Antibiotic activity of organic compounds and their average quasi-valence number

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Summary. It is shown that the average quasi-valence numbers of antibiotics inhibiting protein synthesis are well defined and lie in the region of average quasi-valence numbers of amino acids, while the average quasi-valence numbers of antibiotics inhibiting DNA or RNA synthesis have higher values. Possible explanations of these findings and their implications on the design and selection of antibiotics are discussed.

Material and methods. Carcinogenic and cytostatic properties of organic substances have been analyzed recently in the framework of simple valence theory[1,2]. It was shown that the average quasi-valence number Z*, defined as the ratio of all atomic valence electrons[3] and the number of atoms in a given molecule, has different values for potential carcinogens and noncarcinogens[1], as well as in the case of alkylating cytostatics and antimetabolites[2]. The results obtained in 2 previous works stressed the importance of the average electronic charge carried by organic molecules in complex biological systems.

The correlation of some biological effects of chemical substances and their Z* values opened a hope of obtaining a simple parameter which influences or governs the behaviour of organic molecules in living matter. In order to check this inviting possibility in a more systematic way, we turned our attention to antibiotics - a class of organic substances characterized by multiplicity and by diversity of action.

Results and discussion. In our analysis of the antibiotic - Z* relationship, we shall use the data from the recent 'Encyclopaedia of Antibiotics' by Glasby[4], which covers a great number of antibiotics, giving their molecular formulae, structures, origins, activities, etc. On the basis of the known molecular formulae for 1002 antibiotics we have calculated the corresponding Z* values and obtained the results presented in figure 1.

The distribution of antibiotics has some characteristic features: sharp cut-off at lower Z*, tailing towards higher Z*, and a small and rather wide bump around Z* = 3.15. We shall now concentrate our attention on 3 distinct groups of antibiotics with well-defined action on the molecular level: inhibitors of protein synthesis, inhibitors of DNA synthesis and inhibitors of RNA synthesis.

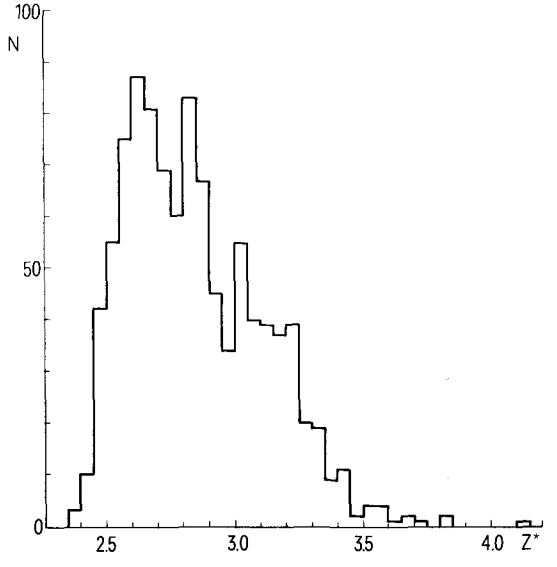

Fig. 1. Number of antibiotics of all types vs. average quasi-valence number Z*.

The table and the corresponding figure 2 contain all inhibitors of protein synthesis discussed by Pestka[5] for which we were able to find the molecular formulae. For comparison of the Z* values listed in the table, we also give the Z* values for amino acids, and for purine and pyrimidine bases. As can be seen, out of 64 antibiotics inhibiting protein synthesis, 62 lie in the region of amino acid Z* values. Only althiomycin ($Z^* \simeq 3.34$) and sparsomycin ($Z^* = 3.30$) fall out of this region. However, this may be due to the uncertainty of their molecular formulae. The molecular weights of these compounds listed by Pestka[5] do not agree with their formulae given by Glasby[4]. If we form a mean value of Z* for all antibiotics inhibiting protein synthesis listed in the table, we get: $\overline{Z^*}_{64} = 2.78 \pm 0.15$, which overlaps with the mean value of Z* for amino acids: $\overline{Z^*}_{20} = 2.82 \pm 0.18$. It is important to notice that potential carcinogens[1] and alkylating cytostatics[2] also cover the region of amino acid Z* values. For this reason it is not surprising that some antibiotics which are inhibitors of protein synthesis are carcinogenic.

On the other hand, antibiotics inhibiting DNA synthesis or inhibiting RNA synthesis[7] (table, d and e) are characterized by a higher $\overline{Z^*}$; $\overline{Z^*}_{14} = 3.00 \pm 0.15$ and $\overline{Z^*}_{21} = 2.95 \pm 0.17$, respectively, which are closer to the Z* values of purine and pyrimidine bases. Due to the rather small number of these kinds of antibiotics, we can take them only as control groups. Other substances which are inhibitors of nucleic acid synthesis[6] (table, f) possess higher Z* values, too. For comparison we also quote the Z* values of some nucleic acid derivates. For 56 derivates, the mean Z* value is 3.34 ± 0.16[8].

