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Determination of thermodynamics of halogen groups in solutions of drug molecules

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The contribution of the halogen groups (F, Cl, Br, I) to solute activity and partition coefficients has been investigated using literature data. The activity coefficient for an aromatic solute at infinite dilution is increased as the size of the halogen group increases. Partition coefficients are affected similarly but there is variation among group values for a given halogen. This is related to group position and the partition solvent. Preferred group values for partition have been selected and for different solvent systems mean preferred values can be calculated for two general solvent classifications; polar and non-polar. There is excellent correlation between group values and the size of the halogen function as given by surface area. The group values for non-polar solvents are related to those of the polar solvents through the Hammett electronic substituent constant. The use of the group values in structure-activity relations is discussed with reference to the thermodynamic model of Higuchi and Davis.

It has been shown recently (Davis, Higuchi & Rytting, 1972; Davis, 1973) that the thermodynamic properties of drug molecules in solution can be assumed to be an additive-constitutive property of the various functional groups. Group values for the free energy term (and possibly the enthalpy and entropy terms) can be determined from experimental data and used subsequently in *a priori* predictions of a multiplicity of solution properties, (including solubility, partition behaviour) and in analyses of the structure-activity relations of congeneric drug series. The methylene group was examined by Davis & others (1972) and the methyl group by Davis (1973). In this paper, various halogen functions in aromatic and aliphatic solutes and their effect on activity and partition coefficients are covered in detail. Many data exist for the solubility and partition properties of halogenated aromatic organic compounds from which group values can be calculated. However, the aliphatic halogenated compounds are poorly represented and consequently few reliable group contribution values can be determined.

ACTIVITY COEFFICIENTS

The halogenation of an aromatic compound gives rise to a higher activity coefficient for the solute in water. That is, its water solubility will decrease. The effect on the log of the activity coefficient per halogen is very nearly additive and mean group values ($\Delta \log \gamma_w^\infty$) can be calculated from the extensive compilation of Tsonopoulos (1970) (Table 1). The group contributions increase as the size of the halogen function increases. The halogen groups may be considered as being rather inert functions such that the effects of halogenation and alkylation will be similar, but that the dependence of the group contribution on size will be slightly different (Tsonopoulos, 1970). For example, chlorobenzene has a smaller molar volume than toluene, but the latter has a lower activity coefficient in aqueous solution and therefore a higher water solubility.

Some group values for α-substitution in aromatic compounds can be also obtained from the data for Tsonopoulos (1970). In general, these are smaller than the values given in Table 1, but there are too few data to arrive at a quantitative value for the difference between ring and α-substitution.

Table 1. *Halogen group contributions to solute activity coefficients in water at infinite dilution* ($\Delta log\gamma_w^\infty$) (After Tsonopoulos, 1970.)

Group	$\Delta \log \gamma_w^\infty$	Number of solutes considered	Van der Waals radius (Å)
F	0·14	1	1·35
Cl	0·70	14	1·80
Br	0·92	5	1·95
I	1·40	2	2·13

Solubility data for aliphatic halogenated compounds are meagre and those that exist suggest that substitution by halogen can have a complex effect on the log activity coefficient. For example, the data presented by Deno & Berkheimer (1960) indicate that the addition of chloro groups to the same carbon atom in an aliphatic solute produces an approximately additive effect, but their addition to different carbon atoms in an aliphatic solute produces a variable result.

PARTITION COEFFICIENTS

Aromatic halogen

Partition coefficient data for halogenated aromatic solutes have been examined critically as before (Davis & others, 1972; Davis, 1973) and group contributions to the log of the partition coefficient (log F values) have been determined by comparing the partition behaviour of a substituted compound with that of the parent compound (Table 2). The data are classified in the first instance by solvent and then by the position of the halogen function in the aromatic ring (2, 3, 4 etc.). Table 2 shows that the group contributions are dependent on both the solvent system and the position of the group. Halogen substitution in the 2 position results in a pronounced interaction of the halogen with the functional group of the parent compound (electronic and steric effects) and the group values are very different to those for the same substituent in the 3 or 4 positions. In general, 2-substitution results in a larger log F value than for other positions if the organic solvent is non-polar and the converse if the solvent is polar. This can be associated tentatively with dominant solute-solute interactions in the first case and dominant solute-solvent interactions in the second case since solutes containing halogen groups will exhibit a dipole. For polar solvents there will be the chance for marked dipole-dipole interactions between solute and solvent.

For those cases where the interaction between the halogen group and other functional groups is minimal we have selected preferred group values as before (Table 2). Within a given solvent classification, these values are reasonably constant and we are able to list mean preferred values under two broad solvent classifications—polar and non-polar (Table 3). In general, the group values for the polar solvents are much higher than those for the non-polar solvents indicating that the presence of dipole-dipole solvent-solute interactions results in a significantly higher value for log F.

