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Contents

Multiple regression analysis has given some very useful results. It functions best in industry when a large series of closely related candidate drugs is on hand and a speedy indication is needed concerning what should be synthesized next. However for the purpose of finding scientific correlations among substances that are not closely related chemically, the biological situation is usually found to be more complex than such an equation can accommodate. For example the initial distribution of a drug need not depend on lipophilicity but on the use of facilitated channels that exist for the uptake of such natural products as sugars, purines, amino acids and even choline (p. 121). For these reasons those of a scholarly cast of mind, provided that they have the time and facilities, will continue to examine the connection between physicochemical properties and pharmacological action, in all their fine details and rewarding complexity.

In fact much steric and electronic information about receptors is available from sources other than regression analysis. For example, where the receptor is the active site on an enzyme, details (obtained by X-ray diffraction analysis) are often available from the Cambridge (UK) or Brookhaven (USA) crystal-structure databanks. In other cases one can usefully superimpose (on a transparent surface) scale drawings of all the drugs that act on the receptor. The shared features constitute what is called a 'hyper-molecule' to which the receptor should be complementary in outline and charge (Balaban, *et al.*, 1980). If an approximate image of the receptor can be generated on the screen of an Evans and Sutherland computer-graphics (computer controlled) Picture System the images of candidate drugs can then be applied in a contrasting colour. In this way the ability of the candidate to make a good fit may be judged (Blaney, *et al.*, 1982).

8.4 How one methyl group can significantly change the action of a drug

It is quite common to find a pair of closely related molecules where the first has a strong biological action whereas the other has none. How can two such substances which may differ in composition by only a single methyl group perform so differently in a biological test? In this Section a study of methyl groups will be made as examples of what are commonly termed 'chemically inert' groups. Yet these groups if suitably placed can profoundly change the chemical behaviour of molecules by well-understood steric and electronic effects. Their altered biological properties reflect these changes.

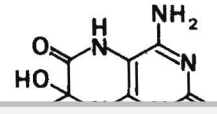
Steric influences

(*a*) *Steric influences on solubility.* It might b
molecule of a methyl group would alwa
methyl group is water-repelling. It usu
interesting exceptions. In order that a su
molecules must be forced apart by brea
alcohols, methanol and ethanol, readily
forms such a large part of each mole
hydrogen-bonded to water molecules. Bu
chain becomes a more dominant featu
interstices, it cannot force the water mo
squeezed out of the water, dragging the v
low solubility of the higher alcohols. Yet
by shifting the hydroxyl group to the ce
alcohol, which is consequently more sol
butanol (Ginnings and Baum, 1937).
acids are more soluble than 2-aminopro
folding.

Unusual solubilizing effects of methy
sulfonamides, e.g. sulfadiazine (*8.40*), and
of complexity and rigidity. In such mole
prevent strainless adsorption of dissolved
the solid phase. This anomaly displaces
increased solubility (Gilligan and Plum

A methyl group can hinder addition c
thus greatly increasing the lipophilicity
activity is apt to depend. Such addition
(Albert, 1976). Several naturally-occu
(*8.51*) which is present in the human kid
become secondary alcohols. However the
largely suppresses the hydration giving a
natural products are covalently hydrated
by a neighbouring *C*-methyl group.

(*b*) *Steric influence on chelation.* The anti
(Section 8.3) is seriously decreased if a m
(Albert, *et al.*, 1947). This deactivation



effect at the biological interface. Even in solution this substance (2-methyl-8-hydroxyquinoline) has lost its affinity for Al^{3+} (while retaining it for Fe^{3+}) because of the steric effect of the methyl group.

(*c*) *Steric influences on receptors and enzymes.* Most molecules that fit the muscarine receptor for acetylcholine have a quaternary nitrogen atom of which one substituent is a straight chain of five atoms in length. Addition of one more methylene group to this chain causes a dramatic loss of biological effect. At least two of the other substituents on the nitrogen atom must be methyl groups to achieve maximal action. If one of these is substituted by either hydrogen or ethyl, a sharp drop in activity takes place. On p. 100 we noted how the addition of a methyl group to the molecule of acetylcholine (*6.2*) to give methacholine (*6.1*) hindered hydrolysis of the molecule by acetylcholinesterase so strongly that the momentary pharmacological action exerted by ACh became a durable, and clinically valued, one. The biological effect of the vitamin thiamine (*8.53*) is very sensitive to addition or loss of a methyl group. When tested on pigeons, the activity drops to 5% if the methyl group is removed from the pyrimidine ring, and to less than 1% if the methyl group is removed from the thiazole ring. Finally if an extra methyl group is inserted into the thiazole ring, between nitrogen and sulfur, the vitamin action is completely lost (Schultz, 1940).