Antibiotics[7]: inhibitors of cell-wall synthesis (Z* around 3.0), inhibitors of mitochondrial action (Z* around 2.6), and inhibitors of reverse transcriptase (Z* around 2.9) influence the distribution presented in figure 1. Some of them, together with the antibiotics inhibiting DNA or RNA synthesis, contribute to the bump at $Z^* \simeq 3.15$ and cause tailing towards higher Z*. The sharp cut-off of the distribution at low Z* corresponds to the borderline value of amino acids.

It is also interesting to analyze the Z* values for a group of chemically closely related antibiotics. In the penicillin group of antibiotics (table, g), with the exception of penicillin BT, all antibiotics have rather close Z* values. This may

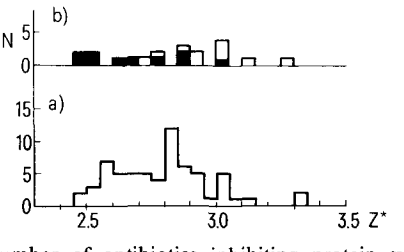

Fig. 2. *a* Number of antibiotics inhibiting protein synthesis vs. average quasi-valence number Z*. *b* Number of amino acids vs. average quasi-valence number Z* (shaded-essential, nonshaded-nonessential amino acids).

Average quasi-valence numbers of some organic compounds

Name of compound	Molecular formula	Z*
a) Amino acids †		
Leucine (+)	$C_6H_{13}NO_2$	2.45
Isoleucine (+)	$C_6H_{13}NO_2$	2.45
Lysine (+)	$C_6H_{14}N_2O_2$	2.50
Valine (+)	$C_5H_{11}NO_2$	2.53
Threonine (+)	$C_4H_9NO_2$	2.63
Arginine (+)	$C_6H_{14}N_4O_2$	2.69
Proline	$C_5H_9NO_2$	2.71
Alanine	$C_3H_7NO_2$	2.77
Phenylalanine (+)	$C_9H_{11}NO_2$	2.78
Asparagine	$C_4H_8N_2O_2$	2.88
Methionine (+)	$C_5H_9NO_2S$	2.89
Tryptophan (+)	$C_{11}H_{12}N_2O_2$	2.89
Glutamine	$C_5H_{10}N_2O_3$	2.90
Tyrosine	$C_9H_{11}NO_3$	2.92
Histidine (+)	$C_6H_9N_3O_2$	3.00
Serine	$C_3H_7NO_3$	3.00
Glycine	$C_2H_5NO_2$	3.00
Cysteine	$C_3H_7NO_2S$	3.00
Glutamate	$C_5H_8N_2O_3$	3.11
Aspartate	$C_4H_7NO_4$	3.25
b) Purine and pyrimidine bases		
Thymine	$C_5H_6N_2O_2$	3.20
Cytosine	$C_4H_5N_3O$	3.23
Adenine	$C_5H_5N_5$	3.33
Guanine	$C_5H_5N_5O$	3.50
