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Study on Structure – Activity Relationship of Organic Compounds —Applications of a New Highly Discriminating Topological Index

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Abstract

In this paper, a new highly discriminating topological index $EATI_1$ is proposed based on the extended adjacency matrix, and, used in structure-property relationship (QSPR) and structure-activity relationship (QSAR) studies. Satisfactory results have been obtained by using $EATI_1$ to predict the physical and chemical properties and biological activities of some organic compounds.

1. Introduction

It is well know that the chemical behavior of a compound is dependent upon its structure. Quantitative structure–activity relationships (QSAR) and quantitative structure –property (QSPR) relationships have been shown to be a powerful research tool and are being used in many fields. The two major types of molecular predictors used in QSAR/ QSPR are: (i) parameters that bear relation to free energy and usually represent some important physicochemical properties of molecules, e.g., hydrophobic, electronic, and steric parameters, and (ii) topological indices which are numeric quantities that are mathematically derived from the structure graph of a molecule. In recent years, the latter type of predictor has gained substantial attention in explaining biological activities and physical and chemical properties of organic compounds. Many topological indices such as the Wiener index[1 - 3], Randic index [4], Hosoya index[5], and Balaban index[6] etc, have been proposed to convert chemical structure into numerical values. However, there are only few topological indices which can be used to describe the molecular structures containing multiple bonds and heteroatoms. At present, one of the most popular indices is the molecular connectivity descriptor suggested by Kier and Hall[7]. The index general a_N put forward by Xu et al[8,9], has also been successfully used in QSAR studies of neutral phosphorus extractants and in discrimination of cis/ trans isomers. Except that topological indices can be applied to QSAR/ QSPR studies, they can also be used for structure encoding of organic compounds. For this, superior discriminability must be possessed by indices. Over a hundred of topological indices have been described, but only Balaban's BID[10] index was shown to have a remarkable discriminating power, not reaching its initial degenerate value with alkane isomers containing 20 carbon atoms.

Recently, two new topological indices have been suggested by our laboratory, named $EATI_1$ and $EATI_2$. They describe the molecular structure not only of alkanes but also of molecules containing heteroatoms, multiple bonds and rings. The $EATI_1$ index as $EATI_2$[11] is also a highly discriminative descriptor, which can differentiate all the isomers, acyclic alkanes up to n=20. Simutaneously, the $EATI_1$ index shows a fairly good quality in structure-property/ activity correlation studies. In this paper our

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attention is focused on the correlation studies, thus, the selectivity on $EATI_1$ index will be only briefly discussed.

2 Method

Topological index $EATI_1$ proposed by us is generated from the invariant of a weighted graph of a compound, i.e., using different weights from atoms and bonds. In this paper, covalence radii and the number of the valence electrons of an atom are used to describe heteroatoms, and "1","2","3" are assigned to single, double and triple bonds, respectively.

The topological index $EATI_1$ is defined as follows.

(1) The adjacency matrix A is: $A=\{a_{ij}\}$. where,

$$a_{ij}=\begin{cases}0 & \text{if the vertices i and j are not neighbors}\\ 1 & \text{if the vertices i and j are neighbors with sigle bond}\\ 2 & \text{if the vertices i and j are neighbors with double bond}\\ 3 & \text{if the vertices i and j are neighbors with triple bond}\end{cases}$$

Then, the adjacency matrix A is extended to $EA=\{(ea)_{ij}\}$, whereas $(ea)_{ij}$ is defined as:

$$(ea)_{ij}=\begin{cases}\dfrac{\sqrt{(Radii)_i}}{6} & i=j\\ \dfrac{(\sqrt{a_{ij}})*W_{ij}}{6} & i\neq j\end{cases}$$

where, $(Radii)_i$ represents the covalence radii of an atom, W_{ij} is the weight of an edge connecting two atoms, which is calculated using the following equation,

$$W_{ij}=\frac{1}{\sqrt{\delta_i^v*\delta_j^v}}.$$

$$\delta^v=Z^v-h$$

where, Z^v is the number of valence electrons of atom i or atom j, h shows the number of hydrogen atoms attached to atom i or atom j.

(2) The sum of power series of EA matrix EA^* is:

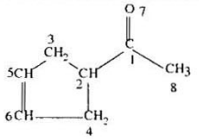
$$EA^*=\sum_{k=0}^{N-1}(EA)^k$$

where N represents the number of atoms in a molecule. When k=0, $(EA)^0$ is a unit matrix in above equation.