Table 2. *Halogen group contributions (ring systems) to partition between water and organic solvent.*

Solvent and Group X	log F_x	System	Reference (1st author only)
Hexane			
Cl	0·62*	Pentachlorophenol	Parker (1965)
Heptane			
4F	0·00*	Amphetamine	Beckett (1969)
2Cl	1·17	Aniline	Kemula (1968)
3Cl	0·76*	,,	and Leo (1971
4Cl	0·66*		,,
	0·78*	Amphetamine	Beckett (1969)
4Br	0·95*	,,	,,
4I	1·08*	,,	,,
		,,	
Dodecane			
4Br	0·66*	Phenol	Burton (1964)
2I	1·55	,,	,,
Cyclohexane			
2F	0·45	Phenol	Pinney (1969)
	0·25	Conjugated heterenoids	Currie (1966)
3F	−0·02*	Phenol	Pinney (1969)
	0·10*	Conjugated heterenoids	Currie (1966)
4F	−0·13*	Phenol	Pinney (1969)
	0·05	Conjugated heterenoids	Currie (1966)
F	0·07*a	Pentafluorophenol	Pinney (1969)
	0·24*a	Trifluorophenol	,,
2Cl	0·80	Phenol	Burton (1964)
	1·23	Aniline	Kemula (1968)
	0·80	Conjugated heterenoids	Leo (1971) Currie (1966)
3Cl	0·17*	Phenol	Burton (1964)
	0·87	Aniline	Kemula (1968) and Leo (1971)
	0·55*	Conjugated heterenoids	Currie (1966)
4Cl	0·39*	Phenol	Burton (1964)
	0·67*	Aniline	Kemula (1968) and Leo (1971)
	0·45*	Conjugated heterenoids	Currie (1966)
	0·34*	Methylphenol	Burton (1964)
2Br	1·13	Phenol	Burton (1964)
	0·70	Conjugated heterenoids	Currie (1966)
3Br	0·35	Phenol	Burton (1964)
	0·60*	Conjugated heterenoids	Currie (1966)
4Br	0·78*	Phenol	Burton (1964)
	0·50*	Conjugated heterenoids	Currie (1966)
3I	0·67*	Phenol	Burton (1964)
4I	0·97*	,,	,,
Benzene			
4F	0·29*	Phenyl boronic acid	Soloway (1960)
2Cl	1·11	Aniline	Kemula (1968) and Leo (1971)
3Cl	0·93*	Aniline	Williams (1930)
4Cl	0·71	Phenyl boronic acid	Soloway (1960)
	0·86*	Aniline	Kemula (1968) and Leo (1971)
3Br	1·20*	Aniline	Flurscheim (1910) and Leo (1971)
4Br	1·09*	Aniline	Flurscheim
	0·90*	Phenyl boronic acid	Soloway (1960)

Solvent and Group X	log F_x	System	Reference (1st author only)
Toluene			
2Cl	0·69	Benzoic acid	Smith (1929)
3Cl	0·70*	,,	,,
4Cl	0·82*	,,	,,
Xylene			
2Cl	0·20	Benzoic acid	Smith (1921)
2I	1·27	,,	,,
Carbon tet.			
2Cl	1·48	Aniline	Kemula (1968)
3Cl	1·12	,,	and Leo (1971)
4Cl	1·06	,,	,,
$CCl_4/CHCl_3$			
4F	0·13	Alkyl sulphate ion pairs	Harris (1971)
Chloroform			
2Cl	0·40	Benzoic acid	Smith (1929)
	0·70	Sulphonamide	Kakeya (1969)
3Cl	0·50	Sulphonamide	Kakeya (1969)
	0·53*	Sulphanilamide	Garrett (1969)
	0·34*	Benzyl piperidines	Quintana (1967)
4Cl	1·22	Benzoic acid	Smith (1929)
	0·14	Amphetamine	Vree (1969)
	0·38*	Sulphonamide	Kakeya (1969)
	0·42*	Benzyl piperidines	Quintana (1967)
Cl	0·49*	Phenothiazines	Persson (1968)
6Cl	0·05	Quinolinium compounds (Ion-pair)	Plakogiannis (1970)
3, 4Cl	0·38*a	Sulphonamide	Kakeya (1969)
5, 7Cl	0·64a	8-Quinolinol	Dyrssen (1956)
2Br	0·41	Benzoic acid	Smith (1929)
3Br	1·54	,,	
	0·70*	Sulphanilamide	Garrett (1969)
4Br	0·63*	Sulphonamide	Kakeya (1969)
6Br	0·21	Quinolinium compounds (Ion-pair)	Plakogiannis (1970)
5, 7Br	0·79a	8-Quinolinol	Dyrssen (1954)
2I	0·59	Benzoic acid	Smith (1921)
	0·50	Quinolinium compounds (ion pair)	Plakogiannis (1970)
3I	1·02*	Sulphanilamides	Garrett (1969)
5, 7I	0·79a	8-Quinolinol	Dyrssen (1956)
Oils			
4Cl	1·13	Phenylacetic acid	Bittenbender (1939)
4Br	1·61		
4I	1·38		
Ether			
F	0·19*	Steroids	Flynn (1971)
2Cl	0·30	Benzoic acid	Smith (1921)
Cl	0·70*	Steroids	Flynn (1971)
2I	1·27	Benzoic acid	Smith (1921)
4I	0·88	Benzene sulphonic acid	Keston (1950)
Methyl dodecanoate			
2F	−0·21	Phenol	Burton (1964)
3F	0·35*	,,	,,
2Cl	0·13	,,	,,
3Cl	0·75*	,,	,,
4Cl	0·97*	,,	,,
	0·82*	Methyl phenol	,,
2Br	0·27	Phenol	,,
3Br	0·91*	,,	
Isobutanol			
Cl	0·21	Sulphonamides	Scholtan (1968)
Br	0·77	,,	,,
I	0·97	,,	,,
Cyclohexanol			
3Cl	0·85*	Phenoxyacetic acid	Leo (1971)
Cyclo-hexanone			
3Cl	0·82a	Phenoxyacetic acid	Leo (1971)
Methyl isobutyl ketone			
3Cl	0·78*	Phenoxyacetic acid	Leo (1971)