Uracil	$C_4H_4N_2O_2$	3.50
c) Antibiotics inhibiting protein synthesis		
Althiomycin	$C_{27}H_{28}N_8O_{10}S_3$ (?)	3.34 (?)
Dihydrostreptomycin	$C_{21}H_{41}N_7O_{12}$	2.86
Streptomycin	$C_{21}H_{39}N_7O_{12}$	2.91
Bluensomycin	$C_{21}H_{39}N_5O_{14}$	2.94
Gentamycin C_1	$C_{21}H_{43}N_5O_7$	2.55
Kanamycin	$C_{18}H_{36}N_4O_{11}$	2.81
Neomycin B	$C_{23}H_{46}N_6O_{13}$	2.80
Neomycin C	$C_{23}H_{46}N_6O_{13}$	2.80
Paramomycin	$C_{23}H_{45}N_5O_{14}$	2.83
Spectinomycin	$C_{14}H_{24}N_2O_7$	2.81
Kasugamycin	$C_{14}H_{25}N_3O_9$	2.94
Amicetin	$C_{29}H_{44}N_6O_9$	2.77
Bamicetin	$C_{28}H_{40}N_6O_9$	2.79
Plicatin	$C_{25}H_{35}N_5O_7$	2.81
Blasticidin S	$C_{17}H_{26}N_8O_5$	2.93
Gougerotin	$C_{16}H_{24}N_7O_8$	3.11
Hikizimycin	$C_{13}H_{29}N_3O_{10}$	2.84
Chloramphenicol	$C_{11}H_{12}N_2O_5Cl_2$	3.06
Edeine A	$C_{32}H_{58}H_{10}O_{10}$	2.69
Edeine B	$C_{33}H_{60}N_{12}O_{10}$	2.71
Fusidic acid	$C_{31}H_{48}O_6$	2.45
Acetoxycycloheximide	$C_{17}H_{25}NO_6$	2.73
Cycloheximide	$C_{15}H_{23}NO_4$	2.60
Streptovitacin A	$C_{15}H_{23}NO_5$	2.68
Streptimidone	$C_{16}H_{23}NO_4$	2.64
Lincomycin	$C_{18}H_{34}N_2O_6S$	2.59
Clindamycin	$C_{18}H_{34}N_2O_5S$	2.53
Celesticetin	$C_{24}H_{36}N_2O_9S$	2.81
Carbomycin	$C_{40}H_{67}NO_{16}$	2.65
Erythromycin	$C_{37}H_{67}NO_{13}$	2.53
Leucomycin A_1	$C_{40}H_{67}NO_{14}$	2.59
Niddamycin	$C_{40}H_{65}NO_{14}$	2.62
Oleandomycin	$C_{35}H_{61}NO_{12}$	2.55
Spiramycin III	$C_{46}H_{78}N_2O_{15}$	2.57
Tylosin	$C_{45}H_{77}NO_{17}$	2.60
Negamycin	$C_9H_{20}N_4O_4$	2.70
Pactamycin	$C_{28}H_{38}N_4O_8$	2.79
Puromycin	$C_{22}H_{29}N_7O_5$	2.89
Sparsomycin	$C_{31}H_{21}N_3O_6S_2$ (?)	3.30 (?)
Griseoviridin	$C_{22}H_{27}N_3O_7S$	2.97
Mikamycin A	$C_{31}H_{39}N_3O_9$	2.83
Ostreogrycin A	$C_{28}H_{35}N_3O_7$	2.79
Staphylomycin M_1	$C_{28}H_{36}N_3O_8$	2.81
Streptogramin A	$C_{24}H_{37}N_3O_7$	2.68
Virginiamycin M	$C_{28}H_{38}N_3O_7$	2.72

