Chem-Bioinformatics and QSAR: A Review of QSAR Lacking Positive Hydrophobic Terms

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Contents

I. Introduction

The incredible rate of increase of information in all areas of human endeavor, especially in science, and the arrival of powerful inexpensive computers, just in time, has given rise to the discipline of information science. Books and journals can no longer organize and integrate the huge volume of new information hitting us each day even with only a small fraction of the world's population contributing. For instance, *Chemical Abstracts* reports on over 1000 articles and patents per day. After a 10-day vacation, you are behind by another 10 000 reports. Now with the recent director of NIH advocating that any and all should publish unreviewed work on the worldwide web, what will this add to our state of bewilderment?

We believe that in the small area of chemical−biological interactions, the time is ripe to organize QSAR from the bioinformatics viewpoint. The system that we are developing cannot only keep account of what has been done, but also provides manifold possibilities for comparing results from all kinds of biological systems, from DNA to humans, from the point of view of the hydrophobic, electronic, and steric characteristics of the various types of congeners.

In the past 38 years, since its advent,[1] a huge and constantly expanding effort has developed to understand chemical−biological interaction in mathematical terms. This is spread across a bewildering variety of sciences: drug and pesticide research, environmental toxicology, biochemistry, molecular biology and the many subfields of medicine such as cancer research, antibacterials, HIV, etc. At the same time, one must try to understand mechanistic organic chemistry and the many aspects of mathematical modeling. Many small, and some not so small, companies have developed computerized programs to assist in this enormous undertaking.

The time has come to start thinking of the field of chemical−biological interactions as a science in its own right. To do so, it is essential to have a common language. Our group at Pomona College has been working in this direction for the past 40 years. The approach has been to use the electronic and steric parameters developed by physical organic chemists together with hydrophobic parameters based on octanol/water partition coefficients.

In the early 1980s, Robert Langridge's effort to model protein structure in 3-D terms and color commenced a revolution (now called molecular modeling) within the QSAR revolution[3−5] that has expanded to the so-called 3-D state. Now there are a surprising and confusing number of computerized approaches to integrate these seemingly different fields into the makings of a unified science. Since the parametrization of chemistry and biology is in such an explosive state, one might think that it is too early to try for the broad view. However, our feeling is that the data from this past century, from such a wide

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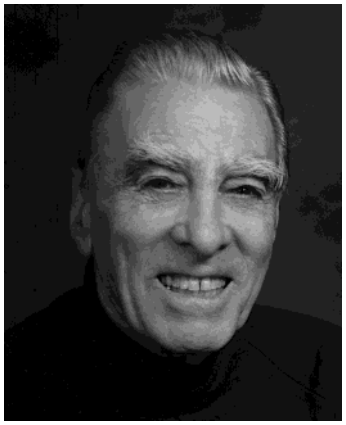


Corwin Hansch received his undergraduate education at the University of Illinois and his Ph.D. degree in Organic Chemistry from New York University in 1944. After working with the DuPont Company, first on the Manhattan Project and then in Wilmington, DE, he joined the Pomona College faculty in 1946. He has remained at Pomona except for two sabbaticals: one at the Federal Institute of Technology in Zurich with Professor Prelog and the other at the University of Munich with Professor Huisgen. The Pomona group published the first paper on the QSAR approach relating chemical structure with biological activity in 1962. Since then, QSAR has received widespread attention. Dr. Hansch is an honorary fellow of the Royal Society of Chemistry and recently received the ACS Award for Computers in Chemical and Pharmaceutical Research for 1999.

Alka Kurup received her undergraduate degree in Pharmacy in 1981 from Birla Institute of Technology and Science in Pilani, India. In 1988, she received her Masters degree from the College of Pharmacy in Manipal, India. For two years she assumed Inchargeship and Quality Control of the Pharmacy Manufacturing Wing at Kasturba Medical College in Manipal. In 1991, she joined Birla Institute of Technology and Science as a faculty member in the Department of Pharmacy. She completed her Ph.D. degree in 1997 under the supervision of Professor S. P. Gupta with her thesis regarding QSAR studies of anticancer drugs. She joined Professor Hansch's group in July 1998 to pursue postdoctoral research. Currently, she is involved in building the C-QSAR database. Her research interests include QSAR and computer-aided drug design.

Rajni Garg received her M.Sc. degree in Chemistry (1984) from Meerut University and M.Phil. (1988) degree from Delhi University, India. Her M.Phil. dissertation work was on peptide synthesis. She was a faculty member in the Chemistry Department of Birla Institute of Technology and Science, Pilani, India, from 1991 to 1996, where she taught organic and physical chemistry. She received her Ph.D. degree in 1996 under the supervision of Professor S. P. Gupta. Her doctoral work was on QSAR studies on anti-HIV agents. In February 1997, she joined Professor Corwin Hansch as a postdoctoral researcher, and she is currently involved in building a C-QSAR databank. Her research interests include QSAR and computer-assisted drug design.

Hua Gao received his Ph.D. degree in Pharmaceutical Sciences at the University of Southern California. He joined Professor Corwin Hansch in 1995 as a Postdoctoral Research Associate and worked at BioByte Corporation as a Scientist. After working in MDS Panlabs as a Scientist, he joined Pharmacia & Upjohn as a Research Scientist. In 2000, Dr. Gao was awarded the "Corwin Hansch Award in QSAR and Modelling", a prestigious international award for his outstanding contribution to QSAR, given by the QSAR and Modelling Society. His research interests include QSAR, structure-based drug design, combinatorial library design, and cheminformatics.

variety of test systems, can be the basis for testing the many new approaches computational and theoretical scientists are trying to formulate.

Over the years we have been impressed by the great importance of hydrophobic effects in chemical−biological interactions as brought out by quantitative structure−activity relationships (QSAR). Now that we have a good sample of the literature in the form of 7300 biological QSAR (from DNA and enzymes to humans) and 8300 from mechanistic organic chemistry for comparison, it seems timely to examine those instances where hydrophobic terms are not significant. It is our belief that, at this point in time, further advances in understanding biological QSAR can best be attained by comparative studies,[2−11] that is, studies among biological QSAR to obtain lateral support for a new study and comparison with the much more precise work from mechanistic organic chemistry to facilitate elucidation of reaction mechanisms. Considering QSAR for purified enzymes and more or less purified receptors, where one might expect hydrophobic terms to be lacking, we now have 2129 examples of which 1164 (55%) lack hydrophobic terms in the form of log P or π. For the more complex systems from organelles to whole organisms, we have 3677 examples, of which 2937 (80%) contain hydrophobic terms. For 709 examples of receptors, only 300 (42%) contain a log P or π term. Such QSAR are based on electronic and steric parameters [Es, MR,

molar volume, or sterimol parameters (B1, B5, *L*)].[10d] About one-half (346) contain an electronic term. We have elected in this review to consider mostly those QSAR that contain an electronic term and with a few exceptions that contain small negative hydrophobic terms or steric parameters. Our primary objective is to look for direct relationships from mechanistic organic chemistry to enhance our understanding of mechanism and to try to understand why hydrophobic terms are sometimes missing even in the case of whole animal studies. Even in the simplest case of cells, we find examples that lack hydrophobic terms. In these examples one might hypothesize that the hydrophobic character of chemicals might help them to cross cell membranes. Some ideas for the lack of such terms come readily to mind. The crucial reaction could be occurring on the cell surface, or possibly active transport could be involved, or else the advantage gained in membrane crossing could be canceled by interaction with a polar receptor.

II. Methods

All the activity data has been collected from the literature (reference is given with the individual data sets). The activity is expressed in molar concentration, *C*. I_{50} is the 50% inhibitory concentration, $T_{1/2}$ is the half-life for the specific activity, *k* is the rate constant, and *K* is the equilibrium constant. The variation in the activity, if any, is specified with the respective QSAR.