* Preferred values. Halogen(s) not *ortho* to polar function, sterically hindered *etc.*
a) Value per Halogen atom.

Table 2—*cont.*

Solvent and Group X	log F_X	System	Reference (1st author only)
Octanol			
2F	0·01	Phenoxyacetic acid	Fujita (1964)
	0·04	Phenylacetic acid	
	0·25	Phenol	Leo (1971)
	0·24	Phenol	
	0·32	Aniline	
3F	0·13	Phenoxyacetic acid	Fujita (1964)
	0·19*	Phenylacetic acid	
	0·28*	Benzoic acid	
	0·47	Phenol	
	0·40	Aniline	
	0·36*	Aniline	Leo (1971)
	0·46	Phenol	
4F	0·15*	Phenoxyacetic acid	Fujita (1964
	0·19*	Phenylacetic acid	
	0·28*	Benzoic acid	
	0·31	Phenol	
	0·25	Aniline	
	0·33	Phenol	Machleidt (1972)
	0·21*	Aniline	Leo (1971)
	0·30*	Phenol	
	0·31*	Acetanilides	Dearden (1971)
F	0·14*	Benzene	Fujita (1964)
6F	0·08	Quinazolinones	Wulfert (1969)
2Cl	0·59	Phenoxyacetic acid	Fujita (1964)
	0·11	Benzoic acid	
	0·69	Phenol	
	0·43	Sulphonamide	Kakeya (1969)
	0·72	Toluene	Leo (1971)
	0·97	Aniline	
	0·70	Phenol	
	0·64	β-Nitrostyrenes	Currie (1966)
	0·69	Phenol	Machleidt (1972)
3Cl	0·76*	Phenoxyacetic acid	Fujita (1964
	0·68*	Phenylacetic acid	
	0·83*	Benzoic acid	
	1·04	Phenol	
	0·98	Aniline	
	0·61*	Nitrobenzene	
	0·98*	Sulphonamide	Kakeya (1969)
	0·58*	Toluene	Leo (1971)
	0·95*	Anilines	
	1·02*	Phenol	
	0·46	β-Nitrostyrenes	Currie (1966)
4Cl	0·70*	Phenoxyacetic acid	Fujita (1964)
	0·70*	Phenylacetic acid	
	0·87*	Benzoic acid	
	0·86*	Benzyl alcohol	
	0·93	Phenol	
	0·54*	Nitrobenzenes	
	0·53*	Sulphonamides	Kakeya (1969)
	0·63*	Toluene	Leo (1971)
	1·12	Methyl phenol	
	0·89*	Aniline	
	0·95*	Phenol	
	0·33	β-Nitro-styrenes	Currie (1966)
	0·71*	Acetanilides	Dearden (1971)
	0·87*	Phenol	Machleidt (1972)
2, 3Cl	0·92a	Anilines	Leo (1971)
2, 4Cl	0·88a	,,	
3, 4Cl	0·57*a	Sulphonamides	Kakeya (1969)
2, 4,6Cl	0·67a	Phenol	Helmer (1968)
Cl	0·71	Pentachlorophenol	Leo (1971)