Average quasi-valence numbers of some organic compounds

Name of compound	Molecular formula	Z*
Mikamycin B	$C_{45}H_{54}N_8O_{10}$	2.85
Ostreogrycin B	$C_{45}H_{54}N_8O_{11}$	2.88
Staphylomycin S	$C_{28}H_{36}N_3O_8$	2.81
Streptogramin B	$C_{45}H_{54}N_8O_{10}$	2.85
Vernamycin B_α	$C_{44}H_{52}N_8O_{10}$	2.88
Virginiamycin S	$C_{42}H_{47}N_7O_{10}$	2.92
Tetracycline	$C_{22}H_{24}N_2O_8$	3.04
Chlortetracycline	$C_{22}H_{23}N_2O_8Cl$	3.04
Tenuazonic acid	$C_9H_{15}NO_3$	2.64
Siomycin A	$C_{74}H_{92}N_{19}O_{19}S_5$	3.00
Thiopeptin B	$C_{72}H_{90}N_{18}O_{22}S_6$	3.06
Thiostrepton	$C_{69}H_{80}N_{18}O_{17}S_5$	3.06
Crotocin	$C_{19}H_{24}O_5$	2.71
Trichodermin	$C_{17}H_{24}O_4$	2.58
Trichothecin	$C_{15}H_{20}O_4$	2.67
Verrucarin A	$C_{27}H_{34}O_9$	2.80
Lankamycin	$C_{42}H_{72}O_{16}$	2.58
Methymycin	$C_{25}H_{43}NO_7$	2.50
Pleuromutilin	$C_{22}H_{34}O_5$	2.49
d) Antibiotics inhibiting DNA synthesis		
Antharamycin	$C_{16}H_{17}N_3O_4$	3.00
Bleomycin	$C_{50}H_{72}O_{21}N_{14}S_2$	3.02
Bruneomycin	$C_{25}H_{22}O_8N_4$	3.22
Lucensomycin	$C_{36}H_{53}O_{13}N$	2.72
Mitomycin	$C_{16}H_{19}N_3O_6$	3.05
Myxin	$C_{13}H_{10}O_4N_2$	3.31
Nalidixic acid	$C_{12}H_{12}N_2O_3$	3.03
Novobiocin	$C_{31}H_{36}O_{11}N_2$	2.95
Phleomycin	$C_{53}H_{91}N_{17}O_{32}Cu$	3.00
Pluramycin	$C_{20}H_{25}NO_5$	2.75
Primycin	$C_{55}H_{102}O_{17}N_2^+ \cdot 0.5\ SO_4^{2-}$	2.52 (?)
Streptonigrin	$C_{25}H_{22}N_4O_8$	3.22
Streptozotocin	$C_8H_{15}O_7N_2$	3.09
Tubercidin	$C_{11}H_{14}N_4O_4$	3.09
e) Antibiotics inhibiting RNA synthesis		
Aburamycin	$C_{57}H_{84}O_{25}$	2.78
Actinomycin	$C_{62}H_{86}N_{12}O_{16}$	2.78
alpha-Amanitin	$C_{39}H_{54}N_{10}O_{14}S$	2.97
Aureolic acid	$C_{52}H_{76}O_{24}$	2.82
Chromocyclomycin	$C_{48}H_{62}O_{21}$	2.90
Chromomycin	$C_{21}H_{24}O_9$	3.00
Cordycepin	$C_{10}H_{13}N_5O_3$	3.10
Decoyinine	$C_{11}H_{13}N_5O_4$	3.21
Echinomycin	$C_{50}H_{60}N_{12}O_{12}S_2$	2.97
Gliotoxin	$C_{13}H_{14}N_2O_4S_2$	3.20
Hadacidin	$C_3H_5NO_4$	3.54
Miracil D	$C_{20}H_{24}N_2OS$	2.63
Mithramycin	$C_{52}H_{76}O_{24}$	2.82
Nogalamycin	$C_{38}H_{51}NO_{17}$	2.90
Psicofuranine	$C_{11}H_{15}N_5O_5$	3.17
Rifampicin	$C_{43}H_{58}N_4O_{12}$	2.75
Sibiromycin	$C_{24}H_{31}O_7N_3$	2.83
Streptolydigin	$C_{32}H_{44}N_2O_9$	2.71
Streptovaricins	-	2.82–2.89
Toyokamycin	$C_{12}H_{13}N_5O_4$	3.24
Variamycin	$C_{52}H_{76}O_{24}$	2.82
f) Inhibitors of nucleic acid synthesis		
- Analogs of adenosine		
6-Mercaptopurine	$C_5H_4N_4S$	3.57
Xylosyladenine	$C_{10}H_{13}N_5O_5$	3.27
Tubercidin	$C_{11}H_{14}N_4O_4$	3.09
- Analogs of guanosine		
Imuran	$C_9H_7N_7O_2S$	3.69
Cordycepin	$C_{10}H_{13}N_5O_3$	3.10
Formycin	$C_{10}H_{11}N_4O_5$	3.37
- Analogs of uridine and cytidine		
6-Azauridine	$C_8H_{11}N_3O_6$	3.36
5-Aminouridine	$C_9H_{13}N_3O_6$	3.23
- Analogs of deoxythymidine		
5-Azaorotic acid	$C_4H_3N_3O_4$	4.14
Showdomycin	$C_9H_{11}NO_6$	3.26

Average quasi-valence numbers of some organic compounds

Name of compound	Molecular formula	Z*
g) Penicillin group of antibiotics		
Penicillin BT	$C_{14}H_{22}O_4N_2S_2$	2.82
Penicillin N	$C_{14}H_{21}O_6N_3S$	2.98
Penicillin O	$C_{13}H_{18}O_4N_2S_2$	2.97
Penicillin S	$C_{14}H_{18}O_4N_2S_2Cl$	2.95
Penicillin V	$C_{16}H_{18}O_5N_2S$	3.05
Penicillin V potassium salt	$C_{16}H_{17}O_5N_2SK$	3.05

† Essential amino acids are marked with (+).

provoke some questions. Does the large deviation from $Z^* \simeq 3.0$ necessarily lead to less penicillin-like antibiotic activity or not? What would happen if one attaches low or high Z* groups, like CH_3 or NO_2, for example, to a normal penicillin molecule? Does a small modification of the given molecule, which causes a slight change of its Z*, create a new effective drug which can solve the problem of resistance to the original antibiotic already used? These questions and similar ones require new investigations and better understanding of the Z* role.