(3) Topological index $EATI_1$ is obtained finally by summing the squares of the diagonal elements of matrix EA^*.

$$EATI_1=\sum_{i=1}^{N}\left[(ea^*)_{ii}\right]^2$$

where, $(ea^*)_{ii}$ is the diagonal element of matrix EA^*. For instance, the structure graph, the corresponding matrix and the calculation results of $EATI_1$ index of structure I are shown as follows.



Structure I

$$A=\begin{vmatrix}0&1&0&0&0&0&2&1\\1&0&1&1&0&0&0&0\\0&1&0&0&1&0&0&0\\0&1&0&0&0&1&0&0\\0&0&1&0&0&2&0&0\\0&0&0&1&2&0&0&0\\2&0&0&0&0&0&0&0\\1&0&0&0&0&0&0&0\end{vmatrix}$$

Adjacency matrix A

0.14634434	0.28867513	0.00000000	0.00000000	0.00000000	0.00000000	0.28867513	0.50000000
0.28867513	0.14634434	0.40824829	0.40824829	0.00000000	0.00000000	0.00000000	0.00000000
0.00000000	0.40824829	0.14634434	0.00000000	0.40824829	0.00000000	0.00000000	0.00000000
0.00000000	0.40824829	0.00000000	0.14634434	0.00000000	0.40824829	0.00000000	0.00000000
0.00000000	0.00000000	0.40824829	0.00000000	0.14634434	0.47140452	0.00000000	0.00000000
0.00000000	0.00000000	0.00000000	0.40824829	0.47140452	0.14634434	0.00000000	0.00000000
0.28867513	0.00000000	0.00000000	0.00000000	0.00000000	0.00000000	0.14337209	0.00000000
0.50000000	0.00000000	0.00000000	0.00000000	0.00000000	0.00000000	0.00000000	0.14634434

EA matrix

2.49913859	1.25705111	0.62589398	0.62589398	0.37436718	0.37436718	0.78618944	0.36603888
1.25705111	2.84353607	1.64521457	1.64521457	1.15329190	1.15329190	0.35570921	0.61787380
0.62589398	1.64521457	2.46299949	1.09125461	1.56894120	1.14326258	0.16517986	0.28681574
0.62589398	1.64521457	1.09125461	2.46299949	1.14326258	1.56894120	0.16517986	0.28681574
0.37436718	1.15329190	1.56894120	1.14326258	2.62983350	1.74961996	0.08566207	0.14868664
0.37436718	1.15329190	1.14326258	1.56894120	1.74961996	2.62983350	0.08566207	0.14868664
0.78618944	0.35570921	0.16517986	0.16517986	0.08566207	0.08566207	1.40879638	0.41946705
1.36603888	0.61787380	0.28681574	0.28681574	0.14868664	0.14868664	0.41946705	1.90022957

EA^* matrix

$EATI_1$=18.83736659

The program for computing $EATI_1$ index is devised by our laboratory, which was written in C language, and installed on a PC/ 486.

3 Application to correlation

Topological indices developed for the purpose of obtaining correlations with physicochemical properties and biological activities of chemical substances have been applied extensively. The current major applications include bibliographical species classification, physicochemical parameter evaluation, and pharmaceutical drug design. In this section, the main application of the $EATI_1$ index is to give correlation with logP values (P=partition coefficient between n-octanol and water). The logP, which seems to be the key factor related to the transport process through cell membranes and to many other biological events, has been found to be an exclusive parameter in many quantitative structure -bioactivity relationship studies and has been widely used in the practice of today's rational drug design methods. Therefore, exactly computing the logP values for interesting compounds, or reliably estimating the values of logP for new compounds often not synthesized as yet, may be essential for predicting their biological activity. Correlations between biological activities and $EATI_1$ index for nitrogen-containing and heterocyclic compounds were also developed in this study.

(1) Alkanes It is of interest to test methods on data for alkanes because good data are generally available for complete isomer sets. In this paper, the values of $EATI_1$ and the corresponding logP of 44 alkanes are listed in Table I (column $logP_{(expt)}$).

