References and Notes

1. E. G. Wever and M. Lawrence, *Physiological Acoustics* (Princeton Univ. Press, Princeton, 1954). Chapter 10 is an excellent summary of the protection theory as well as several other theories.
2. R. Galambos and A. Rupert, *J. Acoust. Soc. Am.* **31**, 349 (1959); F. B. Simmons, *Ann. Otol. Rhinol. Laryngol.* **68**, 1126 (1959); *ibid.* **69**, 1063 (1960); *ibid.*, in press.
3. The environment was a conditioned-avoidance shuttle box, in which the cat had been trained almost daily for 2 months, at threshold. For the figured test, suprathreshold sounds were used, to which it was obvious that the cat paid no attention.
4. More gross fluctuations have been described by Starr (personal communication), attributable to contractions associated with body movement. These, of course, also occurred in our cats but were usually recognizable. See, for example, II*B* here, at about 12 seconds after "tone on."
5. R. M. Pritchard, *Sci. Am.* **204**, 72 (1961).
6. This work was supported by National Institutes of Health grants B-2167 and B-3407.

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Chemical Indexing: An "Atom Total" Based on Cyclic Features of Structure

Abstract. The atom-total of a compound may be obtained from an equation which substitutes cyclic features of structure for hydrogen atoms. This method is useful for checking a compound's molecular formula against its structural formula or systematic name. While it applies to all chemical compounds, it is of most value for compounds with complex ring structures.

Writers as well as editors and indexers of technical papers generally make an atom count of an organic structure and check this total against the total of the previously determined molecular formula.

This method may work well enough with simple structures. However, when applied to complex structures, it is tedious, time-consuming, and often inaccurate. This results from the difficulty of including all the hydrogen atoms around the structure.

If the atom-total could be obtained by exclusion of hydrogen atoms from the count, the checking might possibly be simplified. Since it might be assumed that the other univalent atoms have replaced hydrogen in the molecule, all univalent atoms would be excluded from the count.

Soffer has shown how to generalize molecular formulas in terms of the number of cyclic features of structure (*1*). He has expressed this relationship in the following equation:

$$\rho = 1 + \tfrac{1}{2}\,\Sigma\, n_v(v-2)$$

where ρ is the number of cyclic features (rings and multiple bonds) and n is the number of atoms of covalence v. Soffer's equation can be solved for number of univalent atoms n_{I} as follows:

$$\rho = 1 + \tfrac{1}{2}\,[-n_{\text{I}} + n_{\text{III}} + 2n_{\text{IV}} + 3n_{\text{V}} + 4n_{\text{VI}} \ldots]$$

or

$$2\rho = 2 - n_{\text{I}} + n_{\text{III}} + 2n_{\text{IV}} + 3n_{\text{V}} + 4n_{\text{VI}} \ldots$$

Then

$$n_{\text{I}} = 2 + n_{\text{III}} + 2n_{\text{IV}} + 3n_{\text{V}} + 4n_{\text{VI}} \ldots - 2\rho$$

In its general form, the equation is

$$n_{\text{I}} = 2 + \sum_{v=2}^{8} n_v(v-2) - 2\rho.$$

Since cyclic features can be noted separately as rings and multiple bonds, the term ρ is expressed as the sum of rings R and double bonds Δ, or $\rho = R + \Delta$. (For this purpose, double bonds exist as two-membered rings.) Each triple bond contributes two cyclic features to the structure. Therefore triple bonds are expressed as 2Δ. However, for most cases the equation is

$$n_{\text{I}} = 2 + \sum_{v=2}^{8} n_v(v-2) - 2(R+\Delta). \quad (1)$$

Feldman (*2*) has used an equation similar to this to solve for number of hydrogen atoms for another purpose.

Derivation of an equation which eliminates consideration of univalent atoms from the atom-total is possible by substitution of Eq. 1 in an equation which expresses the total number of atoms in a molecule. The atom-total is, logically, the summation of all atoms, n, of covalence v.

$$T = \Sigma\, n_v$$

or

$$T = n_{\text{I}} + n_{\text{II}} + n_{\text{III}} + n_{\text{IV}} + n_{\text{V}} + n_{\text{VI}} + n_{\text{VII}} + n_{\text{VIII}} \quad (2)$$

where Roman numerals refer to the covalances of the respective atoms.

