

## The Even/Odd Disparity in Organic Compounds

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There are more organic compounds with an even number of carbon atoms than with an odd number. This disparity could result mainly from the methods used in synthetic chemistry to build large molecules from smaller ones. Samples of C<sub>28</sub>, C<sub>47</sub> and C<sub>48</sub> compounds have been examined in this context.

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**Introduction.** – There are more organic compounds with an even number of carbon atoms than with an odd number. Our initial note [1] drawing attention to this disparity attracted the interest of the press [2] and of many colleagues who provided a variety of comments. Some found it surprising, unexpected, and even mysterious, while others found it trite, commonplace and self-evident. Although several factors that might affect the even/odd ratio had occurred to us at the time, none of them seemed particularly convincing as a general explanation for the observed imbalance. We had therefore refrained from any attempt at interpretation [3].

There is no question about the reality of the even/odd disparity. *Tables 1* and *2* give the numbers of compounds taken according to C-atom count in the *Beilstein* database (1779 to 1 March 1999) [4]; the subset of natural products as defined by *Beilstein* is also given. Statistics are provided for the total and for the single-component compounds<sup>1)</sup> till C<sub>80</sub>, and for the total compounds only in the C-atom range C<sub>81</sub> to C<sub>246</sub>. The even/odd disparity is obvious from the numbers of C even and C odd compounds and is especially striking at higher C-contents. The cumulative numbers (till C<sub>246</sub>) are 3603818 with C odd and 4100997 with C even. The excess is 497179 out of a 7704815 total, or 6.45%. The standard deviation of a randomly distributed even/odd sample of size *N* is  $N^{1/2}$  or 2776. Thus, the observed excess amounts to *ca.* 179 standard deviations! The vast majority of the compounds (97.3%) contain up to 40 C-atoms. Of the remainder with the number of C-atoms > 40, the excess amounts to 15.45%, and for the number of C-atoms > 120 it reaches 30.6%. In these upper reaches, more than two out of three compounds contain an even number of C-atoms!

*Fig. 1* shows the histograms of these distributions. What might look like a weak even/odd alternation is discernible in *Fig. 1, a*, where it stands out against the strongly peaked distribution with its tip around the number of C-atoms = 12 to 16. It becomes unmistakable, however, once the distribution begins to flatten out at larger C-atom

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<sup>1)</sup> This group excludes molecular complexes, salts, solvates and the like.

Table 1. *Total and Single-Component Compounds and Natural Products in the Beilstein Database*

Number of C-Atoms	Total compounds	Single-component compounds	Total natural products	Single-component natural products
1	27667	5281	79	38
2	55612	13091	184	72
3	34111	21941	144	133
4	80822	44605	299	265
5	87017	67547	469	430
6	219765	124414	884	813
7	194675	155387	787	757
8	261589	224133	1010	987
9	301708	267674	1180	1157
10	398589	353879	2463	2432
11	385052	352490	1543	1504
12	448872	404855	1821	1798
13	415943	380682	1804	1776
14	449059	411571	2059	2033
15	432029	398350	9290	9248
16	429718	392152	3630	3591
17	371075	340231	4029	3996
18	366895	332519	3595	3563
19	312855	283252	4537	4469
20	326362	296382	10682	10537
21	271628	246771	5904	5776
22	249534	227410	4858	4788
23	192373	175170	2602	2575
24	184002	166527	2715	2683
25	132613	121124	2808	2786
26	128193	117348	2273	2242
27	111810	102469	3240	3152
28	104815	96082	2822	2783
29	79366	73515	2683	2647
30	89489	83285	5694	5667
31	56335	52270	1785	1768
32	59033	54681	1874	1856
33	40333	37149	1117	1094
34	44358	40945	1166	1147
35	29504	27392	1260	1237
36	36940	33222	1204	1172
37	22239	20619	883	870
38	24242	22385	696	690
39	16366	15185	680	658
40	21408	19748	1126	1095
41	14197	13188	768	745
42	18857	16686	970	949
43	10837	10072	478	466
44	14841	13500	434	427
45	9617	8907	534	519
46	10734	9927	388	385
47	7330	6874	456	453
48	11495	10349	702	693
49	5720	5310	247	240
50	7320	6719	316	300
51	5253	4871	260	243

Table 1 (cont.)