Sometimes a methyl group increases the biological effect of a drug by making it a poorer fit for a destructive enzyme. Thus amphetamine (*7.24*), which is 1-methyl-2-phenylethylamine, has a much more prolonged hypertensive effect than 2-phenylethylamine. This has been traced to the resistance of amphetamine to monoamine oxidase, the enzyme that quickly destroys the lower homologue (Blaschko, 1952). Similarly, the action of corticosteroids and the steroid sex hormones can be intensified by inserting a methyl, or a fluorine, substituent – a steric device that has produced several clinically valuable drugs. Such seemingly inert substituents turn the steroids into poorly-fitting substrates for their natural destructive enzymes (Ringold, 1961).

Electronic influences

The methyl group is the commonest substituent that releases electrons no matter whether inductive or mesomeric mechanisms are operating.

(*a*) *Electronic influences on ionization*.* Because of its electron-releasing nature a methyl group, if attached to a nearby carbon atom, strengthens a base and weakens an acid. Also a methyl group attached to nitrogen, to give a secondary amine, is base-strengthening although most tertiary amines are weaker than

the biological test is made. When as us
cation) is far more biologically active th
change in ionization can decide whether

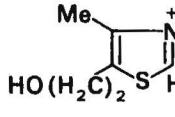
The triphenylmethane dyestuffs (*8.5*
strength upon *N*-alkylation, illustrate h
ionization in this series as Table 8.5 il
virtually created here by the insertion

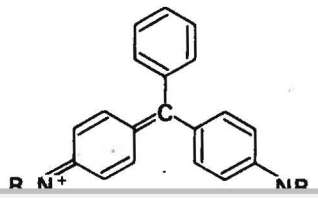
Although it is obvious that methyla
ability to ionize, the consequences of su
series are particularly interesting. In ac
the trioxo form (*8.55*) and forms the mon

Table 8.5 Connexion between ionizatio
triphenylmethane bases.

Substance	*Formula*	pK_{eq}
Doebner's violet	(8.54a)	5.38
Malachite green	(8.54b)	6.90
Brilliant green	(8.54c)	7.90

From Goldacre and Philips, 1949





a fairly strong acid (pK_a 3.9). The insertion of two alkyl groups into the 5-position removes any possibility of an anion being formed in the 5-position. Consequently the anion is formed from *N*-3 but is much weaker. Thus barbital (5,5-diethylbarbituric acid) has a pK_a of 7.9 and hence is 10^4 times weaker as an acid than barbituric acid! The consequences of the insertion of these ethyl groups on the structure–activity relationship is momentous. A substance with a pK_a of 3.9 is completely ionized at pH 7.3, and hence unlikely to pass the blood–brain barrier. However when as in barbital the pK_a is 7.9 the substance is 80% non-ionized at pH 7.3, and hence passes through without difficulty.

(*b*) *Electronic influences on reduction–oxidation potentials.* The electrons released to the rest of the molecule by a *C*-methyl substituent lower the redox potential (E_0). As a result the affected substance becomes a more active reducing agent (and is more easily oxidized) than the unmethylated homologue. Redox potentials are used to record the equilibrium between oxidized and reduced forms.

An example of this lowering of E_0 is the insertion of a methyl group into the 2-position of 1,4-naphthaquinone which depresses the potential (by 76 mV) to 408 mV (Fieser and Fieser, 1935). In another example the reduction potential of NAD (p. 20) is −180 mV, a value so low that a substituted NAD of slightly lower potential could, most likely, not become reduced to its NADH. Any analogue that cannot be reduced in the living cell cannot act as a hydrogen carrier. It is apparently for this reason that 2-methyl-nicotinamide has no biological activity, even if the effect of the methyl group may be partly steric.

