 monosubstitutional sites at **n** or **m** to be attached at **n-n** and **m-m**-dimers:

$2 \times 3 (\mathbf{n-n} + 2 \mathbf{n})$; $2 \times 3 (\mathbf{n-n} + 2\mathbf{m})$; $2 \times 3 (\mathbf{m-m} + 2\mathbf{n})$; $2 \times 3 (\mathbf{m-m} + 2\mathbf{m}) = 24$ tetramers.

For **m-n**-dimers there are 4 possibilities x 3 monosubstitutional sites and thus:

$4 \times 3 (\mathbf{m-n} + 2\mathbf{n})$ and $4 \times 3 (\mathbf{m-n} + 2\mathbf{m}) = 24$ tetramers. Thus, in summary there are $24 + 24 = 48$ achiral tetramers of the branched type made from **m** and/or **n** inositols solely.

2.e.2. *muco-* and/or *neo-*inositols together with a D/L-pair of *chiro*-inositols (**D & L**):

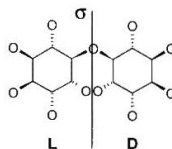
The situation is a little more complex for these combinations. Besides the twelve branched achiral forms already mentioned in chapter 1.c. (*Figure 5*) from **m-n + D & L**, the combinations **n-n + D & L** as well as **m-m + D & L** have to be considered. From *Figure 8* and *Figure 9* as well as from the discussion in the preceding chapter, we know that there are two pairs of related positions for branched and one pair for linear tetramers of this sort **m-m** as well as in **n-n** - achiral dimers. Due to the three different substitutional sites in **D** and **L**, there are 8 times three linear possibilities each of the structures **D-n-n-L** and **D-m-m-L** (48 linear isomers). And in the branched series there are 12 x **m-n(D)-L** (from chapter 1.c.) + 6 x **m-m(D)-L** + 6 x **n-n(D)-L** isomers. Thus there are 24 branched and 48 linear achiral isomers in this group.

In addition, there is the possibility of having a central **D & L** - pair (see *Figure 10*) as in chapter 2.c.3. to which there can be attached either 2 **n** or 2 **m** (at five possible positions). Thus there are 3 (*meso*- **D & L** - pairs) x 5 (positions at those) x 3 (monosubstitutional sites at both **n** or **m**) x 2 (**n** or **m**) isomers. This yields 90 achiral tetramers of this sort, which are all linear.

2.e.3. D- and L-*chiro* - inositols exclusively:

As stated above, there are three *meso*-forms possible for a dimer made of a **D & L** - pair (*Figure 10*):

Figure 10: One of three possible meso-dimers made from D- and L-chiro - inositol



As can be seen from *Figure 10*, at such dimers there are 5 positions related by a plane of symmetry, which can lead to achiral *meso* forms on appropriate substitution (by **D** and **L**). But there are two *meso* possibilities of attaching these inositols to the central dimer: **D-L-D-L** and **L-L-D-D**. Thus there are 3 (forms of *meso*-dimers: **L₁-D₁**, **L₂-D₂** and **L₃-D₃**) x 5 ("meso-positions") x 3 (monosubstitutional positions at **D** and **L**, counted only once because of

symmetry-relation) x 2 (possible *meso*-arrangements) = 90 achiral *meso*-tetramers made from two D- & L- pairs of *chiro*- inositols, which are all linear.

Summary and conclusions:

The results from chapters 1. and 2. are summarized in Table IV:

Tetramers	Linear	Branched	Sum
m+n+D+L; (all four different)	24,300	6,480	30,780
[Achiral isomers thereof]	0	12	12
m,n,D,L; (all combinations)	259,560	69,120	328,680
[Achiral isomers thereof]	326	72	398

Table IV: Number of Tetramers made from D- & L-chiro, muco- and neo-Inositols

- As can be seen from this compilation, the number of possible tetramers in our selected sample of inositols increases dramatically (approximately tenfold), if combinations of all sorts with multiple occurrences of a specific inositol within the tetramer are allowed.
- The second observation is the fact, that - although there are still some quite close examinations necessary - the use of the results obtained from the program package ISOMERS can help considerably in such enumerations.
- The third observation touches the fact, that the estimation of achiral forms in such molecules with highly populated "chiral positions" entails further pottering about. A concise, straightforward computational method for the estimation of such isomers seems highly desirable, but within now lies well beyond our computational possibilities. Substitution with chiral structures at "chiral positions" renders the whole problem again more complicated. With this paper we would like to make a contribution in this direction to spur on potential theoreticians for better (simpler) solutions¹².
- These facts still impede our efforts towards a compilation of all possible combinations including all nine known inositols. We will try to tackle this problem in the future, provided a general algorithm for such problems can be found¹³. Up to our knowledge, even the very useful package MOLGEN¹⁴ does not allow for stereochemical and/or symmetrical input.