Number of C-Atoms	Total compounds	Single-component compounds	Total natural products	Single-component natural products
52	6388	5843	240	229
53	4169	3879	257	254
54	6404	5843	395	359
55	4343	3937	271	237
56	5295	4761	275	248
57	3446	3217	189	171
58	4027	3741	189	182
59	2436	2293	188	180
60	4439	3951	200	192
61	2527	2373	107	102
62	3097	2846	121	112
63	2443	2248	143	135
64	2991	2715	106	104
65	1848	1759	78	77
66	2621	2443	67	64
67	1564	1482	41	41
68	2447	2309	105	104
69	1524	1451	36	34
70	1872	1708	56	55
71	1088	1039	18	18
72	2140	1982	28	28
73	1004	944	17	17
74	1288	1197	26	25
75	1062	1013	66	65
76	1400	1312	28	28
77	817	771	15	15
78	1162	1075	31	28
79	753	709	5	4
80	1180	1067	18	18

values, for example in the range of 40 to 80, as in *Fig. 1,b*. The corresponding histogram for natural products shows a quite different distribution with prominent peaks at the number of C-atoms 10, 15, 20 and 30, multiples of the C<sub>5</sub> isoprene unit (see *Fig. 1,c*). Indeed, there is persuasive recent evidence that natural products constitute a distinctive sub-class of organic molecules [5]. However, natural products make up only a small proportion of organic compounds, less than 5%. Hence, any explanations based on preferred biosynthetic pathways to natural products cannot possibly account for the overall observed predominance of compounds with an even number of C-atoms.

Among the factors that have been considered are:

1) The prevalence of the acetate pathway in biosynthesis [6]. But this could apply only to natural products, a small proportion of the total and does not seem to be important even there (see *Fig. 1,c*).

2) The presence of dimers or other polymers containing an even number of subunits [7]. But only a tiny proportion of the total population fall into these categories, mostly at higher C-atom contents.

3) The occurrence of derivatives of hexose sugars or of aromatic rings [8]. But only a tiny proportion is built exclusively from such units.

Table 2. Total Organic Compounds in the Beilstein Database in the Range  $C_{81}$  to  $C_{246}$ 

Number of C-atoms	Total number of compounds	Number of C-atoms	Total number of compounds	Number of C-atoms	Total number of compounds	Number of C-atoms	Total number of compounds
81	764	115	125	149	29	183	4
82	989	116	212	150	70	184	20
83	490	117	136	151	28	185	3
84	1049	118	186	152	47	186	4
85	499	119	104	153	30	187	3
86	610	120	293	154	37	188	3
87	513	121	101	155	25	189	12
88	834	122	135	156	61	190	1
89	401	123	115	157	16	191	5
90	613	124	166	158	25	192	24
91	324	125	58	159	19	194	10
92	574	126	160	160	54	195	11
93	313	127	54	161	17	196	5
94	369	128	178	162	66	197	1
95	438	129	73	163	20	198	7
96	638	130	90	164	35	199	1
97	256	131	64	165	17	200	6
98	371	132	180	166	12	202	1
99	298	133	63	167	28	204	5
100	430	134	57	168	56	208	2
101	202	135	57	169	14	210	14
102	365	136	133	170	22	212	2
103	208	137	39	171	13	214	1
104	361	138	94	172	24	216	1
105	223	139	45	173	9	218	1
106	238	140	113	174	16	220	1
107	149	141	65	175	12	222	1
108	410	142	70	176	18	224	1
109	147	143	40	177	11	225	1
110	251	144	174	178	5	240	2
111	180	145	38	179	4	242	4
112	338	146	55	180	24	246	3
113	116	147	63	181	6		
114	209	148	99	182	8		

4) The possible existence of as yet unknown fundamental principles or rules. The imagination is unbounded, but on the basis of a sample of 86 C-containing interstellar molecules [9], there is no evidence of any preference for molecules with an even number of C-atoms in outer space. On the contrary, as might be expected,  $C_1$  molecules predominate. The frequencies are 35 ( $C_1$ ), 18 ( $C_2$ ), 17 ( $C_3$ ), 5 ( $C_4$ ), 4 ( $C_5$ ), higher  $C_n$ , 2 or less.

We and others have also considered the H-, N-, and O-atom content of organic molecules, but the even/odd disparities in these cases can be accounted for by simple valency rules. It has been noted, for example, that there is a smooth even/odd alternation in the H-atom content in organic molecules [10]. A stable molecule must contain an even number of electrons. Thus the number of odd-valent atoms must be even. For example, an odd number of H-atoms is only possible if there is an odd number of non-H odd-valent atoms. This has a probability of less than 50%, for not all compounds contain non-H odd-valent atoms (N, P, F, Cl and Br are the most common),

and there is no reason to suppose that there is any preference for an odd number of these. Other reasons for the prevalence of compounds with an even number of C-atoms are applicable only to special classes of compounds. For instance, odd-membered cyclic  $\pi$ -systems cannot be alternant according to *Hückel* theory.

It is then with a certain diffidence that we present some further observations on this subject. These have not led to any ‘explanation’ of the phenomenon. The appearance of a compound in the *Beilstein* database is subject not only to the laws of chemistry but also in part to economic and sociological influences. The number of compounds in this database is but an infinitesimal fraction of the total possible number of molecules that could ever be made [11]. Compounds have been made depending on the methods and materials used by and available to chemists and on the goals set by them, which may be very different from place to place and from time to time. We can hardly therefore expect to arrive at any far reaching generalisations; the most we can hope for is to notice tendencies.