A regression model was developed with the 44 alkanes:

$$\log P = -2.4384 + 28.934(EATI_1)^{1/4} \quad (1)$$

R=0.9943 s=0.5009 n=44

where, R is the correlation coefficient , F denotes the F-test value, s is the standard deviations and n is the number of the samples. The logP values calculated by eq 1 are also listed in Table I (column $\log P_{(calc)}$).

Table I. The $EATI_1$ Index and logP of Alkanes

NO	Compound	$EATI_1$	$\log P_{(expt)}$	$\log P_{(calc)}$	NO	Compound	$EATI_1$	$\log P_{(expt)}$	$\log P_{(calc)}$
1	propane	5.5033	2.36	1.99	23	n-undecane	61.0264	5.50	5.64
2	n-butane	8.2812	2.86	2.47	24	n-dodecane	74.0844	6.00	6.05
3	2-methylpropane	7.5616	2.76	2.36	25	n-tridecane	89.8201	6.50	6.47
4	n-pentane	13.0594	3.50	3.06	26	n-tetradecane	107.5356	7.00	6.88
5	2-methylbutane	12.2591	2.30	2.97	27	n-pentadecane	128.4968	7.50	7.30
6	2,2-dimethylpropane	10.9918	3.11	2.83	28	n-hexadecane	152.3428	8.00	7.73
7	n-hexane	17.6033	3.00	3.48	29	n-heptadecane	180.2613	8.50	8.17
8	2-methylpentane	16.7336	2.80	3.42	30	n-octadecane	212.2181	9.00	8.61
9	3-methylpentane	16.7836	2.80	3.42	31	n-nonadecane	249.4065	9.50	9.06
10	2,2-dimethybutane	15.3759	3.82	3.29	32	eicosane	292.1281	10.00	9.53
11	n-heptane	24.1702	3.50	3.97	33	henicosane	341.6727	10.50	10.00
12	2,2-dimethylpentane	21.6168	3.10	3.80	34	docosane	398.7096	11.00	10.50
13	2,4-dimethylpentane	22.0759	3.10	3.83	35	tricosane	464.7233	11.50	11.00
14	n-octane	30.8962	4.00	4.38	36	tetricosane	540.8229	12.00	11.52
15	2,2,4-trimethylpentane	26.8459	5.02	4.15	37	pentacosane	628.8045	12.00	12.06
16	2-methylheptane	29.6681	3.91	4.31	38	hexacosane	730.2893	13.00	12.61
17	2,3-dimethylhexane	28.5316	3.82	4.24	39	heptacosane	847.5542	13.50	13.17
18	2,3,3-trimethylpentane	26.5833	3.91	4.13	40	octacosane	982.8724	14.00	13.77
19	n-nonane	39.7309	4.50	4.82	41	nonacosane	1139.1765	14.50	14.38
20	2,2,3-trimethylhexane	34.9011	4.23	4.59	42	triacotane	1319.5843	15.00	15.00
21	n-decane	49.2220	5.00	5.22	43	dotriacontane	1768.4222	16.00	16.32
22	2,2,3,3-tetramethylhexane	41.4404	4.64	4.90	44	tetracontane	5642.1131	21.00	22.63

(2) Alcohols Because the most interesting structures possessing activity are rather complex molecules with multiple bond and / or heteroatoms, it is quite important that topological indices are able to characterize these kinds of molecules. The alcohol we studied in this paper contains one heteroatom, oxygen. Significant correlations between logP and the topological index $EATI_1$ have been found in this study. The supporting data are presented in Table II

The regression equation to describe the relationships between logP and $EATI_1$ index is :