Substitution of Eq. 1 for n_{I} in Eq. 2 gives

$$T = 2 + n_{\text{II}} + 2n_{\text{III}} + 3n_{\text{IV}} + 4n_{\text{V}} + 5n_{\text{VI}} + 6n_{\text{VII}} + 7n_{\text{VIII}} - 2(R+\Delta)$$

or, in its general form,

$$T = 2 + \sum_{v=2}^{8} n_v(v-1) - 2(R+\Delta). \quad (3)$$

For most compounds, the equation can be reduced to

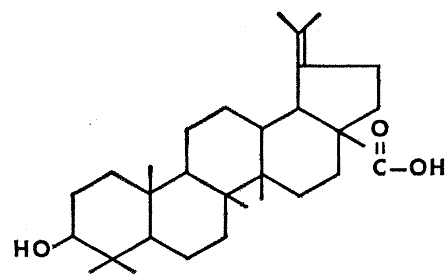
$$T = 2 + n_{\text{II}} + 2n_{\text{III}} + 3n_{\text{IV}} + 4n_{\text{V}} - 2(R+\Delta)$$

or, more specifically,

$$T = 2 + 3n_{\text{C}} + 2n_{\text{N,PIII}} + n_{\text{O,SII}} + 4n_{\text{PV}} - 2(R+\Delta)$$

where n_{C} is the number of carbon atoms; $n_{\text{N,PIII}}$ is the number of nitrogen or phosphorus(III) atoms; $n_{\text{O,SII}}$ is the number of oxygen or sulfur(II) atoms; and n_{PV} is number of phosphorus (V) atoms. Examples are as follows:

1) For betulinic acid, $C_{30}H_{48}O_3$ (81), the structure is



The structure shows that the equation must be

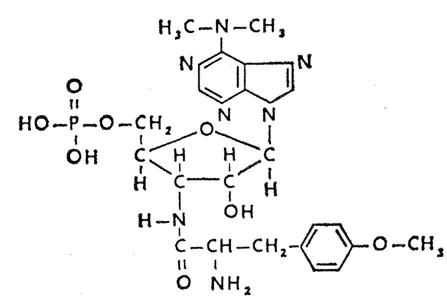
$$T = 2 + 3n_{\text{C}} + n_{\text{O}} - 2(R+\Delta)$$

and $n_{\text{C}} = 30$, $n_{\text{O}} = 3$, $R = 5$, and $\Delta = 2$.

$$T = 2 + 3(30) + 3 - 2(5+2) = 81.$$

From the molecular formula, 30 + 48 + 3 = 81, the total number of atoms in betulinic acid.

2) The molecular formula of puromycin 5′-phosphate is $C_{22}H_{30}N_7O_8P$ (68).



The equation is

$$T = 2 + 3n_{\text{C}} + 2n_{\text{N}} + n_{\text{O}} + 4n_{\text{P}} - 2(R+\Delta)$$

and $n_{\text{C}} = 22$, $n_{\text{N}} = 7$, $n_{\text{O}} = 8$, $n_{\text{P}} = 1$, $R = 4$, and $\Delta = 9$.

$$T = 2 + 3(22) + 2(7) + 8 + 4(1) - 2(4+9) = 68.$$

If the components of a given systematic name are familiar, the values for the n's, R, and Δ might be determined from the fundamental ring system plus increments, thus eliminating entirely the structural formula. For example:

1) The acetate of 17-hydroxy-6-methylprogesterone has a molecular formula of $C_{24}H_{34}O_4$ (62). From the name, n_{C} must be 21 (from progesterone) plus 2 (from acetate) plus 1

(from methyl-), or $n_C = 24$; n_O is 2 (from progesterone) plus 1 (from acetate) plus 1 (from hydroxy-), or $n_O = 4$; $R = 4$; and Δ is 3 (from progesterone) plus 1 (from acetate), or $\Delta = 4$.

$$T = 2 + 3(24) + 4 - 2(4 + 4) = 62.$$

2) If the systematic name, 2-chloro-10-(3-dimethylaminopropyl)-phenothiazine, is given, the total can be computed easily by adding increments to the fundamental phenothiazine ring system as follows: $n_C = 12 + 2 + 3 = 17$; $n_N = 1 + 1 = 2$; $n_S = 1$; $R = 3$; and $\Delta = 6$. The total is 40, the same as that of $C_{17}H_{19}ClN_2S$, the molecular formula of the compound.

The preceding methods of checking atom-totals are especially useful in the editing of technical reports and the indexing of chemical compounds according to their molecular formulas. The examples show that time might possibly be saved and that the possibility of error might be reduced for complex molecular structures. A few glances at a molecule's structure provide all information necessary for computing the molecule's total number of atoms.