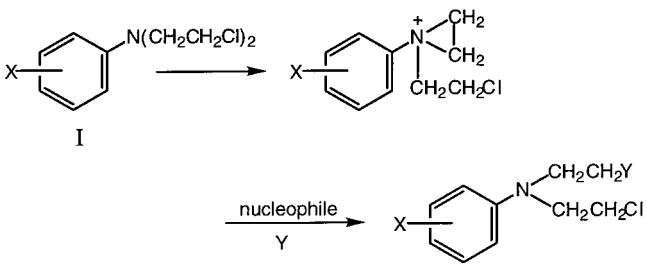
All the physicochemical parameters are autoloaded from our C-QSAR database, and the QSAR regression analysis was executed with our C-QSAR program. The parameters used in this report have been discussed in detail along with their application.[10d] Here we provide a brief definition. Clog *P* is the calculated octanol/water partition coefficient of the molecule, and π is that of the substituent. Clog *P* applies to the neutral form of partially ionized compounds. B1, B5, and *L* are Verloop's sterimol parameters for the substituents. B1 is the measure of the width of the first atom of a substituent, B5 is an attempt to define overall volume, and *L* is the substituent length. CMR is the calculated molar refractivity for the whole molecule, and MR is that for the substituent. These values have been scaled by 0.1.

The electronic Hammett parameters σ, σ^-, and σ^+ apply to the substituent effects on aromatic systems. Taft's σ^* applies to the aliphatic system.

In the QSAR equations, *n* is the number of data points, r^2 is the square of the correlation coefficient, q^2 is the measure of quality of fit, and *s* is the standard deviation. The number in the parentheses are for 95% confidence intervals.

III. Carcinogenesis and Mutagenesis

Our attention was first directed to studies on mutagenicity and cancer,[8,11,13] where QSAR have electronic terms but lack hydrophobic terms. In many of these it is relatively easy to see that chemical reactivity is involved in the crucial toxic step. An illustrative example is that of aniline mustards that appear to operate by the following mechanism.[8]



The following examples (see ref 8 for others) illustrate the situation from reaction with water to reaction in whole animals.

Table 1. Hydrolysis of I in Aqueous Acetone at 66 °C[8]

		log *k*		
no.	substituents	obsd	calcd (eq 1)	σ
1	3-COOEt	−4.59	−4.69	0.37
2	4-Br	−4.46	−4.44	0.23
3	4-CH_2COOEt	−4.04	−3.89	−0.07
4	4-CH_2COOH	−3.99	−3.89	−0.07
5	4-$CH{=}CHC_6H_5$	−3.95	−3.89	−0.07
6	4-CH_2CH_2COOEt	−3.88	−3.89	−0.07
7	4-$CH_2CH_2CH_2COOEt$	−3.84	−3.70	−0.17
8	4-$CH_2CH_2CH_2COOH$	−3.65	−3.70	−0.17
9	4-C_4H_9	−3.61	−3.72	−0.16
10	4-NHCOMe[a]	−3.52	−4.02	0.00
11	4-OC_2H_5	−3.38	−3.57	−0.24
12	4-OH	−3.32	−3.34	−0.37

[a] Data point not included in deriving equation.

Hydrolysis of I in aqueous acetone at 66 °C (Table 1)[8]

$$\log k = -1.84(\pm 0.41)\sigma - 4.02(\pm 0.08) \quad (1)$$

$$n = 11,\ r^2 = 0.923,\ s = 0.116,\ q^2 = 0.875$$

outlier: 4-NHCOMe

Table 2. Substitution of I with Nitrobenzylpyridine in Ethanol at 80 °C[8]

		log *k*		
no.	substituents	obsd	calcd (eq 2)	σ
1	4-H	−1.89	−2.24	0.00
2	4-COOH	−2.34	−2.24	0.00
3	4-$(CH_2)_3COOH$	−1.38	−1.84	−0.17
4	4-CHO	−3.48	−3.24	0.42
5	4-$CONH_2$	−3.30	−3.10	0.36
6	4-SO_2NH_2	−4.00	−3.67	0.60
7	4-OH	−1.31	−1.36	−0.37
8	4-NH_2	−1.38	−0.67	−0.66
9	4-NHCOMe	−1.53	−2.24	0.00
10	4-SCOMe[a]	−2.57	−3.29	0.44

[a] Data point not included in deriving equation.

Substitution of I with nitrobenzylpyridine in ethanol 80 °C (Table 2)[8]

$$\log k = -2.38(\pm 0.99)\sigma - 2.24\ (\pm 0.37) \quad (2)$$

$$n = 9,\ r^2 = 0.821,\ s = 0.472,\ q^2 = 0.648$$

outlier: 4-SCOMe

Table 3. Half-Life of I in Fetal Calf Serum[8]

no.	substituents	log $T_{1/2}$ obsd	log $T_{1/2}$ calcd (eq 3)	σ
1	3-SO_2Me	−1.75	−1.69	0.60
2	4-CONMe	−1.10	−1.21	0.36
3	3-$CONMe_2$	−0.77	−1.05	0.28
4	H	−0.40	−0.48	0.00
5	4-SMe	−0.86	−0.48	0.00
6	4-Me	−0.18	−0.14	−0.17
7	3-Me	−0.54	−0.34	−0.07
8	4-OMe	0.40	0.07	−0.27
9	3-OMe	−0.80	−0.72	0.12
10	4-NH_2	0.87	0.86	−0.66
11	3-NH_2	−0.20	−0.16	−0.16
12	4-NO[a]	−1.14	−2.32	0.91

[a] Data point not included in deriving equation.

Half-life of I in fetal calf serum (Table 3)[8]

$$\log T_{1/2} = -2.02(\pm 0.45)\sigma - 0.48(\pm 0.15) \quad (3)$$

$$n = 11,\ r^2 = 0.921,\ s = 0.212,\ q^2 = 0.895$$

outlier: 4-NO

Table 4. Nucleophilic Substitution by X−$C_6H_4SCH_2CH_2Br$ with Nitrobenzylpyridine in 4:1 Acetone:Water[8]

no.	substituents	log k obsd	log k calcd (eq 4)	σ
1	3-NO_2	−5.58	−5.50	0.71
2	3-COOEt	−4.75	−4.87	0.39
3	3-Cl	−4.90	−4.83	0.37
4	4-Cl	−4.59	−4.55	0.23
5	3-OMe	−4.28	−4.33	0.12
6	3-Cl,4-OMe	−4.17	−4.31	0.11
7	H	−4.11	−4.10	0.00
8	3-Me	−3.94	−3.96	−0.07
9	4-Me	−3.82	−3.76	−0.17
10	3,4-di-Me	−3.64	−3.62	−0.24
11	4-OMe	−3.61	−3.56	−0.27
12	3-Me,4-OMe	−3.43	−3.43	−0.34

Nucleophilic substitution by X−$C_6H_4SCH_2CH_2Br$ with nitrobenzylpyridine in 4:1 acetone:water (Table 4)[8]

$$\log k = -1.97(\pm 0.16)\sigma - 4.10(\pm 0.05) \quad (4)$$

$$n = 12,\ r^2 = 0.987,\ s = 0.076,\ q^2 = 0.979$$

Table 5. I_{50} of Chinese Hamster UV4 Cells by *I*[8]

no.	substituents	log 1/C obsd	log 1/C calcd (eq 5)	σ
1	4-NO_2[a]	4.80	3.80	0.78
2	3-NO_2	4.02	3.97	0.71
3	4-SO_2Me	3.76	3.95	0.72
4	3-SO_2Me	4.12	4.25	0.60
5	4-$CONMe_2$	4.84	4.86	0.36
6	3-$CONMe_2$	5.12	5.07	0.28
7	H	5.92	5.78	0.00
8	4-SMe	5.79	5.78	0.00
9	4-Me	6.40	6.21	−0.17
10	3-Me	5.92	5.95	−0.07
11	4-OMe	6.35	6.46	−0.27
12	3-OMe	5.57	5.47	0.12
13	4-NH_2	7.15	7.45	−0.66
14	3-NH_2	6.42	6.18	−0.16

[a] Data point not included in deriving equation.