$$\log P = -6.2099 + 37.7930(EATI_1)^{1/4} \quad (2)$$

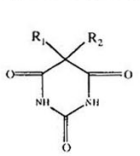
R=0.9797, s=0.1544, n=30

Table II The $EATI_1$ Index and logP of Alcohole Compounds

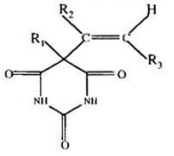
NO	Compound	$EATI_1$	$logP_{(expt)}$	$logP_{(calc)}$	NO	Compound	$EATI_1$	$logP_{(expt)}$	$logP_{(calc)}$
1	1-butanol	10.9199	0.84	0.66	16	2-methyl-2-pentanol	16.2069	1.39	1.37
2	2-butanol	10.6714	0.61	0.62	17	2-methyl-3-pentanol	19.4742	1.67	1.72
3	2-methyl-1-propanol	9.6401	0.61	0.45	18	3-methyl-2-pentanol	18.9726	1.67	1.68
4	1-pentanol	14.7941	1.34	1.21	19	2,2-dimethyl-1-butanol	18.1505	1.57	1.59
5	3-methyl-1-butanol	13.9244	1.14	1.09	20	3,3-dimethyl-1-butanol	17.6859	1.57	1.54
6	2-methyl-1-butanol	14.2054	1.14	1.13	21	2,3-dimethyl-2-butanol	16.1831	1.17	1.37
7	2-pentanol	14.5822	1.14	1.17	22	3,3-dimethyl-2-butanol	17.4689	1.19	1.51
8	3-pentanol	14.9402	1.14	1.22	23	2-methyl-1-pentanol	19.5881	1.78	1.74
9	3-methyl-2-butanol	13.7463	1.14	1.07	24	4-methyl-1-pentanol	19.0956	1.78	1.69
10	2-methyl-2-butanol	13.6573	0.89	1.05	25	4-methyl-2-pentanol	18.8425	1.67	1.66
11	2,2-dimethyl-1-propanol	12.9133	1.36	0.96	26	2-ethyl-1-butanol	19.7700	1.78	1.76
12	1-hexanol	20.1643	1.84	1.80	27	1-heptanol	25.8618	2.34	2.32
13	2-hexanol	19.8458	1.61	1.77	28	1-octanol	33.2002	2.84	2.86
14	3-hexanol	20.4719	1.61	1.82	29	1-nonanol	41.2288	3.57	3.37
15	3-methyl-3-pentanol	19.1139	1.39	1.69	30	1-decanol	51.1217	4.01	3.90

(3) Barbiturates Barbiturates were thought to be nonspecific narcotic agents principally because logP correlates very well with their biological potency[12]. Other studies[13] show a dependence of the action of barbiturates upon chemical structure. Therefore, it was of interest to carry out a correlation analysis of logP and topological parameters. Correlations between the topological index $EATI_1$ and logP for barbiturates have been revealed by this investigation.

The topological index $EATI_1$ and logP of 25 derivatives of barbituric acids, structures II and III , are listed in Table III and Table IV, respectively. The regression equation, correlation coefficient, and standard deviation are:



II



III

$$logP = -6.7054 + 30.0931\ (EATI_1)^{1/4} \quad \ldots\ldots (3)$$

$R=0.9293$, $s=0.2323$, $n=25$

Table III logP and Topological Index $EATI_1$ for Barbiturates with Structure II

NO.	R_1	R_2	$EATI_1$	$logP_{(expt)}$	$logP_{(calc)}$
1	methyl	1-methyl,1-propenyl	45.5731	0.65	1.11
2	ethyl	1-methyl,1-propenyl	56.7947	1.15	1.55
3	propyl	1-methyl,1-propenyl	72.5335	1.65	2.07
4	butyl	1-methyl,1-propenyl	90.4248	2.15	2.57

Table III (Continued)

NO.	R_1	R_2	$EATI_1$	$logP_{(expt)}$	$logP_{(calc)}$
5	methyl	1-methylvinyl	27.8191	0.15	0.20
6	ethyl	1-methylvinyl	36.2377	0.65	0.67
7	propyl	1-methylvinyl	48.2416	1.15	1.22
8	butyl	1-methylvinyl	61.5993	1.65	1.72
9	isobutyl	1-methylvinyl	58.9030	1.45	1.63
10	amyl	1-methylvinyl	76.3821	2.15	2.19
11	isoamyl	1-methylvinyl	73.7142	1.95	2.11

Table IV logP and Topological Index $EATI_1$ for Barbiturates with Structure III

NO.	R_1	R_2	R_3	$EATI_1$	$logP_{(expt)}$	$logP_{(calc)}$
12	methyl	ethyl	methyl	42.2666	1.15	0.97
13	ethyl	ethyl	methyl	52.8092	1.65	1.41
14	propyl	ethyl	methyl	68.6730	2.15	1.96
15	isopropyl	ethyl	methyl	64.1324	1.95	1.81
16	methyl	methyl	ethyl	43.2027	1.15	1.01
17	ethyl	methyl	ethyl	53.9518	1.65	1.45
18	propyl	methyl	ethyl	69.9915	2.15	2.00
19	isopropyl	methyl	ethyl	65.4778	1.95	1.86
20	methyl	propyl	methyl	55.6063	1.65	1.51
21	ethyl	propyl	methyl	68.2438	2.15	1.94
22	methyl	isopropyl	methyl	51.7122	1.45	1.36
23	methyl	butyl	methyl	70.8458	2.15	2.03
24	ethyl	butyl	methyl	85.9379	2.65	2.46
25	ethyl	ethyl	propyl	83.8708	2.65	2.40