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References and Notes

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Increased Incidence of Anencephalus and Spina Bifida in Siblings of Affected Cases

Abstract. In 139 families having a child born with anencephalus or spina bifida, 10 of 308 siblings of the affected children had malformations similar to those of the affected children. The incidence of these malformations in siblings of affected children is significantly greater than the incidence in the general population.

In recent years malformations of the central nervous system have been studied from many points of view, well summarized by Penrose (*1*). Studies of the familial aggregation of these malformations, however, have been few in number. Polman (*2*), investigated the families of 105 anencephalics and found 13 sibs with anencephalus and 11 sibs with spina bifida or other malformations of the central nervous system. Böök and Rayner (*3*) found no affected sibs in 46 anencephalic sibships. Penrose (*1*) found one anencephalic and two spina bifida cases in 21 anencephalic sibships. This report is concerned with a study of 139 sibships of anencephalic and spina bifida cases.

Table 1. Outcome of pregnancies in patients having two or more infants with malformations of the central nervous system. Abbreviations: *Ab.*, abortion; *An.*, anencephalic; *E*, encephalocele; *H*, hydrocephalic; *M*, meningocele, *Mm*, meningomyelocele; *N*, normal; *P.D.*, premature, died; *S.B.*, spina bifida.

Patient number	Pregnancy number									
	1	2	3	4	5	6	7	8	9	10
1	Ab.	S.B.*	N	An.*	N					
2	N	P.D.	P.D.	An.*	N	Mm*	P.D.	N		
3	P.D.	N	N	An.†	N	N	N	N	An.*	An.‡
4	N	N	N	E*	N	N	An.*			
5	N	N	M*	S.B.*	N					
6	P.D.	P.D.	§*	S.B.*	N					
7	H‖	Ab.	Mm*							
8	S.B., H*	N	M*							
9	An.*	N	M*	N						
10	N	An.*	An.*							

* Ascertaining case. † Born outside study area. ‡ Born outside study period. § Premature twins, one with spina bifida. ‖ Not reported on birth certificate.

The records of birth and stillbirth filed at the New York State Department of Health and records of the three maternity hospitals in Albany, New York, were used as source material.

Sibships were ascertained by the following criteria. A case was defined as an infant born at one of the three maternity facilities in Albany, New York, in the years 1945 to 1960, with anencephalus or spina bifida (spina bifida, meningocele, meningomyelocele, myelocele, rachischisis) reported on the certificate of birth or stillbirth. Two procedures were followed to locate the sibs of each case: the hospital record of the mother of each case was searched and her pregnancy history was recorded, and the New York State Department of Health birth indexes were searched for the births noted on the hospital record and for any other births recorded to the mother. In this way all recorded births to these mothers which occurred in upstate New York were discovered.

Copies of the birth records of the index cases and their sibs were assembled into sibships and analyzed. Sixty-four anencephalic and 75 spina bifida sibships were assembled. Three hundred and eight siblings of index cases were found in these families, counting only one index case per family. Nine of the 139 families had a second child with a central nervous system malformation, and one family had a second and a third child with a central nervous system malformation. Five families had a second child with malformation not of the central nervous system. The ten sibships with two or more malformations of the central nervous system are presented in Table 1. In these families 24 of 53 known pregnancies had a normal outcome. This is in marked contrast to the findings of Labrum and Wood (*4*) who found only 4 of 30 pregnancies normal in ten families having two or more malformed infants.

The incidence of anencephalus and spina bifida in upper New York state over the years of this study was 200 cases per 100,000 live and stillbirths. The population incidence was determined with precisely the same definition of a case as was used in ascertaining cases in the sibships. Applying this rate to the 308 siblings one would expect less than one case (0.6) of malformation in this number of births. Actually, ten cases were observed, a statistically significant excess. Eight of the ten cases in sibs were primarily ascertained. One case was born outside of the study area, and one case was born out of the study period.

These findings support the conclusion that anencephalus and spina bifida have a much higher incidence among siblings of affected children than in the general population. On a geographic basis, the highest malformation rates per birth were overwhelmingly confined to low socioeconomic areas in the oldest sections of Albany. This is consistent with Edwards' (*5*) finding of an increased incidence of malformations of the central nervous system in lower socioeconomic groups.

No aggregation in year or month of birth of the affected cases was noted.

In New York state more than 99.4 percent of births occur in hospitals and are reported to the Department of Health. This obviates bias which could