- NumberOfIsomers[Muco, {3}] {= 10}
 NumberOfIsomers[Muco, {2,1}] {= 30}
 NumberOfIsomers[Muco, {1,1,1}] {= 60}
- [7]

NumberOfAchiralIsomers[Muco, {1}] {= 1}

NumberOfAchiralIsomers[Muco, {2}] {= 3}

NumberOfAchiralIsomers[Muco, {1,1}] {= 1}

NumberOfAchiralIsomers[Muco, {3}] {= 2}

NumberOfAchiralIsomers[Muco, {2,1}] {= 2}

NumberOfAchiralIsomers[Muco, {1,1,1}] {= 0}
- [8]

(1) DefineParentCompound[Dimer, {R[2,1],R_σ[2,1]}]

(2) NumberOfIsomers[Dimer, {2},n] {= n; for n = 12: 12}

(3) NumberOfIsomers[Dimer, {1,1},n] {= n*(n - 1) / 2; for n = 12: 66}

(4) NumberOfIsomers[Dimer, 2, n] {= n*(n + 1) / 2; for n = 12: 78}

(5) DefineParentCompound[Trimer, {R[3,2,1],R_σ[3,2,1]}]

(6) NumberOfIsomers[Trimer, {3},4] {= 4}

(7) NumberOfIsomers[Trimer, {2,1},4] {= 24}

(8) NumberOfIsomers[Trimer, {1,1,1},4] {= 12}

(9) NumberOfIsomers[Trimer, 3,n] {= n²*(n + 1) / 2; for n = 4: 40}

(10) DefineParentCompound[LinTetramer, {R[4,3,2,1],R_σ[4,3,2,1]}]

(11) NumberOfIsomers[LinTetramer, {4}] {= 4}

(12) NumberOfIsomers[LinTetramer, {3,1}] {= 24}

(13) NumberOfIsomers[LinTetramer, {2,2}] {= 24}

(14) NumberOfIsomers[LinTetramer, {2,1,1}] {= 72}

(15) NumberOfIsomers[LinTetramer, {1,1,1,1}] {= 12}

(16) NumberOfIsomers[LinTetramer, 4, n] {= (n⁴ + n²) / 2; for n = 4: 136;

(17) for n = 2: 10}
- [9]

(1) DefineParentCompound[BranchTetramer, {R[1,4,2,3],R_σ[1,2,4,3],R_σ[1,3,2,4]}]

(2) NumberOfIsomers[BranchTetramer, {1,1,1,1}] {= 4}
- [10] Numbering as in *Figure 6*:

DefineParentCompound[SymInosDimer, {R[6,7,8,9,10,1,2,3,4,5]}]

NumberOfIsomers[SymInosDimer, 1,n] {= 5n}

NumberOfIsomers[SymInosDimer, {2},n] {= 25n}

NumberOfIsomers[SymInosDimer, {1,1},n] {= 45n*(n - 1) / 2}

NumberOfIsomers[SymInosDimer, 2,n] {= 5n*(9n + 1) / 2}

DefineParentCompound[AsymInosDimer, {R[1,2,3,4,5,6,7,8,9,10]}]

NumberOfIsomers[AsymInosDimer, 1,n] {= 10n}

NumberOfIsomers[AsymInosDimer, {2},n] {= 45n}

NumberOfIsomers[AsymInosDimer, {1,1},n] {= 45n*(n - 1)}

NumberOfIsomers[AsymInosDimer, 2,n] {= 45n²}
- [11]

(1) NumberOfIsomers[Muco, {2}, n] {= 9n}

(2) NumberOfIsomers[Muco, {1,1},n] {= 15n*(n - 1) / 2}

(3) NumberOfIsomers[Muco, 2, n] {= 3n*(5n + 1) / 2}

(4) NumberOfIsomers[Muco, 3, n] {= 10n³}

- [12] Within our knowledge, there are no general approaches to this problem. There are several chemical structure packages on the market or the web resp., but neither contains any useful information in this direction. See e.g.:
<http://www.daylight.com/dayhtml/doc/theory/theory.toc.html#Table of Contents> or :
http://library.wolfram.com/conferences/devconf99/nachbar/Links/index_inl_6.html or
<http://www.biocheminfo.org/klotho/>
One of the referees pointed out, that there are some theoretical approaches to the problem of substitution by chiral substituents, see e.g. the nice review on double-cosets: Ruch, E. ; Klein, D. J. Double Cosets in Chemistry and Physics. *Theor. Chimica Acta* **1983**, *63*, 447-472. Of course, there are other approaches too, like part of the work of S. Fujita on the unit-subduced cycle index approach: See e.g. Fujita, S. Benzene Derivatives with Achiral and Chiral Substituents and Relevant Derivatives Derived from D_{6h} Skeletons. Symmetry-Itemized Enumeration and Symmetry Characterization by the Unit-subduced Cycle Index Approach. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 151-163. But both approaches are rather mathematically oriented and do not spare the ordinary chemist the tedious work of close examination of the symmetries of the individual molecules involved.
- [13] In a review article on carbohydrates [1.Indhorst, T. K. *Chem. i.u. Zeit* **2000**, *34*, 38-52] there is a table relating to the difference between oligomer counts in peptides and in carbohydrates, which shows the number of 34,560 isomers for a tetrasaccharide, provided combinations of four different monosaccharides are considered. This number thus is in almost the same order of magnitude with our results, although there is quite some structural difference between monosaccharides and inositols. There is also one other paper on the enumeration of (acyclic) deoxyalditols, but this method cannot be applied to our problem: Nemba, R. M. ; Fah, M. On the Application of Sieve Formula to the Enumeration of Stable Stereo and Position Isomers of Deoxyalditols. *Tetrahedron* **1995**, *51*, 3831-3840.
- [14] <http://www.mathe2.uni-bayreuth.de/molgen/mg31.html>