erosion. In Nature, the instances of capillary or porous flow are far more numerous and varied than those of turbulent flow, and the phenomenon consequently deserves some attention[15].

Résumé. On a étudié l'écoulement d'une suspension de globules rouges et de diverses solutions, soit dans un tube capillaire de 0,7 mm de diamètre, soit en milieux poreux (papiers de cellulose, papiers de verre, toile de verre) en déterminant la répartition des solutés dans les zones limites solution-solvant et en la comparant aux valeurs théoriques.

Dans le tube capillaire, les globules rouges s'écoulent toujours plus vite que la vitesse moyenne de l'eau. Protéine et polysaccharide font de même tant que la vitesse d'écoulement est assez rapide. Les sels minéraux se déplacent exactement à la même vitesse que l'eau. En milieux poreux, toutes les substances étudiées montrent une avance de 1,1 à 1,4 sur la vitesse de l'eau.

On attribue ce phénomène à la poussée hydrodynamique centripète que reçoivent les solutés dans l'écoulement laminaire cylindrique, qui les déplace vers les lignes de courant plus rapide.

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COGITATIONES

Correlation of the Biological Activity of Organic Compounds by Means of the Linear Free Energy Relationships

During recent years, evidence has been accumulated about the possibilities of correlating the biological activity of substances with physical constants characterizing a certain part or the whole molecule under investigation. Obviously, this attempt is useful not only from the practical viewpoint (possibility of predicting the biological activity) but also for theoretical reasons, primarily for the study of the mechanism of the biological process. For example, relationships between biological activity and chemical reactivity, polarographic half-wave potentials, oxidation-reduction potentials and solubility of the active compounds have been found. This field has recently been reviewed[1]. In this connection it seems especially attractive to investigate the possibility of utilizing the linear free energy relationships well known from theoretical organic chemistry[2-5]. Hitherto, this correlation has been established in several cases by means of the Hammett equation[6-13] and the recently proposed $\alpha\beta$-equation[14-16]. It seems desirable to study this problem in a more systematic way.

Let us suppose that the biological efficiency is governed, for example, by the value of the partition coefficient p of the active compound between a polar and non-polar liquid phase. This means that the biological efficiency is in principle determined by this physical magnitude. Let us suppose, moreover, that the efficiencies $e_{i,1}$ and $e_{i,2}$ are studied of a series of compounds (i denotes the i-th member) in two biological systems (1 and 2); for the dependences on p holds: $e_{i,1} = f_1(p_i)$ and $e_{i,2} = f_2(p_{i,2})$. Evidently, a function exists fitting the relation $e_{i,1} = f(e_{i,2})$ which might be a linear one. In this way we have made the biological data 'independent' of a certain more or less arbitrarily chosen magnitude. Then we can investigate the connection with various types of constants in a more systematic way. This approach was tacitly used in the following discussion (see[14]). It is clear that the same consideration could be applied to the chemical reactivity.

Definitions of some Concepts

Biological Object: the experimental animal or the object on cell or molecular level; this object is treated with the *biologically active* substance which may be any defined organic compounds. In the present work we are concerned with the investigation of compounds (with a certain functional group) whose substituents are structurally related. *Biological system:* the system consisting of a biological object and a series of biologically active compounds in interaction.

The biological effect of the compound under study is a manifestation caused, as a rule, by a number of processes, which take place in a biological system. The process *governing* the magnitude of the biological effect (biological efficiency) is to be termed the *efficiency-determining step*. In principle, this process can be either a chemical reaction between the functional group of the biologically active compound and the reactivity centre in the biological object or a process the nature of which resembles the partition of a compound between two immiscible liquid phases[17]. In the first case we shall speak of a chemical reaction as an efficiency-determining step and in the second case of a physical process.

Linear Free Energy Relationships: These relations can be characterized by Eq. 1

$$E_i - E_r = \phi\varrho_i \qquad (1)$$

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where E_i and E_r mean the free energy change of the investigated equilibrium or kinetic process for the i-th and reference member of the series of structurally related compounds. ϕ and ψ_i are constants the first of which characterizes the given reaction system while the second describes the structural difference between the i-th and reference members; it does not depend on the value of the constant ϕ.