I_{50} of Chinese hamster UV4 cells by I (Table 5)[8]

$$\log 1/C = -2.54(\pm 0.25)\sigma + 5.78(\pm 0.10) \quad (5)$$

$$n = 13,\ r^2 = 0.978,\ s = 0.162,\ q^2 = 0.962$$

outlier: 4-NO_2

Table 6. I_{50} of P388 Leukemia Mouse *T/C* = 180 by *I*[8]

no.	substituents	log 1/C obsd	log 1/C calcd (eq 6)	σ	I	Clog P
1	4-OC_6H_5	3.35	3.47	−0.03	0	5.69
2	3-$CH(NH_2)CH_2COOH$[a]	3.65	5.32	−0.01	0	−0.31
3	3-OCH_2CO_2Et	3.71	3.81	0.12	0	3.66
4	3-CH_2CH_2COOH	3.81	4.24	−0.03	0	3.25
5	H	4.02	4.10	0.00	0	3.49
6	4-OBu	4.02	4.14	−0.27	0	5.10
7	3-OCH_2CH_2COOH	4.04	4.00	0.12	0	3.06
8	3-OCH_2COOH	4.29	4.08	0.12	0	2.80
9	4-CH_2CH_2COOH	4.36	4.32	−0.07	0	3.25
10	2-CH=CHCOOH	4.39	4.35	0.17	1	3.59
11	2-OCH_2CH_2COOH[a]	4.41	5.40	−0.27	1	3.06
12	4-$CH_2C(NH_2)(CH_3)COOH$[a]	4.55	5.17	−0.07	0	0.50
13	4-$(CH_2)_3CHO$	4.72	4.41	−0.17	0	3.60
14	4-CH_2COOH	4.87	4.47	−0.07	0	2.76
15	4-N=CHC_6H_5	5.00	4.99	−0.55	0	4.20
16	4-$CH_2CH(NH_2)COOH$	5.18	5.41	−0.07	0	−0.21
17	3-$CH_2CH(NH)_2COOH$	5.39	5.33	−0.03	0	−0.21
18	2-$CH_2CH(NH_2)COOH$	5.98	6.02	−0.07	1	−0.21

[a] Data points not included in deriving equation.

I_{50} of P388 leukemia mouse T/C = 180 by I (Table 6)[8]

$$\log 1/C = -2.01(\pm 0.79)\sigma - 0.32(\pm 0.08)\text{Clog } P + 0.62(\pm 0.41)I + 5.20(\pm 0.28) \quad (6)$$

$$n = 15,\ r^2 = 0.916,\ s = 0.232,\ q^2 = 0.883$$

outliers: 2-OCH_2CH_2COOH; 4-$CH_2C(NH_2)(CH_3)COOH$; 3-$CH(NH_2)CH_2COOH$

$I = 1$ for ortho subsituents

Table 7. 25% Increase in Lifespan of Mice with B-16 Melanoma by *I*[8]

no.	substituents	log 1/C obsd	log 1/C calcd (eq 7)	σ	Clog P
1	4-Cl	2.74	3.37	0.23	4.38
2	4-CH=CHC_6H_5	2.86	3.28	−0.07	5.78
3	4-CH=$C(CN)_2$	3.00	3.26	0.70	2.78
4	4-$CONHC_3H_7$	3.25	3.54	0.36	3.46
5	4-OC_6H_5	3.35	3.25	−0.03	5.69
6	4-NC_4H_9	3.44	3.51	−0.16	5.58
7	4-CN	3.57	3.10	0.66	3.32
8	3,5-di-$NHCONH_2$[a]	3.69	5.33	−0.06	0.90
9	4-Me	3.86	4.20	−0.17	3.99
10	H	4.38	4.13	0.00	3.49
11	3,4-di-Me	4.45	4.13	−0.24	4.44
12	3,5-di-NH_2[a]	4.45	5.70	−0.32	1.04
13	3,4-di-OMe	4.52	4.52	−0.15	3.17
14	4-OBu	4.56	3.98	−0.32	5.10
15	4-$NHCONH_2$	4.63	5.08	−0.24	2.19
16	4-OMe	4.68	4.57	−0.27	3.51
17	4-$(CH_2)_3COOH$	4.70	4.35	−0.17	3.63
18	4-OEt	4.87	4.30	−0.24	4.04
19	4-OH	4.93	5.03	−0.37	2.82
20	4-NH_2	5.35	5.75	−0.66	2.26
21	4-NH_2,3-Me	5.50	5.68	−0.73	2.71
22	4-$CH_2CH(NH_2)COOH$	6.18	5.81	−0.07	−0.21

[a] Data points not included in deriving equation.

25% increase in lifespan of mice with B-16 melanoma by I (Table 7)[8]

$$\log 1/C = -1.67(\pm 0.53)\sigma - 0.42(\pm 0.13)\text{Clog } P + 5.60(\pm 0.52) \quad (7)$$

$$n = 20,\ r^2 = 0.848,\ s = 0.389,\ q^2 = 0.777$$

outliers: 3,5-di-$NHCONH_2$; 3,5-di-NH_2

Table 8. Twenty-five Percent Increase in Lifespan of Mice with L1210 Leukemia by *I*[8]

		log 1/*C*				
no.	substituents	obsd	calcd (eq 8)	*I*	Clog *P*	σ
1	4-SO_2NH_2	3.55	3.62	0	1.87	0.60
2	3-OCH_2CO_2Et	3.60	3.72	0	3.66	0.12
3	4-OBu	3.76	3.89	0	5.10	−0.32
4	3-OCH_2COOH	3.87	4.03	0	2.80	0.12
5	3-COOH	3.91	3.99	0	3.43	0.00
6	H	4.00	3.97	0	3.49	0.00
7	3-CH=CHCOOH	4.05	4.04	0	3.59	−0.07
8	4-OCH_3	4.28	4.37	0	3.51	−0.27
9	3-CH_2CH_2COOH	4.30	4.10	0	3.25	−0.03
10	2-CH=CHCOOH	4.64	4.79	1	3.59	−0.07
11	2-OCH_2CH_2COOEt	4.67	4.62	1	4.07	−0.07
12	4-CH_2COOH	4.79	4.34	0	2.76	−0.08
13	4-$CH_2CH_2NH_2$	4.83	4.48	0	2.78	−0.17
14	2-OCH_2CH_2COOH	4.89	5.11	1	3.06	−0.16
15	3-$CH(NH_2)CH_2COOH$	4.89	5.30	0	−0.31	0.00
16	4-OCH_2COOEt[a]	4.91	4.15	0	3.66	−0.16
17	4-$CH_2CH(NH_2)COOH$	4.94	5.38	0	−0.21	−0.07
18	4-COOH[a]	4.94	3.99	0	3.43	0.00
19	3-$CH_2CH(NH_2)COOH$	5.71	5.27	0	−0.21	0.00
20	4-$CH_2CH(NH_2)COOH$, 2-Cl	5.83	5.56	1	0.42	0.16
21	2-$CH_2CH(NH_2)COOH$	6.18	6.13	1	−0.21	−0.07

[a] Data points not included in deriving equation.

25% Increase in lifespan of mice with L1210 leukemia by I (Table 8)[8]

$$\log 1/C = -1.53(\pm 0.76)\sigma - 0.35(\pm 0.09)\text{Clog } P + 0.75(\pm 0.31)I + 5.20(\pm 0.27) \quad (8)$$

$$n = 19,\ r^2 = 0.888,\ s = 0.277,\ q^2 = 0.821$$

outliers: 4-OCH_2COOEt; 4-COOH

$I = 1$ for ortho substituents

Table 9. Twenty-five Percent Increase in Lifespan of Mice with B-16 Melanoma[8]

		log 1/*C*			
no.	substituents	obsd	calcd (eq 9)	Clog *P*	σ
1	4-Cl	2.74	3.33	4.38	0.23
2	4-CH=CHC_6H_5	2.86	3.19	5.78	−0.07
3	4-CH=$C(CN)_2$	3.00	2.73	2.78	0.70
4	4-$CONHC_3H_7$	3.25	3.41	3.46	0.36
5	4-OC_6H_5	3.35	3.16	5.69	−0.03
6	4-NC_4H_9	3.44	3.49	5.58	−0.16
7	4-CN[a]	3.57	0.06	3.32	0.66
8	3,5-di-$NHCONH_2$	3.69	3.76	0.90	−0.06
9	4-Me	3.86	4.35	3.99	−0.17
10	H	4.38	4.16	3.49	0.00
11	3,4-di-Me	4.45	4.28	4.44	−0.24
12	3,5-di-NH_2	4.45	4.35	1.04	−0.32
13	3,4-di-OMe	4.52	4.52	3.17	−0.15
14	4-OBu	4.56	4.09	5.10	−0.32
15	4-$NHCONH_2$	4.63	4.57	2.19	−0.24
16	4-OMe	4.68	4.72	3.51	−0.27
17	4-$(CH_2)_3COOH$	4.70	4.48	3.63	−0.17
18	4-OEt	4.87	4.47	4.04	−0.24
19	4-OH	4.93	4.97	2.82	−0.37
20	4-NH_2	5.35	5.47	2.26	−0.66
21	4-NH_2,3-Me	5.50	5.71	2.71	−0.73
22	4-$CH_2CH(NH_2)COOH$[a]	6.18	3.19	−0.21	−0.07

[a] Data point not included in deriving equation.