(4) Nitrogen-Containing Aromatic Molecules The 18 nitrogen-containing aromatic molecules having inhibition activities on the population growth of tetrahymena are applied in this paper. The molecular structures of these compounds are rather complex. In this study, the correlations between the topological index $EATI_1$ and acute toxicities are observed for the 18 selected compounds. Table V shows that satisfactory results can be obtained by using the $EATI_1$ index.The regression analysis is :

$$\log(IGC50)=5.7622-4.4001\log(EATI_1) \quad (4)$$

$$R=-0.9419, \quad s=0.2444, \quad n=18$$

Table V Nitrogen-containing Molecules and Their Activities

NO.	Molecule	$EATI_1$	log(IGC50) (expt)	log(IGC50) (calc)
1	pyridine	11.1231	1.1853	1.1589
2	3-picoline	14.1419	1.0175	0.6999
3	4-picoline	14.1184	0.8921	0.7030
4	3,4-lutidine	17.2819	0.5051	0.3167
5	quinoline	22.7654	-0.0132	-0.2100

Table V (Continued)

NO.	Molecule	$EATI_I$	log(IGC50) (expt)	log(IGC50) (calc)
6	4-phenylpyridine	28.7629	-0.6576	-0.6566
7	acridine	36.8806	-1.3979	-1.1318
8	aniline	13.8859	0.2201	0.7347
9	3-toluidine	17.0599	0.4133	0.3413
10	4-toluidine	17.0485	0.1271	0.3427
11	3,4-xylidine	20.5827	0.2878	-0.0173
12	1-naphthylamine	26.6339	-0.2218	-0.5096
13	4-aminobiphenyl	32.5625	-0.8239	-0.8938
14	nitrobenzene	17.9036	0.0645	0.2494
15	3-nitrotoluene	21.3971	-0.3098	-0.0916
16	4-nitrotoluene	21.3920	-0.2366	-0.0912
17	4-nitro-o-xylene	25.1662	-0.6383	-0.4014
18	4-nitrobiphenyl	36.8386	-1.0000	-1.1296

(5) Heterocylic compounds In order to make further application on $EATI_I$ index, the heterocyclic compound that are more complex than the molecules mentioned above are selected as object in the present work.

The 24 heterocyclic molecules are given in TableVI. The biological descriptor, log biological response (logBR), is defined as the reciprocal of the IGC50. The IGC50 is that the concentration (mmol / L) required to inhibit by 50% the growth of axenic cultures of the common freshwater ciliate tetrahymena pyriformis strain GL-C . Correlations between the topological index $EATI_I$ and activities logBR are observed for these compounds, and the statistical analysis yields the following result,

$$logBR = -2.3932 + 0.1011(EATI_I) \quad (5)$$

$$R = 0.9520 \quad s = 0.3068 \quad n = 24$$

Table VI Heterocylic Compounds and Their Activities

NO	Compound	$EATI_I$	$logBR_{(expt)}$	$logBR_{(calc)}$	NO	Compound	$EATI_I$	$logBR_{(expt)}$	$logBR_{(calc)}$
1	pyridine	11.1231	-1.19	-1.26	13	acridine	36.8806	1.40	1.33
2	3-methylpyridine	14.1419	-1.02	-0.97	14	phenazine	34.7010	1.40	1.12
3	2,6-dimethylpyridine	19.2575	-0.81	-0.45	15	pyrimidine	10.3191	-1.75	-1.35
4	pyrazine	10.2881	-1.82	-1.35	16	pyridazine	10.5133	-1.41	-1.33
5	2-methylpyrazine	13.0932	-1.09	-1.07	17	phthalazine	21.5852	-0.34	-0.22
6	2,3-dimethylpyrazine	16.0380	-0.87	-0.77	18	quinazoline	22.8053	-0.29	-0.09
7	quinoline	22.7654	0.01	-0.09	19	pyrrole	8.6466	-1.11	-1.52
8	2-methylquinoline	26.6079	0.47	0.30	20	indole	19.6948	0.21	-0.40
9	2,6-dimethylquinoline	34.1632	0.68	1.05	21	1,2-dimethylindole	27.3080	0.84	0.37
10	quinoxaline	21.2408	-0.30	-0.25	22	carbazole	33.2822	0.91	0.96
11	2-methylquinoxaline	24.8962	0.02	0.12	23	pyrazole	8.1550	-1.71	-1.57
12	2,3-dimethylquinoxaline	28.6282	0.25	0.49	24	imidazole	8.0084	-1.00	-1.58