Solvent and Group X	log F_X	System	Reference (1st author only
Octanol			
	0·71*	Benzene	Fujita (1964)
5Cl	0·43	Benzothio-diazines	Topliss (1972)
6Cl	0·89*	Benzothio-diazines	Topliss (1972)
	0·69*	Quinolines	Leo (1971)
	0·59	Quinazolinones	Wulfert (1969)
7Cl	0·91*	Benzothio-diazines	Topliss (1972)
	0·57	Quinazolinones	Wulfert (1969)
8Cl	0·35	Quinazolinones	Wulfert (1969)
	0·29	Quinolines	Leo (1971)
2Br	0·75	Phenoxyacetic acid	Fujita (1964)
	0·89	Phenol	
	1·35	Aniline	Leo (1971)
	1·88	Phenol	
3Br	0·94*	Phenoxyacetic acid	Fujita (1964)
	0·91*	Phenylacetic acid	
	0·99*	Benzoic acid	
	1·17	Phenol	
	0·79*	Nitrobenzene	
	1·16*	Aniline	Leo (1971)
	1·06*	Phenol	
4Br	1·02*	Phenoxyacetic acid	Fujita (1964)
	0·90*	Phenylacetic acid	
	0·98*	Benzoic acid	
	1·13	Phenol	
	1·17*	Phenol	Machleidt (1972)
	1·05	Sulphonamide	Kakeya (1969)
	1·32	Aniline	
	1·20*	Phenol	Leo (1971)
	1·13*	Acetanilide	Dearden (1971)
Br	0·86*	Benzene	Fujita (1964)
5Br	0·45	Benzothio-diazines	Topliss (1973)
6Br	1·08*	Benzothio-diazines	Topliss (1972)
7Br	1·08*	Benzothio-diazines	Topliss (1972)
	0·92	Phenoxyacetic acid	Fujita (1964)
	0·53	Benzoic acid	
	1·19	Phenol	Leo (1971)
	2·40	Aniline	
	1·44	Phenol	
3I	1·15*	Phenoxyacetic acid	Fujita (1964)
	1·22*	Phenylacetic acid	
	1·28*	Benzoic acid	
	1·47	Phenol	Machleidt (1972)
	1·52	Phenol	Leo (1971)
	2·04	Aniline	
	1·18*	Phenol	
4I	1·26*	Phenoxyacetic acid	Fujita (1964)
	1·23*	Phenylacetic acid	
	1·14*	Benzoic acid	
	1·45	Phenol	
	2·46	Aniline	Leo (1971)
	1·44*	Phenol	
	1·30*	Acetanilide	Dearden (1971)
I	1·12*	Benzene	Leo (1971)
5I	0·61	Benzothio-diazines	Topliss (1972)
7I	1·32*	Benzothio-diazines	Topliss (1972)
Oleyl Alcoho			
2F	−0·07	Phenol	Pinney (1968)
3F	0·37*		and
4F	0·27*		Burton (1964)
F	0·22*	Tetrafluoro-phenol	Pinney (1968)
	0·22*	Pentafluoro-phenol	
2Cl	0·02	Phenol	Burton (1964
3Cl	0·55*	Phenol	
4Cl	0·81*	Phenol	
	0·67*	Methyl phenol	
2,4Br	0·40a	Phenol	
2,4I	0·67a	Phenol	

* **Preferred values. Halogen(s) not *ortho* to polar function, sterically hindered *etc.***
(a) Value per Halogen atom.

Table 3. *Mean preferred values for log* F_{Hal}. (Figure in brackets is number of values taken for calculation of mean).

	Non-polar solvents							Polar solvents						
Halogen	Hexane	Heptane	Dodecane	Cyclohexane	Benzene	Toluene	$CHCl_3$	Ether	Me Dodecanoate	Octanol	Oleyl alch.	Cyclohexanol	Cyclohexanone	Me Isobutketone
F	—	0·00 (1)	—	0·05 (6)	0·29 (1)	—	—	0·19 (1)	0·35 (1)	0·23 (11)	0·27 (4)	—	—	—
Cl	—	0·73 (3)	—	0·47 (4)	0·83 (2)	—	0·43 (6)	0·70 (1)	0·85 (3)	0·76 (23)	0·68 (3)	0·85 (1)	0·82 (1)	0·78 (1)
Br	0·62 (1)	—	0·66 (1)	0·56 (4)	1·06 (3)	0·76 (2)	0·67 (2)	—	0·91 (1)	1·02 (14)	—	—	—	—
I	—	—	—	0.82 (2)	—	—	1·02 (1)	—	—	1·24 (10)	—	—	—	—

To study these differences further we have calculated weighted means for the data under the two broad headings and have compared these with other group values and parameters describing group size (Table 4). Data for the hydrogen atom have also been included; by definition this has a group value of zero. The correlations between our log F values and other parameters have been tested using linear regression and since the same number of data is being employed in each case, the correlation coefficient can be used as an estimate of the goodness of fit (Tute, 1971).