25% increase in lifespan of mice with B-16 melanoma (Table 9)[8]

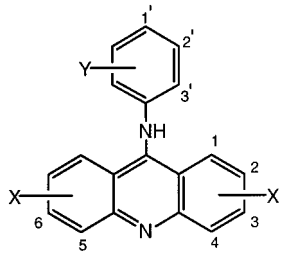
$$\log 1/C = 0.36(\pm 0.27)\text{Clog } P - 0.92(\pm 0.44) \log(\beta \times 10^{\text{Clog } P} + 1) - 2.09(\pm 0.48)\sigma + 3.31(\pm 0.69) \quad (9)$$

$$n = 20,\ r^2 = 0.891,\ s = 0.307,\ q^2 = 0.834$$

outliers: 4-CN; 4-$CH_2CH(NH_2)COOH$

There is an interesting consistency in the electronic terms in these results. Equation 9 is an exception in that it does contain a positive log *P* term, a reason for which is not clear. In two examples, small negative log *P* terms occur. Although these compounds were used in the past to treat people, they are quite toxic since they can react with a wide variety of nucleophiles.

The antitumor activity of compound II has also been compared to a variety of simpler systems.[11] Possibly the most extensively studied class of antitumor agents (from the SAR point of view) was made on anilinoacridines at the Cancer Research Laboratory of the University of Aukland, New Zealand.



II

Therapeutic activity of II in mice (concentration for 40% increase in lifespan) bearing L1210 leukemia[11]

$$\log 1/C = -0.85(\pm 0.08)\sigma^+_X - 2.70(\pm 0.45)\sigma^+_Y - 2.60(\pm 0.52)MR_1 - 1.45(\pm 0.22)MR_6 - 2.33(\pm 0.49)MR_{3'} - 0.66(\pm 0.49)MR_{2'} + 0.75(\pm 0.16)I_{NO2} + 0.35(\pm 0.15)B1_3 - 0.94(\pm 0.23)B1_2 - 0.26(\pm 0.06)\pi_{Y,1'} + 5.67(\pm 0.43) \quad (10)$$

$$n = 226,\ r^2 = 0.811,\ s = 0.337,\ q^2 = 0.791$$

Parameter importance: $\sigma^+_X > \sigma^+_Y > MR_6 > I_{NO2} > MR_1 > MR_{3'} > \pi_{Y,1'} > MR_{2'} > B1_3$

Toxicity (LD_{10}) of II in mice bearing L1210 leukemia[11]

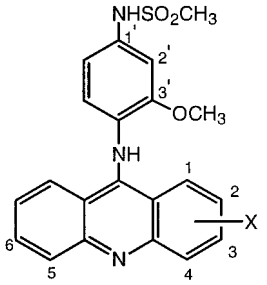
$$\log 1/C = -0.64(\pm 0.08)\sigma^+_X - 2.31(\pm 0.40)\sigma^+_Y - 1.83(\pm 0.44)MR_1 - 0.23(\pm 0.10)MR_4 + 0.46(\pm 0.20)MR_5 - 0.43(\pm 0.25)MR_6 - 1.83(\pm 0.44)MR_{3'} - 0.14(\pm 0.06)\pi_R - 0.45(\pm 0.20)I_{3,6} - 0.71(\pm 0.21)B1_2 + 0.35(\pm 0.15)I_{NO2} + 5.02(\pm 0.30) \quad (11)$$

$$n = 217,\ r^2 = 0.787,\ s = 0.292,\ q^2 = 0.762$$

Parameter importance: $\sigma^+_X > \sigma^+_Y > MR_5 > MR_6 > MR_{3'} > MR_1 > I_{3,6} > \pi_{Y,1'} > I_{NO2}$

In these equations, $B1_2$ and $B1_3$ are sterimol parameters,[10d] MR (molar refractivity)[10d] is a measure of substituent bulk, and $I_{3,6}$ is an indicator variable that takes the value of 1 when substituents are present in both the 3 and 6 positions but otherwise is zero. I_{NO2} is assigned a value of 1 for the presence of a NO_2 group. It is now clear why nitro groups are outliers (section VII). Of most interest to us is that each equation contains a very small negative π that pertains to R in 1′-$NHSO_2R$ of II.

The net take home message is that hydrophobicity is relatively unimportant (and negative) for both the curative and toxic doses. The terms in the two equations are similar, indicating efficacy and toxicity are closely related. However, the intercepts suggest that higher concentrations are required to produce the LD_{10}. Of course, negative σ^+ terms are the most important parameters.



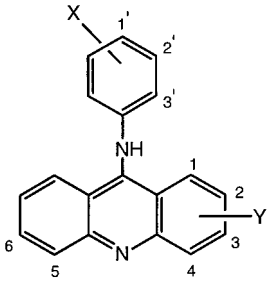
III

I_{50} for L1210 leukemia cells for compound III[11]

$$\log 1/C = -0.58(\pm 0.15)\sigma^+ - 0.26(\pm 0.06)B5_5 - 7.67 \quad (12)$$

$$n = 21,\ r^2 = 0.916,\ s = 0.188,\ q^2 = 0.885$$

Again, at the cell level, we see a negative σ^+ term comparable to eqs 10 and 11 and no hydrophobic term.



IV

Table 10. Association Constants *K* for the Binding of IV to DNA (Poly[D(A−T)])[8]

		log *K*			
no.	substituents	obsd	calcd (eq 13)	σ^+_X	$B5_{3'}$
1	1′-NO_2	5.48	5.73	0.79	1.00
2	1′-SO_2Me	5.86	5.75	0.72	1.00
3	1′-CN	5.70	5.77	0.66	1.00
4	1′-SO_2NH_2	5.96	5.79	0.60	1.00
5	1′-COMe	5.87	5.81	0.50	1.00
6	1′-COOMe	5.88	5.82	0.49	1.00
7	1-$CONH_2$	5.83	5.85	0.36	1.00
8	1′−F	5.91	5.97	−0.07	1.00
9	1′-Cl	5.99	5.92	0.11	1.00
10	1′-Br	6.02	5.91	0.15	1.00
11	1′−I	6.19	5.92	0.14	1.00
12	1′-$NHSO_2C_6H_5$	6.20	6.23	−0.98	1.00
13	H	5.86	5.96	0.00	1.00
14	1′-NHCOMe	6.30	6.12	−0.60	1.00
15	1′-Me	5.99	6.04	−0.31	1.00
16	1′-$NHCOC_6H_5$	6.20	6.12	−0.60	1.00
17	1′-OMe	6.12	6.18	−0.78	1.00
18	1′-OH	6.28	6.21	−0.92	1.00
19	1′-NHC_6H_{13}	6.43	6.47	−1.81	1.00
20	1′-NHC_4H_9	6.45	6.47	−1.81	1.00
21	1′-NHC_3H_7	6.35	6.47	−1.81	1.00
22	1′-NHC_2H_5	6.44	6.47	−1.81	1.00
23	1′-NH_2	6.31	6.32	−1.30	1.00
24	1′-NMe_2	6.51	6.43	−1.70	1.00
25	1′-NHMe	6.55	6.47	−1.81	1.00
26	2′-NO_2	5.56	5.75	0.71	1.00
27	2′-Cl	6.02	5.85	0.37	1.00
28	2′-NHCOMe	5.90	5.90	0.21	1.00
29	2′-$NHSO_2Me$	5.73	5.90	0.20	1.00
30	2′-OMe	5.86	5.92	0.12	1.00
31	2′-OH	6.00	5.92	0.12	1.00
32	2′-Me	6.09	5.97	−0.07	1.00
33	2′-NH_2	6.11	6.00	−0.16	1.00
34	2′-NHMe	6.11	6.01	−0.21	1.00
35	3′-SO_2NH_2	5.67	5.81	0.53	1.00
36	3′-$CONH_2$[a]	5.37	5.01	0.36	3.07
37	2′-NO_2	5.36	5.14	0.79	2.44
38	3′−I	5.33	5.45	0.14	2.15
39	3′-Br	5.35	5.53	0.15	1.95
40	3′-Cl	5.39	5.60	0.11	1.80
41	3′−F	5.59	5.83	−0.07	1.35
42	3′-OH[a]	5.36	5.84	−0.92	1.93
43	3′-OMe	5.50	5.33	−0.78	3.07
44	3′-OC_2H_5	5.20	5.22	−0.81	3.36
45	3′-Me[a]	5.25	5.62	−0.31	2.04
46	3′-C_2H_5	5.18	5.15	−0.30	3.17
47	3′-$CHMe_2$	5.08	5.15	−0.28	3.17
48	3′-CMe_3	5.23	5.14	−0.26	3.17
49	3′-NH_2	5.76	5.93	−1.30	1.97
50	3′-NHCOMe[a]	5.84	5.06	−0.60	3.61
51	3′-COOMe[a]	5.47	4.85	0.49	3.36

[a] Data points not included in deriving equation.