4 Examination of uniqueness

The purpose of topological indices is to classify structures and to serve for structure-property correlations. Nonuniqueness is not nessarily a disadvantage when correlation study is the prime target, because there are compounds with similar or the same properties which require a similar or a same index. However, interest continues in trying to devise an index that would be unique.In this section, we will examine the selectivity of the new index $EATI_1$ introduced in this study.

For examining the selectivity of the $EATI_1$ index, over 610,000 structures and graphs have been detected. Most of the structures and graphs were generated by our generator[14,15]. These structures and graphs include the following families.

(1) Acyclic alkane molecular graphs up to n=20, the total number of alkane isomers being 618,050, can be differentiated without degeneracy by using the $EATI_1$ index.

(2) The structures and graphs used by Randic[16] for examining the uniqueness of ID numbers were selected, containing monocyclic graphs up to n=8(122 cases), bicyclic graphs up to n=7(79 cases), all graphs on five vertices, sesquiterpenes(30 cases), and miscellaneous, etc. The $EATI_1$ index shows a remarkable ability to discriminate among the structures and graphs.

(3) In order to more rigorously determine the uniqueness of $EATI_1$ index,the cyclic graphs having n=8 vertices, the degree of each vertex being 4, offer novel comparison. All of the 204 structures were enumerated (Chart 1-4) by our isomer generator. The $EATI_1$ index also shows a high selectivity, because all of these structures can be discriminated without degeneracy by the $EATI_1$ index.

5 Conclusion

The $EATI_1$ index, suggested by us, correlates significantly with a number of physicochemical properties and biological activities of organic compounds. The study also indicates that the $EATI_1$ topological index has high structural selectivity. The results obtained in this study demonstrate convincingly that the $EATI_1$ index is a useful topological index.

ACKNOWLEDGMENT

The financial support of the National Science Foundation of China is gratefully acknowledged.