**Results and Discussion.** – Although natural products are flagged as such in the *Beilstein* database, the classification of a compound as natural product seems to be somewhat arbitrary. Some synthetic derivatives of natural products are still classed as natural products, others not. Nevertheless, the preference for compounds with an even, number of C-atoms is so much stronger for synthetic compounds than for nominally natural products that any arbitrariness in the definition cannot affect the result. This is shown in *Fig. 2* which shows the variation in the even/odd disparity as a function of C-atom content for each of the categories of single component compounds in the *Beilstein* database (all compounds, natural products)<sup>2)</sup>. This disparity is quantified as  $\Delta N$  and is expressed as a percentage.

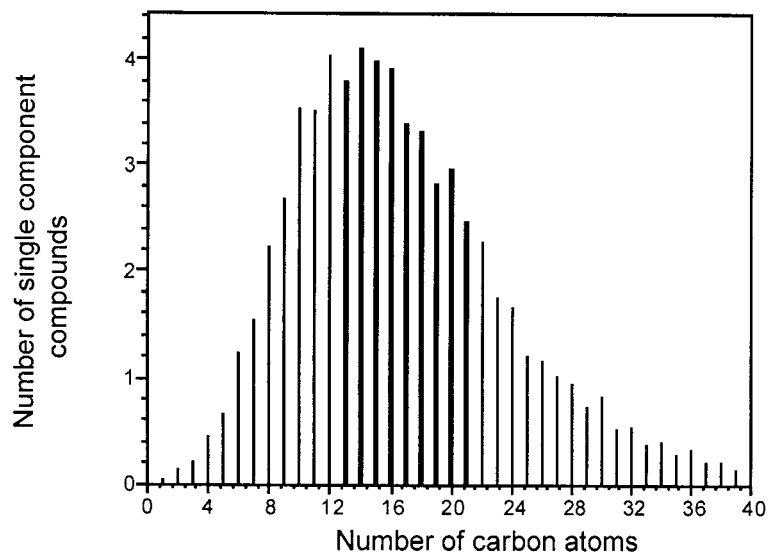
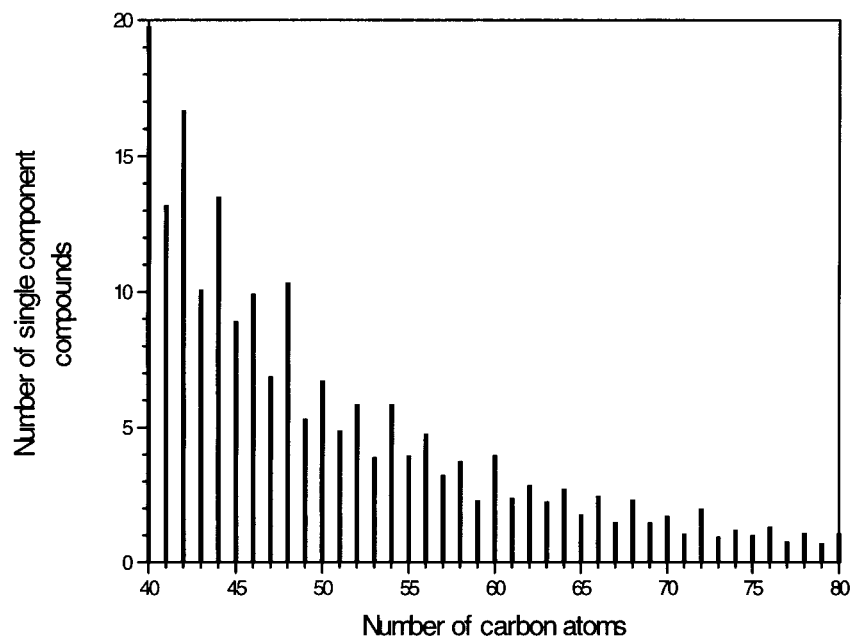
$$\Delta N = 100 \{2N_e - (N_{e-1} + N_{e+1})\} / 2N_e$$

Here,  $N_e$  represents the number of compounds with a given even C-atom count while  $N_{e-1}$  and  $N_{e+1}$  are the numbers of compounds having the immediately adjacent odd C-atom counts. From *Fig. 2*, it is evident that the even/odd ratio rises with increasing C-atom content for all compounds in the *Beilstein* database, but not for the subset of natural products. This might suggest that the origin of the even/odd disparity is to be found in the processes of synthetic chemistry.