Three earlier group approaches to solution behaviour are considered: Irmann (1965)-solubility, McGowan (1952, 1963)-partition coefficients and Tsonopoulos (1970)-activity coefficients. For both solvent classifications the best correlation is obtained with the data of McGowan (1952, 1963). These values were derived from

Table 4. *Correlation between group contribution log F and group size.*

Group	Group value (log F) weighted means		Group values (lit.)			Group radii (e)		Group volume					Group area					Hammet σ
	a_1	a_2	b	c	d	e_1	e_2	f_1	g	h	i	j	k	f_2	l	m	n	4-pos. in aromatic
H	0 (o)	0	0·13	0	0	1·00	0·30	3·44	3·00	3·7	14·9	16·8	0	0·78	8·57	6·6	2·4	0
F	0·07	0·24	0·19	0·19	0·14	1·35	0·64	5·80	8·61	10·5	15·11	26·5	0·12	1·10	16·5	9·7	4·8	0·06
Cl	0·56	0·77	0·67	0·73	0·70	1·80	0·99	12·0	21·1	22·1	22·96	56·0	0·48	1·82	31·9	14·2	7·9	0·227
Br	0·75	1·00	0·79	0·98	0·92	1·95	1·14	14·6	27·5	27·0	26·19	69·5	0·64	2·09	38·0	16·6	9·0	0·232
I	0·91	1·24	1·12	1·22	1·40	2·15	1·33	19·6	37·8	37·0	32·93	90·5	0·90	2·51	45·2	20·2	11·1	0·276
p Non-Polar solv.	—	0·994	0·990	0·997	0·984	0·978	0·972	0·987	0·986	0·982	0·978	0·991	0·991	0·992	0·992	0·983	0·979	
Polar solv.	0·994	—	0·987	0·999	0·986	0·993	0·991	0·992	0·993	0·993	0·973	0·994	0·994	0·999	1·000	0·995	0·995	

(a) a_1 Non-polar solvents a_2 polar solvents: Values are weighted means of values in Table 3.
(b) Group values taken from Irmann's (1965) empirical solubility relation.
(c) Group values calculated from McGowan's (1952, 1963) partition coefficient relation.
(d) Values for activity coefficient contributions—Tsonopoulos (1970).
(e) e_1 van der Waals (Å), e_2 covalent: Values for Courtauld atomic models.
(f) Values from Bondi (1964): f_1-cm³ mol⁻¹ f_2 = (cm³ mol⁻¹) × 10^9.
(g) Group area values calculated from Courtauld molecular models (Å²).
(h) Group volume equivalent at boiling point: Values from Glasstone & Lewis (1963).
(i) Molar volume increment (Exner, 1967a).
(j) Parachor (Exner, 1967b).
(k) Adjusted parachor values: P* = 0·12 (P_S − P_H) (McGowan, 1956).
(l) Group area values calculated from Courtauld molecular models (Å²).
(m) (Parachor)²/³.
(n) (Molar volume)²/³.
(o) Group values for hydrogen are zero by definition.
(p) Statistical Analysis of data. Correlation coefficient. Correlation between goup contributions and other group parameters using linear regression.

estimates of the group parachor (P) and empirical interaction energies (E_A) derived from solubility studies.

$$\log F_X = 0{\cdot}12\,(P_S - P_H) + (E_A^S - E_A^H) \quad .. \quad .. \quad .. \quad (1)$$

Where S and H refer to the substituted and parent compounds respectively.

An exact agreement between the log F values and the $\Delta \log \gamma_w^\infty$ values of Tsonopoulos would be expected if the halogen groups behaved in an ideal manner in the organic solvents used for partition since the partition coefficient (K_D) is related to the activity coefficients for the solute in water and organic solvent (o).

$$\log K_D = \log \gamma_w^\infty - \log \gamma_o^\infty \quad .. \quad .. \quad .. \quad (2)$$

$$\text{and thus } \log F_x = \Delta \log \gamma_O^\infty - \Delta \log \gamma_o^\infty \quad .. \quad .. \quad (3)$$

In fact, Table 4 suggests that the halogen groups deviate positively from Raoult's law in non-polar solvents and negatively from Raoult's law in polar solvents. That is, in the first case there are dominant group-group interactions and in the second case dominant group-solvent interactions.

Halogen groups should act to withdraw electrons from the ring allowing it to interact more strongly with nearby solvent molecules (water or polar organic solvent) and we have therefore, examined multiple correlation between non-polar and polar group values and the Hammett (1940) electronic substituent constant (σ) (a measure of the electron withdrawing capacity of the substituent). This approach is similar to that described by Wulfert, Bolla & Mathieu (1969) who suggested that the electronic properties of a substituent can affect solubility. The equation from a multiple regression analysis is

$$\log F_{polar} = 0{\cdot}99 \log F_{non\text{-}polar} + 0{\cdot}96\sigma + 0{\cdot}04 \quad .. \quad .. \quad (4)$$

(correlation coefficient = 0·995, standard deviation = 0·07), and since the two coefficients are almost unity and the constant is almost zero, we can write

$$\log F_{polar} \simeq \log F_{non\text{-}polar} + \sigma \quad .. \quad .. \quad .. \quad .. \quad (5)$$

There are also reasonable correlations between log F and parameters that describe group size. The best fit being obtained with group area as determined from atomic models (Fig. 1). This close dependence of the halogen group contributions on group area is in line with the suggestion that the energy for hole formation in the solvent (into which the solute is placed) is dependent on the surface area of the solute rather than its volume (Langmuir, 1925; Miller & Hildebrand, 1968; Harris, 1971; Hermann, 1972).