Chart 1

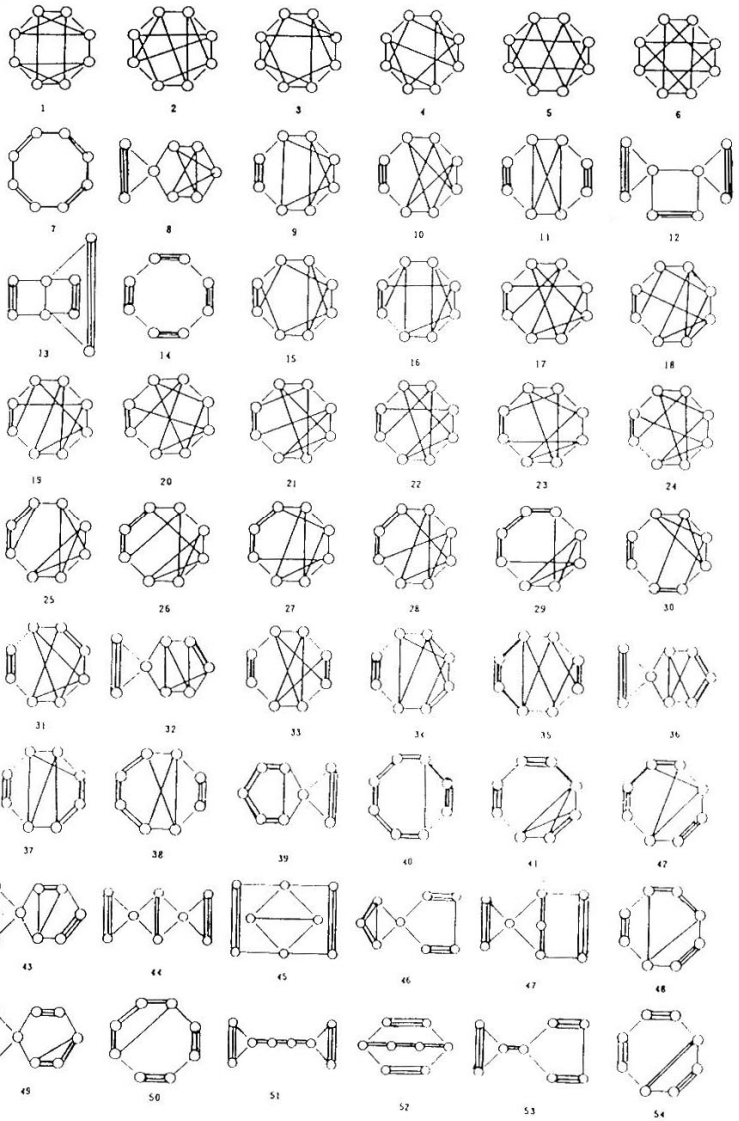

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Chart 2

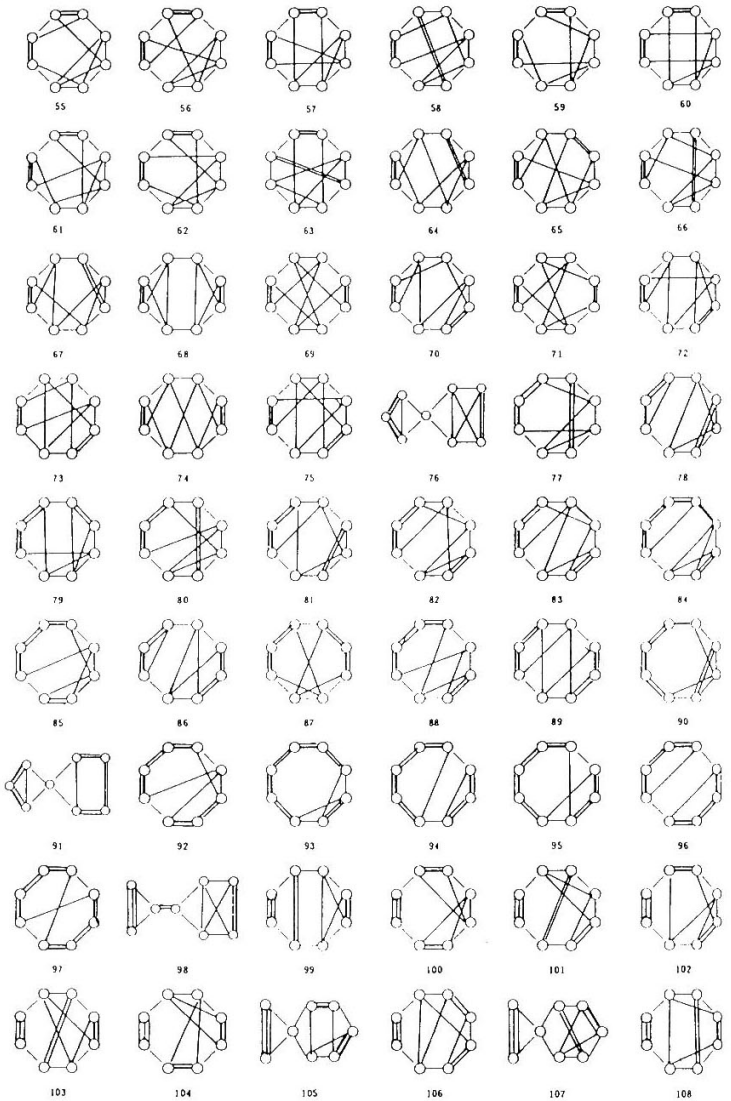
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Chart 3