Association constants K for the binding of IV to DNA Poly[D(A−T)]DNA (Table 10)[8]

$$\log K = -0.28(\pm 0.05)\sigma^+_X - 0.41(\pm 0.05)B5_{3'} + 6.36(\pm 0.08) \quad (13)$$

$$n = 46,\ r^2 = 0.895,\ s = 0.129,\ q^2 = 0.885$$

outliers: 3′-$CONH_2$; 3′-OH; 3′-Me; 3′-NHCOMe; 3′-COOMe

Table 11. Binding of 1′-NHCOOMe, 3′-NHMe, 2,3,4,5-Y-IV to Poly[D(A−T)]DNA[12]

		log K				
no.	substituents	obsd	calcd (eq 14)	σ	$L_{Y,4}$	$B1_{Y,5}$
1	H	6.35	6.36	0.00	2.06	1.00
2	2-Me[a]	5.62	6.45	−0.07	2.06	1.00
3	3-F	5.77	6.29	0.06	2.06	1.00
4	3-Cl	6.13	6.07	0.23	2.06	1.00
5	3-Br[a]	6.87	6.07	0.23	2.06	1.00
6	3-I	6.12	6.14	0.18	2.06	1.00
7	3-Me	6.72	6.57	−0.17	2.06	1.00
8	3-OMe	6.74	6.69	−0.27	2.06	1.00
9	3-NO_2[a]	6.58	5.39	0.78	2.06	1.00
10	4-F	5.82	6.02	0.34	2.65	1.00
11	4-Cl	6.30	6.11	0.37	3.52	1.00
12	4-Me	6.74	6.56	−0.07	2.87	1.00
13	4-OMe	6.57	6.48	0.12	3.98	1.00
14	4-$CONH_2$	6.00	6.30	0.28	4.06	1.00
15	4-CONHMe	6.48	6.34	0.35	5.00	1.00
16	3-F,5-Me	7.37	7.46	−0.01	2.06	1.52
17	3-Cl,5-Me	7.52	7.25	0.16	2.06	1.52
18	3-Br,5-Me	7.52	7.25	0.16	2.06	1.52
19	3,5-di-Me	7.69	7.74	−0.24	2.06	1.52
20	3-F,5-OMe[a]	6.27	6.87	0.18	2.06	1.35
21	3-Cl,5-OMe	6.93	6.66	0.35	2.06	1.35
22	3-Br,5-OMe	6.43	6.66	0.35	2.06	1.35
23	3-Me,5-OMe	7.34	7.15	−0.05	2.06	1.35
24	4,5-di-Me	7.34	7.74	−0.14	2.87	1.52
25	4,5-di-OMe	7.37	7.07	0.24	3.98	1.35
26	4-Me,5-CONHMe	7.12	7.26	0.28	2.87	1.54
27	4-OMe,5-CONHMe	6.95	7.18	0.47	3.98	1.54

[a] Data points not included in deriving equation.

Binding of 1′-NHCOOMe, 3′-NHMe, 2,3,4,5-Y-IV to Poly[D(A−T)]DNA (Table 11)[12]

$$\log K = -1.24(\pm 0.59)\sigma + 0.14(\pm 0.14)L_{Y,4} + 2.09(\pm 0.46)B1_{Y,5} + 3.98(\pm 0.72) \quad (14)$$

$$n = 23,\ r^2 = 0.846,\ s = 0.247,\ q^2 = 0.775$$

outliers: 2-Me; 3-Br; 3-NO_2; 3-F,5-OMe

The above equation fits better with σ than σ^+; still, it is electron-releasing substituents that promote binding.

Binding of 1′,3′-X, 2,3,4-Y-IV to Poly[D(A−T)]DNA (Table 12)[13]

$$\log K = -0.18(\pm 0.15)\sigma^+_Y - 0.54(\pm 0.12)I_1 + 0.17(\pm 0.11)I_2 - 0.94(\pm 0.29)B1_{Y,2} + 0.27(\pm 0.09)L_{Y,4} + 6.71(\pm 0.47) \quad (15)$$

$$n = 37,\ r^2 = 0.882,\ s = 0.170,\ q^2 = 0.839$$

outlier: X = H, Y = 2-Cl, 4-$PO(OMe)_2$

Table 12. Binding of 1′,3′-X, 2,3,4-Y-IV to Poly[D(A−T)]DNA[13]

	substituents		log K						
no.	X	Y	obsd	calcd (eq 15)	I_1	I_2	σ^+_Y	$B1_{Y,2}$	$L_{Y,4}$
1	H	H,4-$P(O)(OMe)_2$	6.26	6.50	0	1	0.00	1.00	2.06
2	H	H,4-SO_2Me	6.15	6.33	0	0	0.00	1.00	2.06
3	H	2-Me,4-$P(O)(OMe)_2$	6.09	6.02	0	1	−0.07	1.52	2.06
4	H	2-Me,4-SO_2Me	5.70	5.86	0	0	−0.07	1.52	2.06
5	H	2-OMe,4-$P(O)(OMe)_2$	6.25	6.15	0	1	0.12	1.35	2.06
6	H	2-OMe,4-SO_2Me	6.00	5.98	0	0	0.12	1.35	2.06
7	H	2-Cl,4-$P(O)(OMe)_2$[a]	6.17	5.68	0	1	0.37	1.80	2.06
8	H	2-Cl,4-SO_2Me	5.62	5.51	0	0	0.37	1.80	2.06
9	H	3-Me,4-$P(O)(OMe)_2$	6.77	6.77	0	1	−0.31	1.00	2.87
10	H	3-Me,4-SO_2Me	6.41	6.61	0	0	−0.31	1.00	2.87
11	H	3-Cl,4-$P(O)(OMe)_2$	7.00	6.87	0	1	0.11	1.00	3.52
12	H	3-Cl,4-SO_2Me	6.89	6.70	0	0	0.11	1.00	3.52
13	H	3-Br,4-$P(O)(OMe)_2$	6.56	6.94	0	1	0.15	1.00	3.82
14	H	3-Br,4-SO_2Me	6.93	6.78	0	0	0.15	1.00	3.82
15	H	3-NO_2,4-$P(O)(OMe)_2$	6.73	6.72	0	1	0.79	1.00	3.44
16	H	3-NO_2,4-SO_2Me	6.51	6.56	0	0	0.79	1.00	3.44
17	H	3-NH_2,4-$P(O)(OMe)_2$	6.90	6.93	0	1	−1.30	1.00	2.78
18	H	3-NH_2,4-SO_2Me	6.82	6.76	0	0	−1.30	1.00	2.78
19	H	4-Me,4-$P(O)(OMe)_2$	6.75	6.51	0	1	−0.07	1.00	2.06
20	H	4-Me,4-SO_2Me	6.52	6.34	0	0	−0.07	1.00	2.06
21	H	4-OMe,4-$P(O)(OMe)_2$	6.53	6.47	0	1	0.12	1.00	2.00
22	H	4-OMe,4-SO_2Me	6.24	6.31	0	0	0.12	1.00	2.06
23	H	4-CONHMe,4-$P(O)(OMe)_2$	6.46	6.43	0	1	0.35	1.00	2.06
24	H	4-CONHMe,4-SO_2Me	6.22	6.27	0	0	0.35	1.00	2.06
25	3′-OMe	H,4-$P(O)(OMe)_2$	5.64	5.95	1	1	0.00	1.00	2.06
26	3′-OMe	H,4-SO_2Me	5.57	5.79	1	0	0.00	1.00	2.06
27	3′-OMe	2-Me,4-$P(O)(OMe)_2$	5.28	5.48	1	1	−0.07	1.52	2.06
28	3′-OMe	2-Me,4-SO_2Me	5.35	5.31	1	0	−0.07	1.52	2.06
29	3′-OMe	3-Cl,4-$P(O)(OMe)_2$	6.40	6.33	1	1	0.11	1.00	3.52
30	3′-OMe	3-Cl,4-SO_2Me	6.06	6.16	1	0	0.11	1.00	3.52
31	3′-OMe	3-Br,4-$P(O)(OMe)_2$	6.44	6.40	1	1	0.15	1.00	3.82
32	3′-OMe	3-Br,4-SO_2Me	6.29	6.23	1	0	0.15	1.00	3.82
33	3′-OMe	4-Me,4-$P(O)(OMe)_2$	6.16	5.97	1	1	−0.07	1.00	2.06
34	3′-OMe	4-Me,4-SO_2Me	6.03	5.80	1	0	−0.07	1.00	2.06
35	3′-OMe	4-OMe,4-$P(O)(OMe)_2$	6.09	5.93	1	1	0.12	1.00	2.06
36	3′-OMe	4-OMe,4-SO_2Me	5.94	5.77	1	0	0.12	1.00	2.06
37	3′-OMe	4-CONHMe,4-$P(O)(OMe)_2$	5.94	5.89	1	1	0.35	1.00	2.06
38	3′-OMe	4-CONHMe,4-SO_2Me	5.54	5.72	1	0	0.35	1.00	2.06

[a] Data point not included in deriving equation.