(*c*) *Electronic influences on reactions where a covalent bond is broken.* The electron-releasing effects of a methyl group described above were of an instantaneously-appearing character. Some time-dependent, i.e. kinetically controlled, effects will now be mentioned. Methyl groups, because of their electron-releasing properties, promote electrophilic substitution, e.g. they make neighbouring amino groups readier to be acylated or to form an azomethine (Schiff base). A methyl group also constitutes a side-chain that is conveniently biodegraded. Thus the metabolic oxidation of a methyl group to a carboxylic acid confers hydrophilic properties on a highly lipophilic molecule and leads to rapid excretion in the urine.

(*d*) *Solubility.* In an aromatic nitrogen-heterocycle such as pyridine replacement by methyl of the hydrogen atom in an –OH, $-NH_2$ or –C(:O)NH– group usually increases solubility in water dramatically. Thus 6-aminopurine (adenine) is soluble to the extent of only 1 part in 1100, whereas 6-dimethylaminopurine dissolves 1 in 120 (Albert and Brown, 1954); countless similar examples are known.

selectivity can be introduced into a molec
discussed in Chapter 9.

Further reading

For the biological effects of inserting che
1985, pp. 43–52.

Follow-up

Consider the traditional (and apparently u
relationships' (SAR) and discuss the exten
its original meaning. Could you think of

9

Selectivity: designing drugs without side-effects. The three sources of selectivity

In Chapter 8 we saw how a biologically inert molecule could be redesigned to endow it with biological activity. However that would be only the first step in the creation of a useful drug because a biologically active substance remains only a toxicant (poison) until it is provided with selectivity also. In other words, it must be further designed to confine its action to the uneconomic cells (p. 101). The extent to which a drug can differentiate between economic and uneconomic cells is the measure of its selectivity. Toxicity in a drug is no drawback, in fact it is the very core of its usefulness. What is important is to arrange for this toxicity to be selective. The present Chapter lists and examines the properties from which selectivity can be derived.

Realization of the importance of selectivity dates from about 1911 when Paul Ehrlich introduced his chemotherapeutic index as the first means of measuring it (p. 111). Today the drug designer's goal is complete selectivity and this has been closely approached in several chemotherapeutic agents such as the penicillins, the antibacterial sulfonamides and several anthelminthics such as piperazine. However for some diseases the best available drugs still have only partial selectivity although current research is steadily improving on this position.

Since 1948 I have been seeking and publicly discussing the *principles* that can introduce selectivity into a biologically-active molecule. This search led me to conclude that three main principles govern this phenomenon:

1. *Comparative accumulation*, by choice of a toxicant that accumulates pre-

3. *Comparative cytology*, by choice of a toxica
feature peculiar to the uneconomic cells

How these principles, singly or jointly, ca
unselective toxicants will now be discussed

9.1 Selectivity through comparativ

Many substances that could be toxic for alm
be made highly selective by favourable diff
even to the hydrogen ion (H^+) surely th
agents. In the form of 10% sulfuric acid, it
cereal crops to destroy weeds, as was dis
confirmed in the University of California's
injurious to the cytoplasm of both wheat a
from penetrating the cereal. Firstly the exter
smooth and waxy whereas that of the weeds
absorbent; hence the acid runs off the form
Secondly the tender new shoot of the cereal a
a leaf-sheath whereas the growing point
vulnerable because it forms the apex of the
economic crop persists because of a select
distribution. (Unfortunately, acidification
to a single season).

Human medicine provides many similar
(e.g. *9.1*) which are, after the penicillins, t
antibiotics. Franklin, working in Mancheste
accumulated by all bacteria whereas they
thanks to a difference in the cytoplasmic me
a result the synthesis of proteins by bacte
bacteria die. Yet when both the economic a
ted it was found that the ribosomes of the
antibiotics as those of the parasites. Howe
these drugs that the tetracyclines do no
mammalian cells. Hence the high ther
(Franklin, 1971).

Selective partitioning is possible between
rare example from anticancer therapy, 5-flu
gists to eliminate two malignant growths –
So selective is this drug that patients are en
into the affected area. The eventual action
present in both healthy and malignant tissu