Aliphatic halogen

There are few data in the literature that can be used to calculate the effect of halogen substitution on the partition coefficients of aliphatic organic solutes (Table 5). The derived log F values are highly dependent on the organic solvent used for the partition experiments. For the case of cyclohexane Currie, Lough & others (1966) have shown that the aliphatic group values are very similar to those calculated for aromatic substituents, whereas for octanol the group values are much smaller. Hansch & Fujita (1964), Hansch & Anderson (1967) and Harris (1971) have attempted to rationalize the difference in the behaviour of aliphatic and aromatic halogen substituents on the basis of electronic effects and the attendant solute-solvent interactions. Harris (1971) has made a notable contribution by splitting the group contribution to the free energy of transfer (−2·303 RT log F) into enthalpy and entropy components

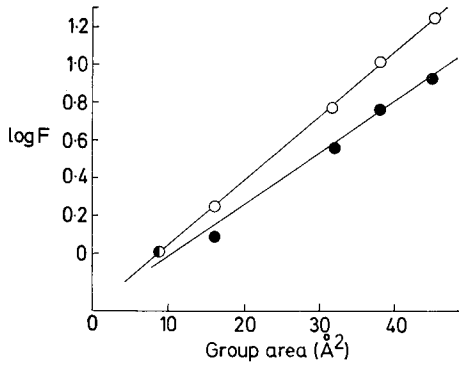

FIG. 1. Correlation of log $F_{halogen}$ with group area for polar (○) and non-polar (●) solvent systems.

(Table 6). In particular, a specific solvation effect associated with the fluorine group is a consequence of a positive enthalpy and entropy of transfer for the aromatic substituent in comparison to negative values for these terms for the group as an aliphatic substituent. Further studies along these lines would be of great interest and would allow us to extend the group contribution approach.

STRUCTURE-ACTIVITY RELATIONS

Higuchi & Davis (1970) have developed recently a model for structure-activity correlation that is based on the assumption that the prevailing condition during drug

Table 5. *Log F values for aliphatic halogen substituents.*

Solvent	F	Cl	Br	I	Solute	Reference (1st author)
Cyclohexane	—	0·70	0·90	—	Conjugated heterenoids	Currie (1966)
$CHCl_3/CCl_4$	0·03	0·32	0·56	—	Alkyl sulphate Ion-pairs	Harris (1971)
1-Octanol	—0·73	—0·13	0·04	0·22	Alkyl benzenes	Iwasa (1965) and Leo (1971)

Table 6. *Thermodynamic values for various organic groups obtained from the extraction equilibria of dextromethorphan alkyl sulphate ion-pairs between water and 25% v/v $CHCl_3$ in CCl_4* (Harris, 1971).

Group	Δ(ΔG) cal mol^{-1}	Δ(ΔH) cal mol^{-1}	Δ(ΔS) cal deg^{-1} mol^{-1}	F
Br	—807	—1789	—3·24	3·80
Cl aliphatic	—439	—1203	—2·52	2·09
F	—38	—449	—1·36	1·06
4-F-aromatic	—179	—	1·41	1·35

1 cal mol^{-1} = 4·184 J mol^{-1}.

distribution will be one of thermodynamic equilibrium or pseudoequilibrium. Furthermore, they assumed that the biological test system is represented by many compartments, biological activity is proportional to the active sites occupied and the drug will be distributed to the various compartments and only an insignificant amount will be attached to the receptor site. They have considered firstly the passage of the parent drug from an aqueous phase through various lipoidal compartments to the receptor site and then the passage of the substituted drug, undergoing the same process. The important quantities in the model were the partition coefficients for transfer of the drug from aqueous phase to the various lipoidal compartments and to the receptor site for both the parent drug and the substituted drug and the volumes of the aqueous (V_w) and lipoidal (V_i) compartments (the volume of the receptor site was assumed to be negligible). Using this model, they were able to derive a simple equation that related R (the ratio of the quantity at the receptor site of the substituted drug (E) relative to the parent drug (E*)) to the respective partition coefficients and the volumes of the various compartments

$$R = E/E^* = \frac{K_r\,(V_w + \sum_{i=1}^{i=n} K_i^*\,V_i)}{K_r^*(V_w + \sum_{i=1}^{i=n} K_i\,V_i)} \qquad (6)$$

On putting sensible values for the various parameters into equation (6) Higuchi & Davis (1970) were able to obtain for a two compartment model analysis of drug distribution, a parabolic relation between the logarithm of the R value and the number of carbon atoms in a homologous series and their model provided a simple equilibrium explanation for the well known bell-shaped relation between the logarithm of a biological response and drug lipophilicity. The one necessary assumption for the parabolic relation was that the affinity of the lipoidal compartment for the methylene group (CH_2) is greater than the affinity of the receptor site for the CH_2 group. In other words, the receptor site is more polar than a general lipoidal compartment.