Table 13. Binding of 1′-NHSO$_2$Me, 3′-NHMe, 2,3,4,5-Y-IV to Poly[D(A−T)]DNA[14]

		log K					
no.	substituents	obsd	calcd (eq 16)	σ^+_Y	$B1_{Y,5}$	$MR_{Y,3}$	$MR_{Y,4}$
1	H[a]	6.42	6.03	0.00	1.00	0.10	0.10
2	2-Me	5.89	6.04	−0.07	1.00	0.10	0.10
3	2-OMe	5.80	6.01	0.12	1.00	0.10	0.10
4	2-Cl	6.22	5.96	0.37	1.00	0.10	0.10
5	3-Me	6.71	6.50	−0.31	1.00	0.57	0.10
6	3-OMe	6.64	6.79	−0.78	1.00	0.79	0.10
7	3-F	5.78	6.04	−0.07	1.00	0.09	0.10
8	3-Cl	6.18	6.46	0.11	1.00	0.60	0.10
9	3-Br	6.99	6.70	0.15	1.00	0.89	0.10
10	3-I[a]	6.42	7.16	0.14	1.00	1.39	0.10
11	3-NO$_2$	6.72	6.44	0.79	1.00	0.74	0.10
12	3-NHMe	7.53	7.22	−1.81	1.00	1.03	0.10
13	3-NHCOOMe	7.21	7.46	−0.60	1.00	1.57	0.10
14	4-Me	6.60	6.32	−0.07	1.00	0.10	0.57
15	4-OMe	6.43	6.41	0.12	1.00	0.10	0.79
16	4-F[a]	6.91	5.96	0.34	1.00	0.10	0.09
17	4-Cl[a]	6.87	6.26	0.37	1.00	0.10	0.60
18	4-Br	6.37	6.42	0.39	1.00	0.10	0.89
19	4-CONH$_2$	6.28	6.50	0.28	1.00	0.10	0.98
20	4-CONHMe[a]	6.11	6.77	0.35	1.00	0.10	1.46
21	1,4-di-Me	6.18	6.38	−0.38	1.00	0.10	0.57
22	1-Cl,4-CONHMe	6.75	6.75	0.46	1.00	0.10	1.46
23	3,4-di-Me	6.96	6.79	−0.38	1.00	0.57	0.57
24	3,5-di-Me	7.23	7.10	−0.38	1.52	0.57	0.10
25	3-F,5-Me	6.66	6.64	−0.14	1.52	0.09	0.10
26	3-Cl,5-Me	7.26	7.06	0.04	1.52	0.60	0.10
27	3-Br,5-Me	7.27	7.30	0.08	1.52	0.89	0.10
28	3-OMe,5-Me	7.16	7.40	−0.85	1.52	0.79	0.10
29	3-Me,5-OMe	6.69	6.88	−0.19	1.35	0.57	0.10
30	3-F,5-OMe	6.44	6.41	0.05	1.35	0.09	0.10
31	3-Cl,5-OMe	6.94	6.83	0.23	1.35	0.60	0.10
32	3-Br,5-OMe	6.94	7.07	0.27	1.35	0.89	0.10
33	3-Cl,5-CONHMe	6.79	7.00	0.46	1.54	0.60	0.10
34	4,5-di-Me	7.00	6.92	−0.14	1.52	0.10	0.57
35	4,5-di-OMe[a]	6.22	6.79	0.24	1.35	0.10	0.79
36	4-Me,5-CONHMe	7.05	6.86	0.28	1.54	0.10	0.57
37	4-OMe,5-CONHMe	6.92	6.96	0.47	1.54	0.10	0.79

[a] Data points not included in deriving equation.

Binding of 1′-NHSO$_2$Me, 3′-NHMe, 2,3,4,5-Y−IV to Poly[D(A−T)]DNA (Table 13)[14]

$$\log K = -0.20(\pm 0.18)\sigma^+_Y + 1.13(\pm 0.33)B1_{Y,5} + 0.89(\pm 0.25)MR_{Y,3} + 0.59(\pm 0.26)MR_{Y,4} + 4.75(\pm 0.46) \quad (16)$$

$$n = 31,\ r^2 = 0.817,\ s = 0.208,\ q^2 = 0.710$$

outliers: 3-I; 4-F; 4-Cl; 4-CONHMe; 4,5-di-OMe; H

Table 14. Binding of 1′-NHSO$_2$Me, 3′-OMe, 3,5-Y-IV to Poly[D(G−C)]DNA[15]

		log K				
no.	substituents	obsd	calcd (eq 17)	$B1_{Y,3}$	$B1_{Y,5}$	σ^+_Y
1	H	5.65	5.67	1.00	1.00	0.00
2	3-NH$_2$	6.13	6.11	1.35	1.00	−1.30
3	3-NO$_2$	6.13	5.90	1.70	1.00	0.79
4	3-Me	6.08	6.01	1.52	1.00	−0.31
5	3-OMe	5.97	6.01	1.35	1.00	−0.78
6	3-Cl	5.98	6.08	1.80	1.00	0.11
7	3-Br	6.12	6.16	1.95	1.00	0.15
8	3-I	6.20	6.27	2.15	1.00	0.14
9	5-CONH$_2$	6.13	6.26	1.00	1.50	0.28
10	5-CONHMe	6.18	6.30	1.00	1.54	0.35
11	5-CONHCH$_2$CONH$_2$	6.40	6.30	1.00	1.54	0.35
12	3-NH$_2$,5-CONHMe	6.82	6.73	1.35	1.54	−0.95
13	3-NO$_2$,5-CONHMe	6.40	6.49	1.70	1.50	1.07
14	3-NO$_2$,5-CONHMe	6.65	6.52	1.70	1.54	1.14
15	3-Me,5-CONH$_2$	6.30	6.60	1.52	1.50	−0.03
16	3-Me,5-CONHMe	6.68	6.64	1.52	1.54	0.04
17	3-Me,5-CONHCH$_2$CONH$_2$	6.69	6.64	1.52	1.54	0.04
18	3-OMe,5-CONHMe	6.82	6.63	1.35	1.54	−0.43
19	3-Cl,5-CONH$_2$	6.58	6.67	1.80	1.50	0.39
20	3-Cl,5-CONHMe	6.65	6.71	1.80	1.54	0.46
21	3-Cl,5-CONHCH$_2$CONH$_2$	6.83	6.71	1.80	1.54	0.46