If we are to find any patterns or tendencies we have to look for them in the *Beilstein* database. However, the task of scanning some 7 million compounds and examining the synthetic paths leading to them is a daunting one, and we were suitably daunted. Instead, we decided to make random selections of compounds with a given number of C-atoms. Thus, out of the 104815 C<sub>28</sub> compounds we printed out the structural formula of 401 randomly selected examples; similarly, of the 7330 C<sub>47</sub> compounds we selected 251 examples, and of the 11495 C<sub>48</sub> compounds we selected 212. For many structural formula in these lists we could make a guess about the synthetic route leading to the compound in question, and for these we undertook occasional checks in the literature

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<sup>2)</sup> The data for single-component compounds are used here. There are no significant differences between the statistics for the total number of compounds and the number of single-component compounds.

a)  $\times 10^5$ b)  $\times 10^3$ 

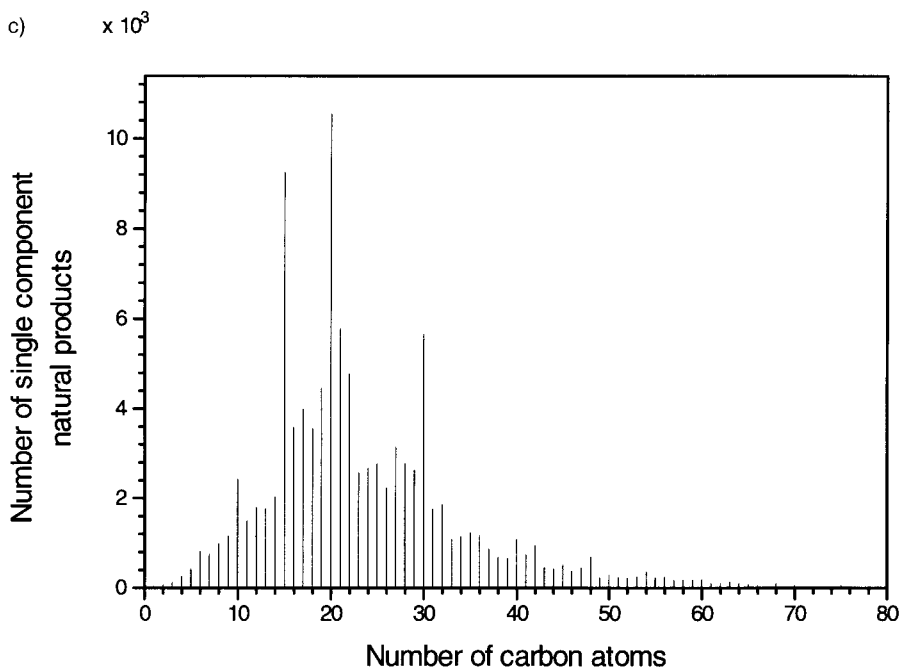


Fig. 1. a) Histogram ( $C_1$  to  $C_{40}$ ) of single-component organic compounds in the Beilstein database. b) Histogram ( $C_{41}$  to  $C_{80}$ ) of single-component organic compounds. c) Histogram ( $C_1$  to  $C_{80}$ ) of single-component natural products. Compare with Fig. 1,a

as to the correctness of our guesses. Many indeed turned out to be more or less correct, if not in every detail.

Our approach was to classify possible synthetic routes into a few categories depending on the number of different fragments that could be imagined as likely precursors of the target molecule (Table 3). Thus, 2A means that the molecule is formally a 'dimer' built from two identical precursors, 3A is a 'trimer', while 2A + B means that the molecule could be assembled in principle from two identical precursors plus another of a different type. To keep things simple, we limited the number of possible precursors to three different types and took 2A + B1 + B2 as the most complex category. Our classification is arbitrary, and the allocation of compounds to the different categories is undoubtedly somewhat subjective, but we do not think we have thereby introduced any serious bias. Molecules that could not be easily assigned to any of the above categories were classified as miscellaneous (MISC). This last category also contains the trivial A + B reaction schemes.

From the information in Table 3, a substantial proportion of C<sub>48</sub> molecules can be imagined to be assembled by combination of two or more identical fragments (2A, 21%; 3A, 8%; 4A, 8%) or from combination of a central symmetric fragment with two other identical fragments (2A + B, 24%). Similarly, a significant proportion of C<sub>28</sub> molecules fall into the 2A (8%) and 2A + B (15%) patterns. In contrast, there appears to be no dominant pattern for assembling the C<sub>47</sub> molecules, which fall overwhelmingly into the MISC category. We can imagine that compounds in the 2A, 3A, 4A or 2A + B