A similar analysis can be conducted using the data for the halogen substituents in Table 4. The F values for the lipoidal compartment are taken as being equivalent

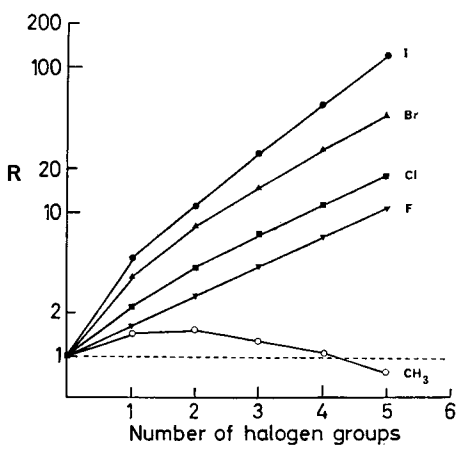

FIG. 2. Two-compartment model analysis of drug distribution (Higuchi & Davis, 1970) $K_D^* = 0{\cdot}6$, $V_w = 1$, $V_1 = 1$. F_r and F_1 values taken from Table 4.

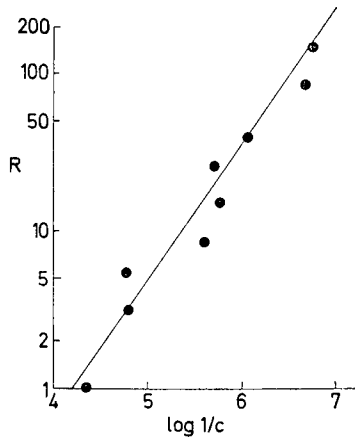

FIG. 3. Relation between R and minimum inhibitory concentration (c) for phenols *vs Ps aeruginosa* (Burton & others, 1964), $V_w = 1{\cdot}0$, $V_1 = 0{\cdot}05$, $K_D^* = 0{\cdot}60$.

to those for the non-polar solvents and the F values for the receptor as those for the polar solvents. A two compartment analysis shows that the log R value increases approximately linearly with the number of added halogen groups and that I>Br>Cl >F (Fig. 2). The shapes of the curves are altered by the choice of lipid compartment volume and the partition coefficient of the parent compound but the overall pattern is not changed. Included in the plot are values of R for methyl substitution; polar and non-polar group values were taken from Davis (1973). In this case the R value passes through a maximum and eventually becomes less than unity. The model can also be used to test combinations of halogen groups and methyl and halogen groups.

As yet, Fig. 2 and similar plots cannot be satisfactorily compared with *in vivo* data since few systematic structure-activity studies have been conducted with polyhalogenated compounds. Data for antimicrobial agents provide a special case where $V_1 \ll V_w$. Double log plots of R versus $(1/c)$ where c is the minimum inhibitory concentration are shown in Figs 3 and 4.

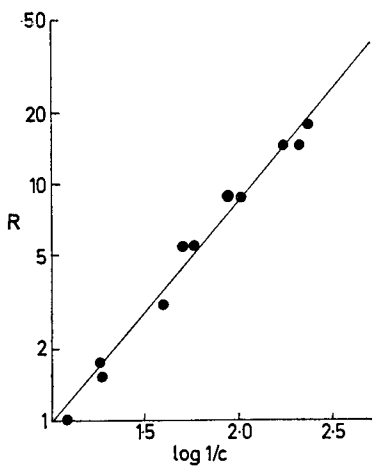

FIG. 4. Relation between R and (1/c) for benzyl alcohols *vs S. aureus, S. albus, Strep. faecaelis* (mixed culture) (Khorna & others, 1967). $V_w = 1{\cdot}0$, $V_1 = 0{\cdot}05$, $K_D^* = 0{\cdot}60$.

REFERENCES

BECKETT, A. H. & MOFFAT, A. C. (1969). *J. Pharm. Pharmac.*, **21**, 144S–150S.

BITTENBENDER, W. A. & DEGERING, E. F. (1939). *J. Am. Pharm. Assoc.*, **28**, 514–519.

BONDI, A. (1964). *J. phys. Chem.*, **68**, 441–451.

BURTON, D. E., CLARKE, K. & GRAY, G. W. (1964). *J. chem. Soc.*, 1314–1318.

CURRIE, D. J., LOUGH, C. E., SILVER, R. F. & HOLMES, H. L. (1966). *Can. J. Chem.*, **44**, 1035–1043.

DAVIS, S. S. (1973). *J. Pharm. Pharmac.*, **25**, 1–12.

DAVIS, S. S., HIGUCHI, T. & RYTTING, J. H. (1972). *Ibid.*, **24**, 30P–46P.

DEARDEN, J. C. & TOMLINSON, E. (1971). *Ibid.*, **23**, 73S–76S.

DENO, N. C. & BERKHEIMER, H. E. (1960). *J. Chem. Eng. Data*, **5**, 1–5.

DYRSSEN, D. (1956). *Acta chem. scand.*, **10**, 341–352.