Binding of 1′-NHSO$_2$Me, 3′-OMe, 3,5-Y-IV to Poly-[D(G−C)]DNA (Table 14)[15]

$$\log K = -0.19(\pm 0.12)\sigma^+_Y + 0.54(\pm 0.21)B1_{Y,3} + 1.28(\pm 0.27)B1_{Y,5} + 3.86(\pm 0.55) \quad (17)$$

$$n = 21,\ r^2 = 0.864,\ s = 0.134,\ q^2 = 0.800$$

Table 15. Binding of 1′-X, 3,6-Y-IV to DNA[16]

	substituents		log 1/C			
no.	X	Y	obsd	calcd (eq 18)	σ^+_X	σ^+_Y
1	OH	H	5.54	5.64	−0.92	0.00
2	NHC$_3$H$_7$	H	6.00	5.83	−1.30	0.00
3	NHC$_2$H$_5$	H	6.00	5.83	−1.30	0.00
4	NH$_2$	H	5.85	5.83	−1.30	0.00
5	NHC$_4$H$_9$	H	6.00	5.83	−1.30	0.00
6	NHCOMe	H	5.57	5.49	−0.60	0.00
7	NHMe	H	6.16	6.08	−1.81	0.00
8	NHSO$_2$C$_6$H$_4$NH$_2$	H[a]	5.62	5.19	0.01	0.00
9	NHCONHMe	H[a]	5.70	5.31	−0.25	0.00
10	NHSO$_2$Me	H	5.43	5.18	0.03	0.00
11	NMe$_2$	H	6.05	6.03	−1.70	0.00
12	NHCOC$_6$H$_4$	H	5.55	5.49	−0.60	0.00
13	NHSO$_2$C$_6$H$_4$	H	5.43	5.67	−0.98	0.00
14	OMe	H	5.36	5.57	−0.78	0.00
15	Br	H	5.14	5.12	0.15	0.00
16	NH(Me)SO$_2$Me	H	5.10	5.07	0.24	0.00
17	SO$_2$NH$_2$	H	5.00	4.90	0.60	0.00
18	Cl	H	4.96	5.14	0.11	0.00
19	COMe	H	4.92	4.94	0.50	0.00
20	CONH$_2$	H	4.89	5.01	0.36	0.00
21	SO$_2$NHMe	H	4.85	4.91	0.57	0.00
22	H	H	4.82	5.19	0.00	0.00
23	CN	H	4.77	4.87	0.66	0.00
24	NO$_2$	H	4.64	4.80	0.79	0.00
25	OH	3-NH$_2$	5.89	6.11	−0.92	−1.30
26	NH$_2$	3-NH$_2$	6.22	6.29	−1.30	−1.30
27	NHMe	3-NH$_2$	6.52	6.54	−1.81	−1.30
28	H	3-NH$_2$	5.41	5.65	0.00	−1.30
29	SO$_2$NH$_2$	3-NH$_2$	5.57	5.36	0.60	−1.30
30	CN	3-NH$_2$	5.22	5.33	0.66	−1.30
31	SO$_2$NHMe	3-NH$_2$	5.64	5.37	0.57	−1.30
32	NHC$_4$H$_9$	3-NH$_2$	6.52	6.29	−1.30	−1.30
33	COMe	3-NH$_2$	5.52	5.41	0.50	−1.30
34	N(Me)SO$_2$Me	3-NH$_2$	5.70	5.54	0.24	−1.30
35	NHCOC$_6$H$_5$	3-NH$_2$	5.77	5.95	−0.60	−1.30
36	Br	3-NH$_2$	5.77	5.58	0.15	−1.30
37	NHSO$_2$Me	3-NH$_2$	5.85	5.64	0.03	−1.30
38	NO$_2$	3-NH$_2$	5.46	5.27	0.79	−1.30
39	H	3,6-di-NH$_2$	5.80	6.12	0.00	−2.60
40	OH	3,6-di-NH$_2$[a]	6.05	6.57	−0.92	−2.60
41	NH$_2$	3,6-di-NH$_2$[a]	6.10	6.76	−1.30	−2.60
42	SO$_2$NH$_2$	3,6-di-NH$_2$	5.92	5.82	0.60	−2.60
43	NHSO$_2$Me	3,6-di-NH$_2$	5.96	6.10	0.03	−2.60

[a] Data points not included in deriving equation.

Binding of 1′-X, 3,6-Y-IV to DNA to give 50% drop in fluorescence of ethidium bound to DNA (Table 15)[16]

$$\log 1/C = -0.49(\pm 0.07)\sigma^+_X - 0.36(\pm 0.07)\sigma^+_Y + 5.19(\pm 0.08) \quad (18)$$

$$n = 39,\ r^2 = 0.872,\ s = 0.178,\ q^2 = 0.850$$

outliers: X = 1′-NHSO$_2$−C$_6$H$_4$-4-NH$_2$, Y = H; X = 1′-NHCONHMe, Y = H; X = 1′-OH, Y = 3,6-di-NH$_2$; X = 1′-NH$_2$, Y = 3,6-di-NH$_2$

Table 16. Binding of 1′,2′,3′-X-IV to DNA[17]

no.	substituents	log 1/C obsd	log 1/C calcd (eq 19)	σ^+_X	$B5_{3'}$
1	1′-NO_2	4.72	4.64	0.79	1.00
2	1′-SO_2Me	4.85	4.64	0.79	1.00
3	1′-CN	4.82	4.69	0.66	1.00
4	1′-SO_2NH_2	4.85	4.71	0.60	1.00
5	1′-COMe	4.85	4.76	0.50	1.00
6	1′-COOME	4.82	4.76	0.49	1.00
7	1′-$CONH_2$	4.75	4.81	0.36	1.00
8	1′−F	4.80	4.99	−0.07	1.00
9	1′-Cl	4.85	4.91	0.11	1.00
10	1′-Br	4.96	4.90	0.15	1.00
11	1′−I	5.09	4.90	0.14	1.00
12	1′-$NHSO_2C_6H_5$	5.24	5.35	−0.98	1.00
13	H	4.80	4.96	0.00	1.00
14	1′-NHCOMe	5.33	5.20	−0.60	1.00
15	1′-Me	5.00	5.08	−0.31	1.00
16	1′-$NHCOC_6H_5$	5.27	5.20	−0.60	1.00
17	1′-OMe	5.13	5.27	−0.78	1.00
18	1′-OH	5.29	5.33	−0.92	1.00
19	1′-NHC_3H_7[a]	5.70	5.07	−0.29	1.00
20	1′-NH_2	5.64	5.48	−1.30	1.00
21	1′-NMe_2	5.70	5.64	−1.70	1.00
22	1′-NHMe	5.92	5.69	−1.81	1.00
23	2′-NO_2	4.57	4.67	0.71	1.00
24	2′-Cl	4.96	4.81	0.37	1.00
25	2′-NHCOMe	4.89	4.87	0.21	1.00
26	2′-$NHSO_2Me$	4.82	4.88	0.20	1.00
27	2′-OMe	4.85	4.91	0.12	1.00
28	2′-OH	5.09	4.91	0.12	1.00
29	2′-Me	4.82	4.99	−0.07	1.00
30	2′-NH_2	5.07	5.02	−0.16	1.00
31	2′-NHMe	5.16	5.04	−0.21	1.00
32	3′-SO_2NH_2	4.75	4.74	0.53	1.00
33	3′-$CONH_2$[a]	4.42	3.68	0.36	3.07
34	2′-NO_2[a]	4.44	3.85	0.79	2.44
35	3′−I	3.90	4.27	0.14	2.15
36	3′-Br	4.24	4.38	0.15	1.95
37	3′-Cl	4.39	4.47	0.11	1.80
38	3′−F	4.57	4.79	−0.07	1.35
39	3′-OH	4.41	4.82	−0.92	1.93
40	3′-OMe	4.47	4.14	−0.78	3.07
41	3′-OC_2H_5	4.07	3.99	−0.81	3.36
42	3′-Me	4.17	4.51	−0.31	2.04
43	3′-C_2H_5	4.08	3.89	−0.30	3.17
44	3′-$CHMe_2$	3.85	3.88	−0.28	3.17
45	3′-CMe_3	4.00	3.87	−0.26	3.17
46	3′-NH_2	4.89	4.95	−1.30	1.97
47	3′-NHCOMe[a]	4.38	3.77	−0.60	3.61
48	3′-COOMe[a]	4.40	3.47	0.49	3.36

[a] Data points not included in deriving equation.