When characterizing the equilibrium or rate process by the equilibrium or rate constants the magnitudes proportional to energy, i.e. logarithms of the constants, occur in Eq. 1 instead of the energies E_i and E_r. The biological efficiency expressed for example by means of the equitoxic concentrations or by the concentrations causing 50% prolongation of the inductive period is often a magnitude proportional to the equilibrium or rate constants of the reaction of the biologically active substance with the respective centre in the biological object. Therefore, $\log k_i$ (k_i means equilibrium or rate constants) can be replaced by the logarithm of the biological efficiency, $\log \tau_i$, expressed by concentration. Recently HANSEN[12] has dealt with this problem in detail. According to the nature of the efficiency-determining step and biologically active compounds, six special forms of Eq. 1 can be suggested. In Eqs. 1a–1f, the constants α, ϱ^*, α_H, ϱ, α_P and X stand for ϕ (Eq. 1) and the constants β, σ^*, β_H, σ, β_P, and A for ψ_i (Table I). The significance of constants α, β[14], ϱ^*, σ^*[3] and ϱ, σ[2] has already been defined, A stands for WHELAND's atomic localization energy[18,19]; the meaning of the constants α_H and α_P (β_H and β_P) is analogous to that of α (β). When the biological data fit some of the equations of the Eq. 1 type, the plot of $\Delta \log \tau_i [\equiv \log(\tau_i/\tau_r)$, where $\tau_i(\tau_r)$ means the efficiency of the *i-th* (reference) member expressed by molar concentrations] against the constants which stand for ψ_i yields a straight line, the slope of which is equal to ϕ.

If we imagine in the place of τ_i the equilibrium or rate constants (Eqs. 1b, 1d and 1f) we see immediately that the relations result which are well known from the theory of chemical reactivity, namely, the TAFT equation[3], HAMMETT equation[2] and the relation including the atomic localization energy[4,5]. Equations 1a, 1c, 1e concern specifically the biological systems. We devoted a considerable interest to Eq. 1a. It is suitable for the correlation of the biological efficiency of various aliphatic compounds of the type R_iX, where R_i means an alkyl and X stands for a functional group. TRČKA et al.[16] have proved the applicability of this equation to series of compounds in which the group X is comparatively large. Until now the TAFT equation (1b) has been utilized only to a limited degree. It seems that the effect of dioxalans on isolated bowels[20] and the toxicity of phenyl alkyl sulphides for white laboratory mice[21] obey this equation. In general, it can be expected that this equation will be used with such aliphatic compounds the functional group of which is relatively highly reactive. Moreover, these compounds should be active in biological objects in which the efficiency-determining proceeds in a place readily accessible to molecules of the biologically active substances, e.g. on the cell surface.

While the Hammett equation 1d has been exploited several times (Table II), only very recently VLACHOVÁ et al.[13] have proved (with *m*- and *p*-substituted phenyl *iso*thiocyanates) that the correlation with Eqs. 1c and 1d can serve for the determination of the nature of the efficiency-determining step. So the recent proposal was

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Tab. I. Linear free-energy relationships in biological systems

Compounds	Efficiency-determining step	
	Physical process	Chemical reaction
Aliphatic compounds	$\Delta \log \tau_i = \alpha\beta$ (1a)	$\Delta \log \tau_i = \varrho^*\sigma^*$ (1b)
m- and *p*-substituted benzene derivatives	$\Delta \log \tau_i = \alpha_H\beta_H$ (1c)	$\Delta \log \tau_i = \varrho\sigma$ (1d)
Polynuclear aromatic compounds	$\Delta \log \tau_i = \alpha_P\beta_P$ (1e)	$\Delta \log \tau_i = \varkappa A$ (1f)

Tab. II. Hammett's ϱ-constants for biological systems

ϱ	Biological object, biologically active compounds, process	Ref.
~0	—, arsenosobenzenes, parasiticidal activity	6
0.55	*Staphylococcus aureus*, G-penicillins, growth inhibition	12
0.7	*Staphylococcus aureus*, chloramphenicol analogues, growth inhibition	12
1.06 (1.62)	Brain acetylcholine esterase, *p*- (*m*-) subst. N-phenylcarbamates, inhibition of acetylcholine hydrolysis	8
1.20	Larvae of the mosquite *Aedes aegypti*, substituted benzoic acids, LD_{50}	12
1.26	White laboratory rats, substituted anilines, methaemoglobine formation	11
1.4	*Escherichia coli*, chloramphenicol analogues, growth inhibition	12
1.53	Dehydrogenase, substituted isatines, activity decrease of aniline dehydrogenase	10
1.76	*Escherichia coli*, substituted phenyl *iso*thiocyanates, breath inhibition	13
2.38	*Escherichia coli*, substituted phenyl *iso*thiocyanates, growth inhibition	13
3.67	Brain acetylcholine esterase, substituted phenyl diethyl esters of phosphoric acid, inhibition	9
5.8	Erythrocytes, substituted phenyl dimethyl esters of phosphoric acid, inhibition of choline esterase	7

confirmed[1]. In systems in which no parallelism between $\log \tau_i$ and σ was established, a sufficiently close correlation was found between $\log \tau_i$ and logarithm of molar solubility of biologically active compounds (see Figures 1 and 2). In this second instance, in fact, a modified $\alpha\beta$-equation is used. The logarithms of molar solubilities of substituted phenyl *iso*thiocyanates have been used as the provisional values of β^H-constants. A more thorough investigation of this and of Eq. 1e has been started. Equation 1e has not yet been used. On the other hand, Eq. 1f has been used. As examples, the relations between the magnitude of the cancerogenic[22–25], cancerostatic[26], and auxin[27] activities and certain quantum chemical reactivity indices should be mentioned. Moreover, it can be expected that in the literature data will be found permitting semiquantitative use of Eq. 1f. As an example could serve the biological activity of bis(β-chloroethyl)-arylamines derived from polynuclear aromatic hydrocarbons[28] (see also[1]).