EXNER, O. (1967a). *Colln. Czech. chem. Commun.*, **32**, 1–23.

EXNER, O. (1967b). *Ibid.*, **32**, 24–55.

FLURSCHEIM, B. (1910). *J. chem. Soc.*, **97**, 84–97.

FLYNN, G. L. (1971). *J. pharm. Sci.*, **60**, 345–353.

FUJITA, T., IWASA, J. & HANSCH, C. (1964). *J. Am. chem. Soc.*, **86**, 5175–5180.

GARRETT, E. R., MIELCK, J. B., SEYDEL, H. K. & KESSLER, H. J. (1969). *J. medl chem.*, **12**, 740–745.

GLASSTONE, S. & LEWIS, D. (1960). *Elements of Physical Chemistry*. 2nd Edn London: Macmillan.

HAMMETT, C. P. (1940). *Physical Organic Chemistry*. New York: McGraw Hill.

HANSCH, C. & ANDERSON, S. M. (1967). *J. org. Chem.*, **32**, 2583–2586.

HANSCH, C. & FUJITA, T. (1964). *J. Am. chem. Soc.*, **86**, 1616–1626.

HARRIS, M. J. (1971). Ph.D. Dissertation, University of Kansas.

HELMER, F., KIEHS, K. & HANSCH, C. (1968). *Biochem.*, **7**, 2858–2863.

HERMANN, R. B. (1972). *J. Phys. Chem.*, **76**, 2554–2559.

HIGUCHI, T. & DAVIS, S. S. (1970). *J. pharm. Sci.*, **59**, 1376–1383.

IRMANN, F. (1965). *Chem. Eng. Techn.*, **37**, 789–872.

IWASA, J., FUJITA, T. & HANSCH, C. (1965). *J. medl Chem.*, **8**, 150–153.

KAKEYA, N., YATA, N., KAMADA, A. & AOKI, M. (1969). *Chem. Pharm. Bull.*, **17**, 2558–2564.

KEMULA, W., BUCHOWSKI, H. & PAWLOWSKI, W. (1968). *Roczniki. Chem.*, **42**, 1951–1965.

KESTON, A. S., UDENFRIEND, S. & LEVY, M. (1950). *J. Am. chem. Soc.*, **72**, 748–753.

KHORNA, M. L., PANDIT, S. Y. & PISHAWIKAR (1967). *J. pharm. Sci.*, **56**, 993–997.

LANGMUIR, I. (1925). *Colloid Symposium Monograph III.* Editor: Holmes, H. N. 48–75. Chemical catalog Co.

LEO, A., HANSCH, C. & ELKINS, D. (1971). *Chem. Rev.*, **71**, 525–616.

MACHLEIDT, H., ROTH, S. & SEEMAN, P. (1972). *Biochim. biophys. Acta*, **255**, 178–189.

MILLER, K. W. & HILDEBRAND, J. H. (1968). *J. Am. chem. Soc.*, **90**, 3001–3004.

MCGOWAN, J. C. (1952). *J. appl. Chem.*, **2**, 323–328.

MCGOWAN, J. C. (1956). *Rec. Trav. Chim.*, **75**, 193–208.

MCGOWAN, J. C. (1963). *Nature*, **200**, 1317.

PARKER, V. H. (1965). *Biochem. J.*, **97**, 658–662.

PERSSON, B. A. (1968). *Acta. pharm. suecica*, **5**, 337–342.

PINNEY, R. J. & WALTERS, V. (1969). *J. Pharm. Pharmac.*, **21**, 415–422.

PLAKOGIANNIS, F. M., LIEN, E. J., HARRIS, C. & BILES, J. A. (1970). *J. pharm. Sci.*, **59**, 197–200.

QUINTANA, R. P. & SMITHFIELD, W. R. (1967). *J. medl Chem.*, **10**, 1178–1180.

SCHOLTAN, W. (1968). *Arzneimittel-Forsch.*, **18**, 505–517.

SMITH, H. W. (1921). *J. phys. Chem.*, **25**, 605–615, 616–627.

SMITH, H. W. & WHITE, T. A. (1929). *Ibid.*, **33**, 1953–1974.

SOLOWAY, A. H., WHITMAN, B. & MESSER, J. R. (1960). *J. Pharmac. exp. Ther.*, **129**, 310–314.

TOPLISS, J. G. & YUDIS, M. D. (1972). *J. medl Chem.*, **15**, 400–403.

TSONOPOULOS, C. (1970). Ph.D. Dissertation, University of California.

TUTE, M. S. (1971). *Advances in Drug Research*, **6**, 1–77.

VREE, T. B., MUSKENS, A. T. J. M. & VAN ROSSUM, J. M. (1969). *J. Pharm. Pharmac.*, **21**, 774–775

WILLIAMS, G. & SOPER, F. G. (1930). *J. chem. Soc.*, **133**, 2469–2474.

WULFERT, E., BOLLA, P. & MATHIEU, J. (1969). *Chim. Ther.*, **4**, 257–259.