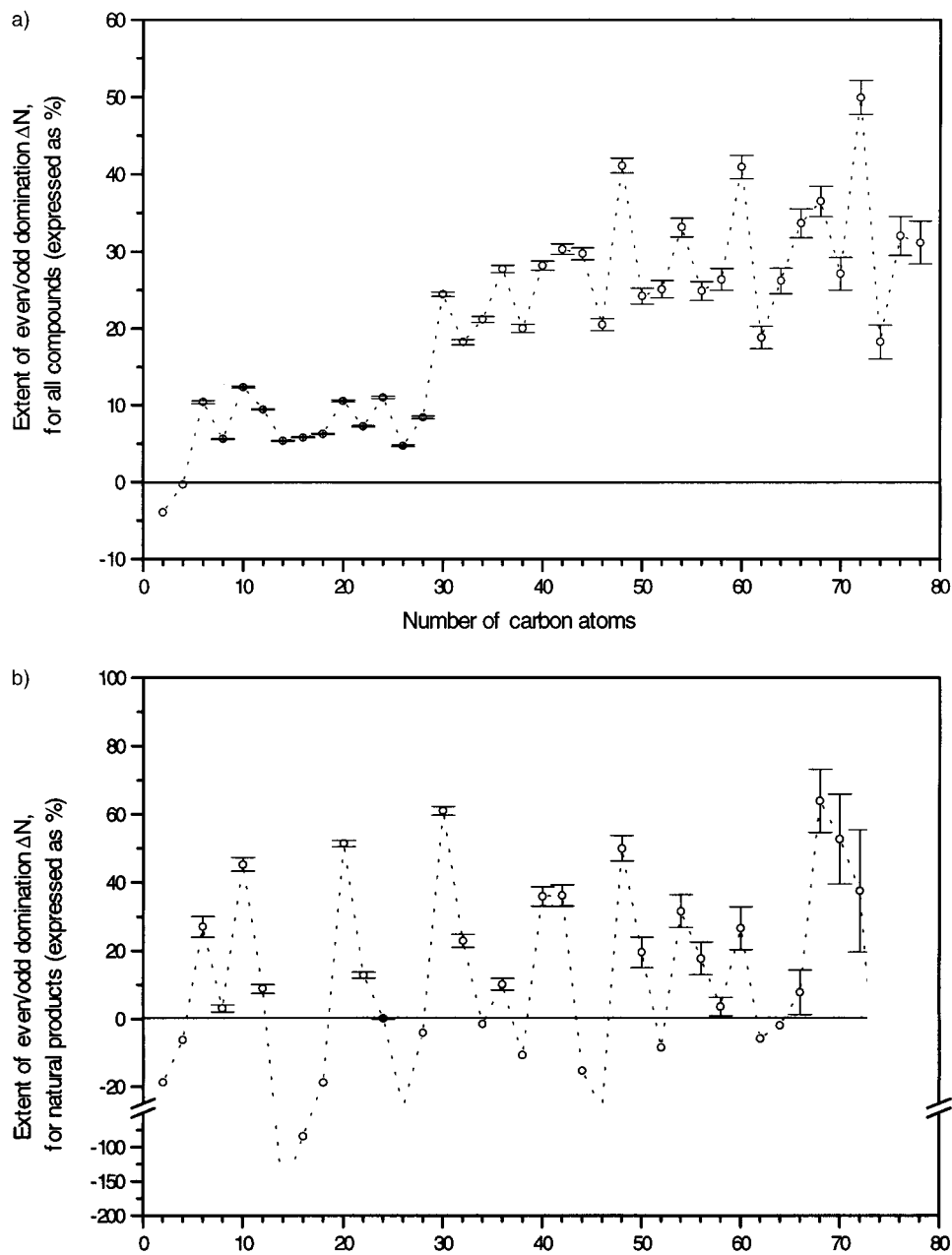


Fig. 2. a) Variation in even/odd disparity as a function of C-atom count a) for all single-component compounds, b) for single-component natural products



Table 3. Possible Synthetic Routes for C-atom Contents,  $C_{28}$ ,  $C_{47}$  and  $C_{48}$ <sup>a)</sup>

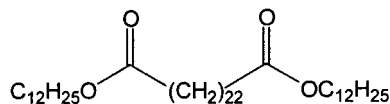
Addition type	$C_{28}$	$C_{47}$	$C_{48}$
2A	34 (8%)	7 (3%)	45 (21%)
3A	3	5	16
4A	3	9	17
6A	0	2	6
7A	0	0	1
8A	0	0	4
2A + B	60	21	50
3A + B	8	3	2
4A + B	3	1	2
6A + B	1	0	0
2A + 2B	5	1	3
2A + B1 + B2	3	0	1
MISC	281 (70%)	202 (80%)	65 (30%)
Number of compounds examined	401	251	212
Total number of compounds	104815	7330	11495

<sup>a)</sup> These routes are defined in terms of addition of smaller components. For classification of addition types, see text.

categories can be prepared in a single synthetic step or in only a few steps from simpler precursors, whereas compounds that do not fall into these categories will tend more to require multi-step syntheses for their preparation. Obviously, compounds that can be made in one or in a few synthetic steps are likely to outnumber those that require long sequences of reactions. Such compounds, lacking simple patterns for assembly, are more inclined to be found in the MISC category. We propose that this difference in the presumed ease of synthesizing  $C_{28}$  or  $C_{48}$  compared to  $C_{47}$  compounds is the main ingredient in the factors leading to the imbalance in the relative *Beilstein* frequencies.