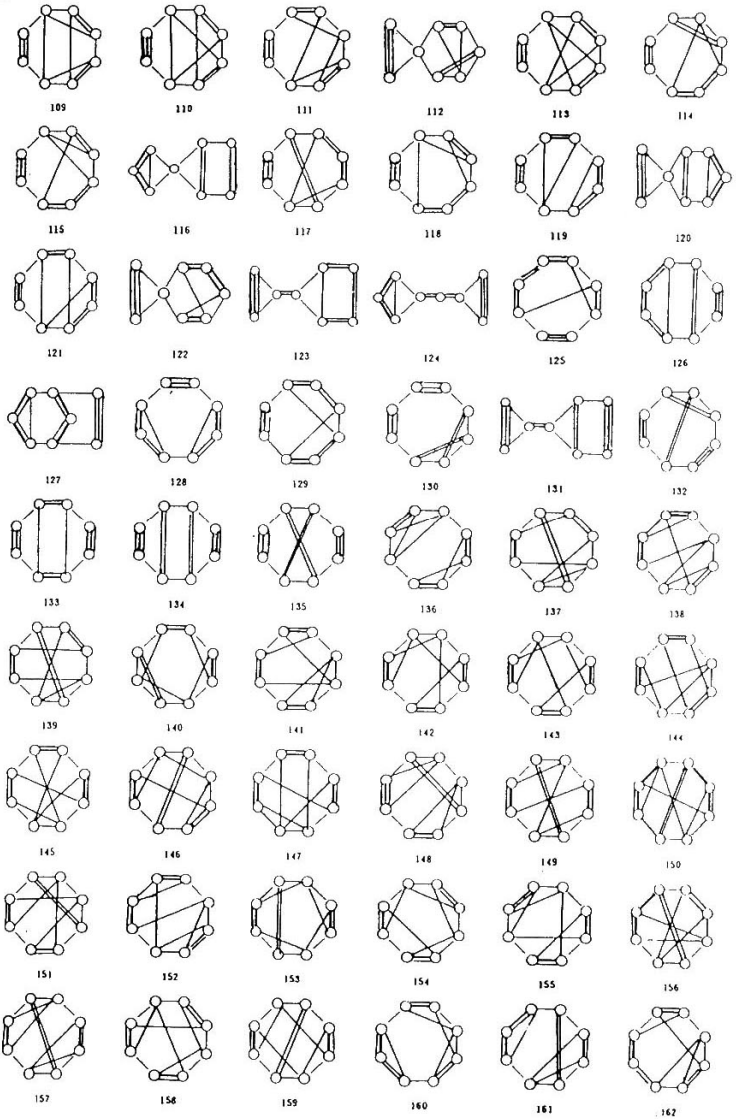
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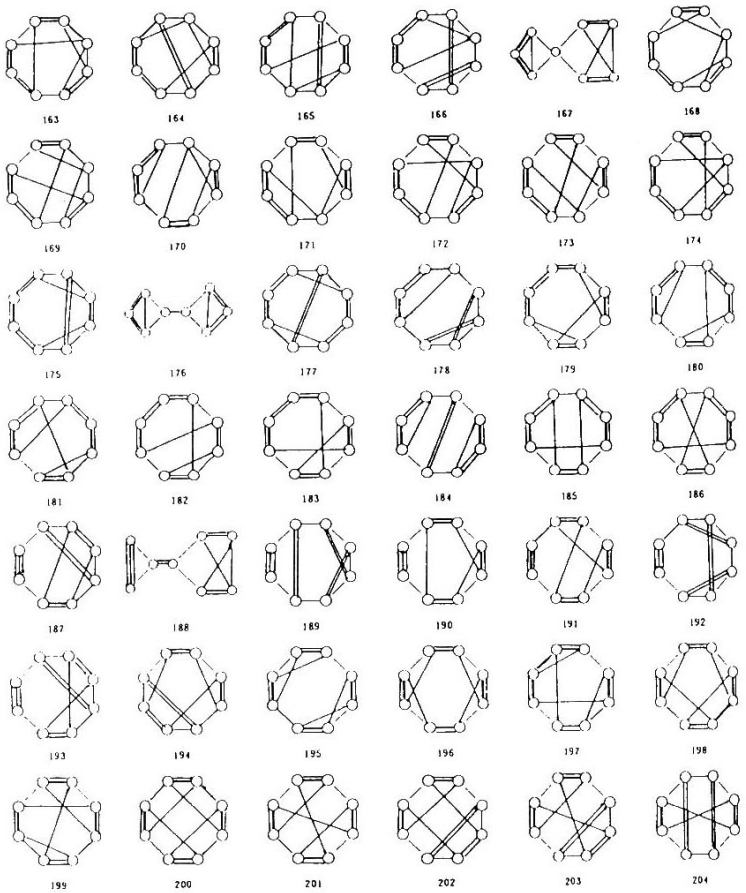
Chart 4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