The fact established in this work that antibiotics inhibiting protein synthesis possess well-defined Z* values (overlapping with the Z* values of amino acids) tells us that the average electronic charge carried by molecules plays an important role in their activity. Most probably during the transport of molecules, or their approach to the reaction centres, some preselection on the basis of their average quasi-valence numbers occurs. More complex characteristics (structural characteristics of molecules, which play a decisive role in molecular interactions in living matter) come into play after the molecular preselection. The selection of molecules according to their Z* values could be explained by the dependence of electrostatical interactions on the potential, for which it was shown[1] that it is a function only of the Z*.

If more detailed investigations of the antibiotic activity - Z* correlation give support to our findings, we shall get guidance for design and selection of new antibiotic drugs. Making necessary chemical modifications of selected substances, we could obtain the desired Z* values, and perhaps accelerate our efforts to create new effective antibiotics. The other benefit of new investigations within the framework of simple valence theory might be connected with better understanding of antibiotic behaviour in living matter[8].

1 V. Veljković and D.I. Lalović, Experientia *33*, 1228 (1977).
2 V. Veljković and V. Ajdačić, Experientia *34*, 639 (1978).
3 In case of halogen elements instead of Z = 7, Z = 1 should be used.
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6 E.F. Gall, E. Cundliffe, P.E. Reynolds, M.H. Richmond and M.J. Waring, in: The Molecular Basis of Antibiotic Action, p. 173. John Wiley & Sons, New York 1972.
7 Y. Miura, Antibiotics and Replication - Table. Document No. 4954, published by Calbiochem, P.O. Box 12087, San Diego, Cal. 92112, USA.
8 V. Veljković and V. Ajdačić, to be published.

Note added in proof: Dr. S. Pestka (private communication) for althiomycin used the formula $C_{16}H_{17}N_5O_6S_2$, as given in J. Antibiot. *28*, 286 (1975), and for sparsomycin $C_{13}H_{19}N_3O_5S_2$, as reported in J. Am. chem. Soc. *92*, 417 (1970). The corresponding Z* are: 3.35 and 3.05, instead of 3.34 and 3.30, respectively.

The inhibitory effects of a dermal extract upon granulation tissue[1]

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Summary. Injection of a water-soluble dermal extract into adult rats resulted in depression of DNA synthesis in granulation tissue at 3 different sites of injury, but not in epithelium. This suggests that connective tissue proliferation may be controlled in part by a chalone-like mechanism.

In vitro studies have shown that factors in cell extracts and dialyzed media from cell cultures can inhibit the growth of WI-38 cells and human cutaneous fibroblasts[2,3]. These studies suggest that a tissue-specific, species non-specific, inhibitory factor may be responsible. However, there are no published reports to support the hypothesis that such a mechanism is operating in vivo. Our experiments demonstrate tissue-specific inhibition of connective tissue promechanism is operating in vivo. Our experiments demonstrate tissue-specific inhibition of connective tissue proliferation in healing wounds at 3 different sites of injury in young adult male rats by a tissue extract of neonatal rat dermis. Species specificity of the tissue extract has not been tested.

Material and methods. In order to prepare a dermal tissue extract free of contaminating epidermis, approximately 100 neonatal Sprague-Dawley rats were decapitated and their skins removed. These skins were immersed for 30 sec in 55 °C water and cooled on ice[4]. Following separation of dermis from epidermis with forceps, the 2 portions of each skin were placed in separate containers of liquid nitrogen. The accumulated dermis tissue was powdered with mortar and pestle, homogenized in 0.02 M Tris-HCl buffer at pH 7.15, and centrifuged at 10,800 × g for 30 min at 4 °C. The supernate was dialyzed against 0.02 M Tris-HCl buffer, lyophylized and stored at −20 °C until ready for use. The dermal extract (DE) was reconstituted with 0.02 M Tris-HCl buffered saline, pH 7.15 to a protein concentration of 10 mg/ml[5]. Neonatal liver extract (LE) was prepared in the same manner.

5 surgical excisions were made in each experimental and control animal. A back wound, 1 cm^2, was made to the depth of the fatty s.c. tissue (figure A). Full thickness excisional wedges were removed from the pinnae of both ears. They were 3 mm wide at the edge and extended 4 mm deep (figure B). And finally, bilateral palatal excisions were made beginning at a line 1 mm medial to each maxillary 1st molar and extending to the cemento-enamel junction of the tooth (figure C). The effects of the tissue extracts upon proliferation of granulation tissue at each wound site, as well as maxillary mucosal epithelium, was evaluated by autoradiography. Tritiated thymidine (0.5 μCi ^{3}HTdR/g b. wt, sp. act. 6.7 Ci/mmole) was injected i.p. 1 h before sacrifice in all cases. In a preliminary experiment, nuclear