Moreover, one cannot help noticing that, whereas 48 has many factors (2, 3, 4, 6, 8, 12, 16, 24), 47 is a prime number. There are thus many formal possibilities to assemble small identical molecular fragments into a symmetrical  $C_{48}$  molecule, whereas there is no way to do this for a  $C_{47}$  molecule. In *Table 1* for the number of C-atoms > 80, although frequencies for C even and C odd both tend to decrease with increasing C-atom count, the frequency of C prime compounds tends to be lower than the frequency of the next higher odd number where this is not a prime. Thus, even among the compounds with an odd number of C-atoms, those with a prime number of C-atoms seem to be further disfavoured.

*Some Case Studies.* In principle, the next step should be to check whether the classification arrived at by inspection of the molecular formulas corresponded to the actual synthetic routes. Some examples are obvious. For example, it is not at all difficult to categorize the diester  $C_{48}H_{94}O_4$  (*Beilstein* Reg. No. 1898243) as being in the 2A + B category.

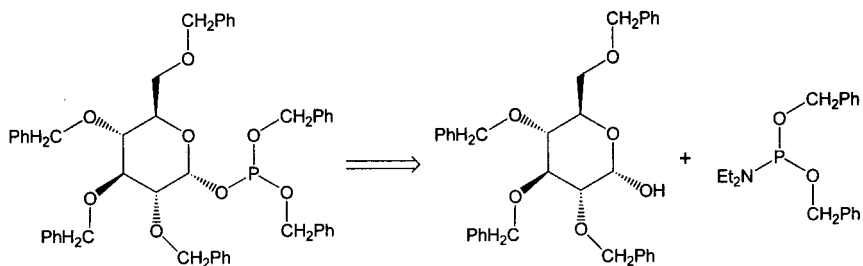


BRN 1898243

Other examples called for scrutiny of the original literature sources but in view of the vastness of such an enterprise, we contented ourselves to making a few spot checks.

*Dibenzyl 2,3,4,6-Tetra-O-benzyl- $\alpha$ -D-glucopyranosyl Phosphite* ( $C_{48}H_{49}O_8P$ , *Beilstein* Reg. No. 6842485; *Scheme 1*) Classified as 6A + B, this compound was prepared

*Scheme 1*

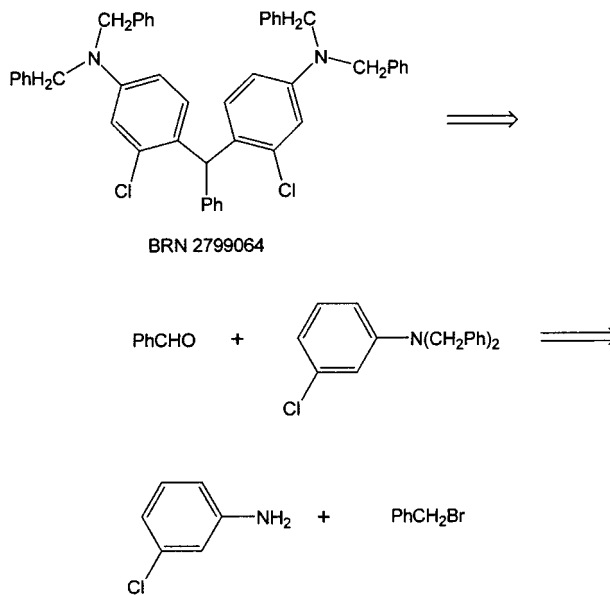


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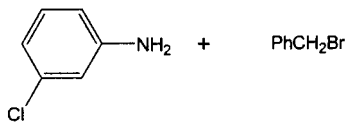
by benzylation of the carbohydrate [12]. A minor qualification is that instead of the six PhCH<sub>2</sub> groups being introduced in a single step, four are added in a first step and the remaining two in a subsequent step. The important point is that the molecule contains components of the same structural type and that these can be added with relative ease in a few steps, so making the target molecule easier to synthesize.

*Bis[4-(dibenzylamino)-2-chlorophenyl]phenylmethane*, ( $C_{47}H_{40}Cl_2N_2$ , *Beilstein* Reg. No. 2799064; *Scheme 2*). This was classified as 4A + B. In the actual synthesis,

*Scheme 2*

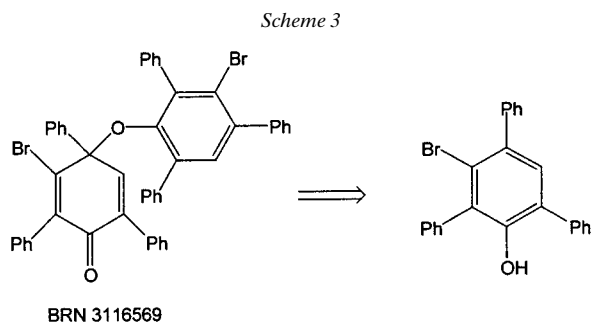


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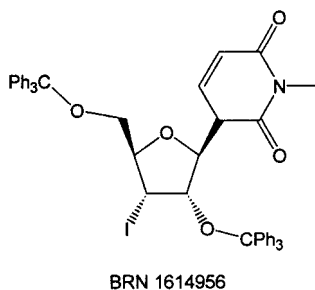


two residues containing four  $\text{PhCH}_2$  groups (4A) were coupled with an aldehyde (B) under acidic conditions to give a substituted triphenylmethane [13].