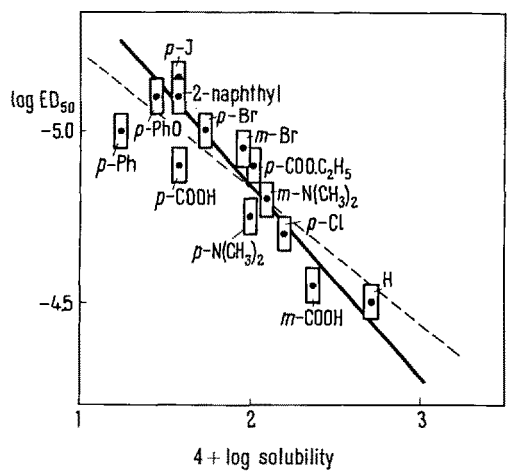

Fig. 1. Growth inhibition of *Candida albicans* on liquid vitamine substrate by *m*- and *p*-substituted phenyl *iso*thiocyanates (ED_{50} means the effective doses) plotted against the logarithm of molar solubilities of biologically active compounds in 50% aqueous ethanol. Correlation coefficient of the whole set $r = 0.874$ (dash line); the same magnitude for the set not including the two most deviated points $r' = 0.959$ (full line).

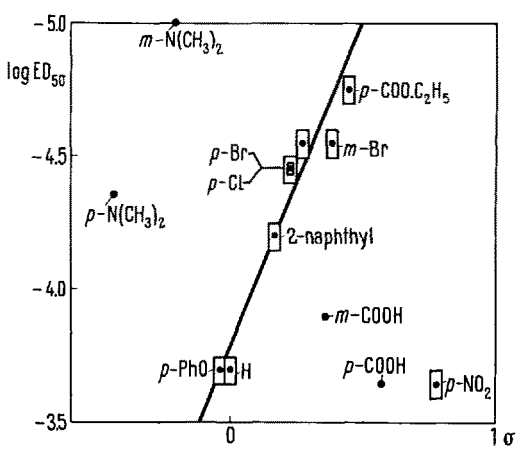

Fig. 2. Growth inhibition of *Escherichia coli* on glycerol substrate by *m*- and *p*-substituted phenyl *iso*thiocyanates plotted against HAMMETT constants σ. Correlation coefficient $r = 0.959$ of the set not including the data for compounds with ionizing groups (designated •) and the nitro derivative (which reacts before reaching the reactive centre in biological system owing to its extreme reactivity).

Applicability of Eqs. 1a–1f. First of all, these equations make it possible to characterize the biological system under study by means of only one constant (ϕ in Eq. 1). This constant serves for calculating the biological efficiency of a derivative not yet experimentally studied. For this calculation, naturally, the value of ψ_k must be known when the activity of the *k-th* derivative is to be evaluated. When the data for a certain compound deviate significantly from the regression line holding for the given biological system, then the idea is supported that the compound acts by a different mechanism.

Furthermore, Eqs. 1a–1f permit a decision whether the efficiency-determining step is a physical process (satisfying Eqs. 1a, 1c, 1e) or a chemical reaction (satisfying Eqs. 1b, 1d, 1f). This is understandable because of the fact that no parallelism exists between the constants β and σ^* and also β_H and σ (the constants β_P and A have not yet been studied). Finally, it is evident that the equations under discussion offer a more rational approach in searching for new compounds in pharmacology and industrial toxicology.

Conclusion. At present it appears topical to determine the accurate values of the constants β_H and β_P (Eqs. 1c and 1e), as well as the scope of their applicability. The most important task seems to be the systematic study of significance the slopes of the dependences 1a–1f. We believe that these values could serve for the interpretation of the nature of the biological process studied. More attention should be paid to the applicability of the Eq. 1b[29].

Zusammenfassung. Die linearen Beziehungen der Änderungen der freien Energie kann man für die Korrelation der biologischen Wirkung verschiedener Typen organischer Verbindungen mit Konstanten angehen, deren Wert durch die Struktur der Substituenten bestimmt wird. Neben den aus der theoretischen organischen Chemie gut bekannten Beziehung (Taftsche und Hammettsche Gleichungen, Korrelation der Reaktivität konjugierter und aromatischer Systeme mit den quantenchemischen Reaktivitätsindizes), die verwendbar sind, wenn der aktivitätsbestimmende Schritt eine chemische Reaktion ist, wurden Gleichungen vorgeschlagen die gültig sind, wenn es sich beim kritischen Schritt um einen physikalischen Prozess handelt.

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