*3-Bromo-4-(3-bromo-2,4,6-triphenylphenoxy)-2,4,6-triphenylcyclohexa-2,5-dienone* ( $\text{C}_{48}\text{H}_{32}\text{Br}_2\text{O}_2$ , *Beilstein* Reg. No. 3116569; *Scheme 3*). Classified as 2A, this dienone is formed by electrochemical coupling of the corresponding phenol [14].



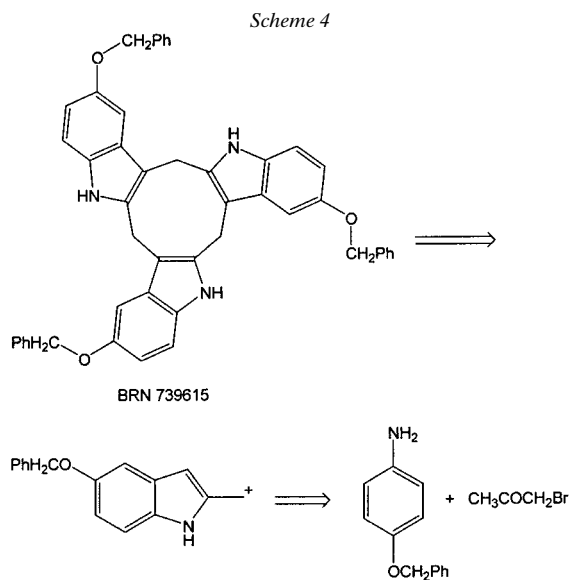
*3-Iodo-3-methyl- $O^{2'}$ , $O^{5'}$ -ditrityl-3'-deoxyuridine*, ( $\text{C}_{48}\text{H}_{41}\text{IN}_2\text{O}_5$ , *Beilstein* Reg. No. 1614956). This is clearly of the 2A + B type wherein the two Tr protecting groups are reacted with the uridine [15].



*2,8,14-Tris(benzyloxy)-5,6,11,12,17,18-hexahydrocyclonona[1,2-b;4,5-b';7,8-b'']triindole* ( $\text{C}_{48}\text{H}_{39}\text{N}_3\text{O}_3$ , *Beilstein* Reg. No. 739615; *Scheme 4*). This 3A trimer was formed by the reaction of 4-(benzyloxy)aniline with bromoacetone to give a resonance-stabilized indole cation, which trimerizes to the product [16].

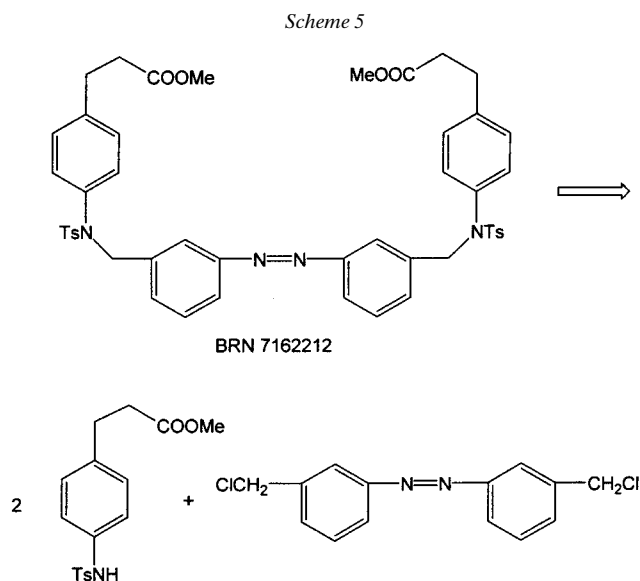
*Dimethyl Diazenebis(m-phenylenemethylene-N-(tosylimino)-p-phenyleneethylene carboxylate)* ( $\text{C}_{48}\text{H}_{48}\text{N}_4\text{O}_8\text{S}_2$ , *Beilstein* Reg. No. 7162212; *Scheme 5*). This dimer was classified as 2A but synthesized by the alkylation of 3-[4-(tosylamino)phenyl]propanoate with bis[3-(chloromethyl)phenyl]diazene [17]. However, the formation of the (*E*)- $\text{N}=\text{N}$  bond by diazotization of the corresponding aniline, a 2A-type synthesis, is also a method of preparation.

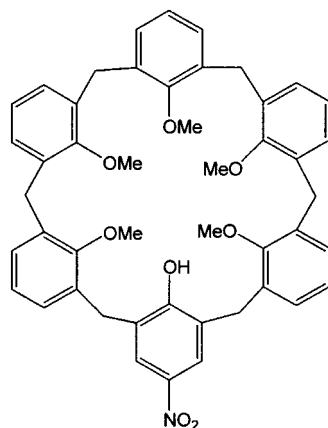
*38,39,40,41,42-Pentamethoxy-35-nitrocalix[6]aren-37-ol* ( $\text{C}_{47}\text{H}_{45}\text{NO}_8$ , *Beilstein* Reg. No. 7406236). This 6A compound was prepared by mono-nitration of the penta-



methoxycalix[6]arene precursor, which in turn was obtained from the parent calix[6]arene [18].

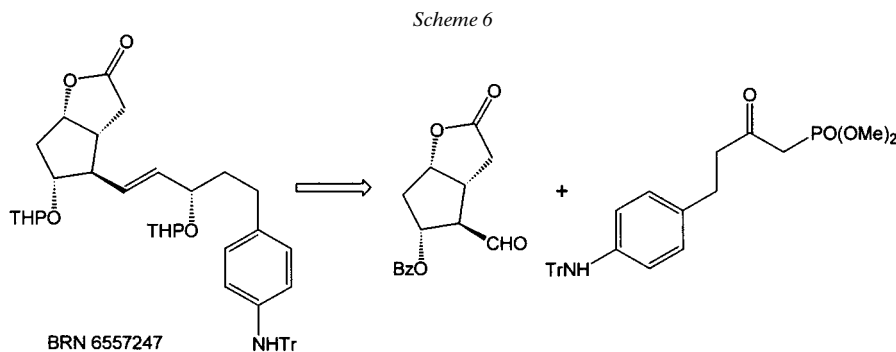
5-(Tetrahydropyran-2-yloxy)-4-{3-(tetrahydropyran-2-yloxy)-5-[4-(tritylamino)phenyl]pent-1-enyl}hexahydrocyclopenta[b]furan-2-one, ( $\text{C}_{47}\text{H}_{53}\text{NO}_6$ , Beilstein Reg. No. 6557247; Scheme 6). The compound was classified as MISC and is synthesized by a multi-step route [19].



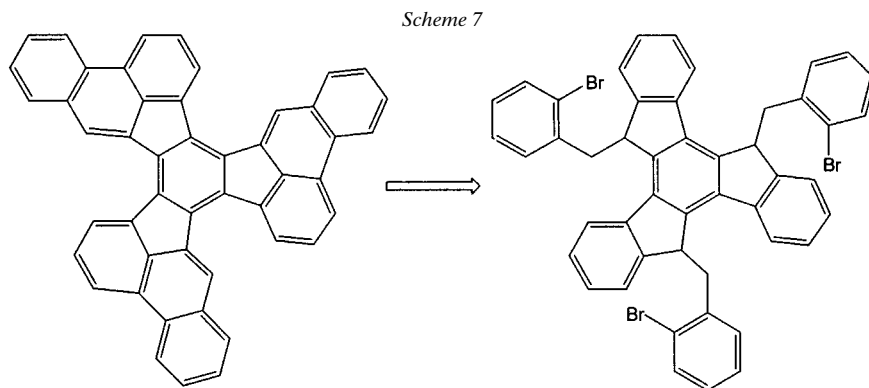


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As a last case (*Scheme 7*), we refer to a recently reported  $C_{48}$  hydrocarbon ( $C_{48}H_{24}$ ) that is not yet included in the *Beilstein* database. This symmetrical molecule may be classified as 3A and is indeed synthesised *via* symmetrical trialkylation [20].



**Conclusions.** – The smaller number of  $C_{47}$  compounds (7330) compared with  $C_{48}$  (11495) can be attributed to the greater difficulty of synthesizing the former. Whereas many of the  $C_{48}$  molecules contain two or more identical fragments, this is not the case for the  $C_{47}$  compounds. The suggestion that this difference is related to ease of synthesizing the compounds seems to be confirmed by spot checks of the actual syntheses. The  $C_{28}$  compounds show similar patterns to the  $C_{48}$  ones, though not so pronounced. Although these examples are limited to only a tiny fraction of the *Beilstein* database, they suggest that the origin of the observed even/odd disparity is to be found in the different ease of synthesis of the two classes of compounds. Generally, there are more simple synthetic routes to compounds with an even number of C-atoms than those with an odd number of C-atoms, so the former are easier to make. Of course,



there may be many other factors, but the one we have identified is probably the dominating one. This factor becomes more and more pronounced with increasing C-atom count. Indeed, for synthetic compounds with C-atom counts above  $C_{50}$ , the possible synthetic routes seem to become progressively limited to dimerisation reactions, leading to an even more conspicuous even/odd disparity in this range. One may ask how this disparity might change in the future as the number of reported organic compounds increases sharply, with the growing popularity of combinatorial chemistry techniques. Will such reasonably projected synthetic activity in the near future lead to a lessening or an accentuation of the even/odd disparity?

In conclusion, the even/odd disparity is unlikely to rest on any fundamental parity rule but seems to result mainly from the activities of the organic chemists who have succeeded in synthesizing such a vast number of compounds. The 'even' ones are on the whole easier to prepare than the 'odd' ones.

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*Received October 11, 1999*