Binding of 1′,2′,3′-X-IV to DNA to give 50% drop in fluorescence of ethidium bound to DNA (Table 16)[17]

$$\log 1/C = -0.40(\pm 0.08)\sigma^+_X - 0.55(\pm 0.07)B5_{3'} + 5.50(\pm 0.11) \quad (19)$$

$$n = 43,\ r^2 = 0.873,\ s = 0.169,\ q^2 = 0.857$$

outliers: 1′-NHC_3H_7; 2′-NO_2; 3′-$CONH_2$; 3′-NHCOMe; 3′-COOMe

Table 17. Binding of 1′-$NHSO_2Me$, 3′-OMe-3,5-Y-IV to [Poly(D(A−T))]DNA[18]

no.	substituents	log K obsd	log K calcd (eq 20)	$B1_{Y,3}$	$B1_{Y,5}$	σ^+_Y
1	H	5.57	5.37	1.00	1.00	0.00
2	3-NH_2	6.21	6.23	1.35	1.00	−1.30
3	3-NO_2	5.65	5.70	1.70	1.00	0.79
4	3-Me	5.95	5.98	1.52	1.00	−0.31
5	3-OMe	5.83	6.02	1.35	1.00	−0.78
6	3-Cl	6.06	6.07	1.80	1.00	0.11
7	3-Br	6.29	6.20	1.95	1.00	0.15
8	3-I	6.35	6.39	2.15	1.00	0.14
9	5-$CONH_2$	5.47	5.53	1.00	1.50	0.28
10	5-CONHMe	5.54	5.53	1.00	1.54	0.35
11	5-$CONHCH_2CONH_2$	5.39	5.53	1.00	1.54	0.35
12	3-NH_2,5-CONHMe	6.29	6.39	1.35	1.54	−0.95
13	3-NO_2,5-$CONH_2$	5.96	5.87	1.70	1.50	1.07
14	3-NO_2,5-CONHMe	5.71	5.86	1.70	1.54	1.14
15	3-Me,5-$CONH_2$	6.40	6.15	1.52	1.50	−0.03
16	3-Me,5-CONHMe	6.22	6.14	1.52	1.54	0.04
17	3-Me,5-$CONHCH_2CONH_2$	6.00	6.14	1.52	1.54	0.04
18	3-OMe,5-CONHMe	6.38	6.18	1.35	1.54	−0.43
19	3-Cl,5-$CONH_2$	6.33	6.24	1.80	1.50	0.39
20	3-Cl,5-CONHMe	6.29	6.23	1.80	1.54	0.46
21	3-Cl,5-$CONHCH_2CONH_2$	6.06	6.23	1.80	1.54	0.46

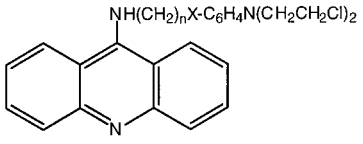
Binding of 1′-$NHSO_2Me$, 3′-OMe-3,5-Y-IV to [Poly-(D(A−T))]DNA (Table 17)[18]

$$\log K = -0.41(\pm 0.12)\sigma^+_Y + 0.94(\pm 0.22)B1_{Y,3} + 0.56(\pm 0.28)B1_{Y,5} + 3.86(\pm 0.57) \quad (20)$$

$$n = 21,\ r^2 = 0.850,\ s = 0.139,\ q^2 = 0.770$$

Equations 10−20, where various forms of anilinoacridines bind to various DNA, all lack hydrophobic terms. In addition, they all contain negative σ^+ terms, except 14, which is based on a negative σ term. The two parameters are rather collinear in eq 14; nevertheless, the correlation with σ^+ is significantly poorer ($r^2 = 0.839$). It is possible that the geometry of the binding is such that through-resonance in the transition state is inhibited to various degrees. Another similarity is that eqs 14, 17, and 20 all have positive $B1_{Y,5}$ terms though the range of coefficients is rather wide (0.56−2.09). A recent publication[19] gives the X-ray crystallography of a 9-aniline acridine bond to DNA hexanucleotide $d(CGTACG)_2$. This is interesting, but as yet the meaning is not apparent.

1. Combined Anilinoacridines–Aniline Mustards



V

In the above structure, n was varied from 2 to 6 and X was varied as CH_2, O, S, SO_2. The parameter σ was taken as CH_3X.

Table 18. I_{50} of Anilinoacridine−Aniline Mustards V toward P388 Leukemia Cells[11]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 21)	σ
1	$O(CH_2)_2$	7.14	7.13	−0.27
2	$O(CH_2)_3$	7.33	7.13	−0.27
3	$O(CH_2)_4$	7.20	7.13	−0.27
4	$O(CH_2)_5$	7.30	7.13	−0.27
5	$(CH_2)_3$	7.21	6.94	−0.15
6	$(CH_2)_4$	7.07	6.94	−0.15
7	$(CH_2)_5$	7.09	6.94	−0.15
8	$(CH_2)_6$	6.87	6.94	−0.15
9	$S(CH_2)_2$	6.43	6.70	0.00
10	$S(CH_2)_3$	6.44	6.70	0.00
11	$S(CH_2)_4$	6.31	6.70	0.00
12	$S(CH_2)_5$	6.42	6.70	0.00
13	$SO_2(CH_2)_2$	5.64	5.56	0.72
14	$SO_2(CH_2)_3$	5.58	5.56	0.72
15	$SO_2(CH_2)_4$	5.72	5.56	0.72
16	$SO_2(CH_2)_5$[a]	6.12	5.56	0.72

[a] Data point not included in deriving equation.

I_{50} of anilinoacridine−aniline mustards V toward P388 leukemia cells (Table 18)[11]

$$\log 1/C = -1.59(\pm 0.34)\sigma + 6.70(\pm 0.12) \quad (21)$$

$$n = 15,\ r^2 = 0.890,\ s = 0.215,\ q^2 = 0.865$$

outlier: $(CH_2)_5SO_2$

Table 19. I_{50} of Anilinoacridine−Aniline Mustards V toward Hamster Ovary Cells AA8[11]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 22)	σ
1	$O(CH_2)_2$	6.57	6.55	−0.27
2	$O(CH_2)_3$	6.42	6.55	−0.27
3	$O(CH_2)_4$	6.55	6.55	−0.27
4	$O(CH_2)_5$	6.68	6.55	−0.27
5	$(CH_2)_3$	6.51	6.34	−0.15
6	$(CH_2)_4$	6.36	6.34	−0.15
7	$(CH_2)_5$	6.51	6.34	−0.15
8	$(CH_2)_6$	6.28	6.34	−0.15
9	$S(CH_2)_2$	5.92	6.08	0.00
10	$S(CH_2)_3$	5.96	6.08	0.00
11	$S(CH_2)_4$	5.86	6.08	0.00
12	$S(CH_2)_5$	6.15	6.08	0.00
13	$SO_2(CH_2)_2$	4.74	4.84	0.72
14	$SO_2(CH_2)_3$	5.01	4.84	0.72
15	$SO_2(CH_2)_4$[a]	5.77	4.84	0.72
16	$SO_2(CH_2)_5$[a]	6.24	4.84	0.72

[a] Data points not included in deriving equation.

I_{50} of anilinoacridine−aniline mustards V toward hamster ovary cells AA8 (Table 19)[11]

$$\log 1/C = -1.73(\pm 0.25)\sigma + 6.08(\pm 0.08) \quad (22)$$

$$n = 14,\ r^2 = 0.948,\ s = 0.138,\ q^2 = 0.919$$

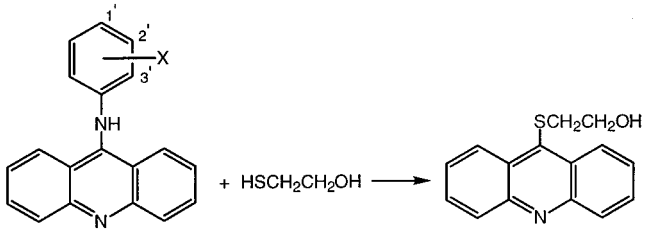
outliers: $(CH_2)_4SO_2$; $(CH_2)_5SO_2$

The coefficient, ρ, for σ in eqs 21 and 22 resemble eqs 1−9 but the intercepts are higher for similar cells, indicating greater potency. In neither equation do we find a hydrophobic term. One wonders if reaction first occurs with the mustard moiety and then is followed by a second reaction with the acridine moiety.

Table 20. Half-Life ($T_{1/2}$) of Substituted 9-Aniline Acridines Exposed to Thiols[8]

		log $T_{1/2}$			
no.	substituents	obsd	calcd (eq 23)	σ	$B1_{3'}$
1	1′-SO_2NH_2	1.08	0.95	0.60	1.00
2	1′-$CONH_2$	0.75	0.59	0.36	1.00
3	1′-Cl	0.38	0.40	0.23	1.00
4	H	−0.02	0.06	0.00	1.00
5	1′-OMe	−0.32	−0.34	−0.27	1.00
6	1′-OH	−0.49	−0.48	−0.37	1.00
7	1′-NH_2	−0.70	−0.91	−0.66	1.00
8	1′-$NHSO_2Me$	−0.04	0.11	0.03	1.00
9	1′-$NHSO_2Me$,2′-OMe	0.04	0.28	0.15	1.00
10	1′-$NHSO_2Me$,3′-OMe	0.26	0.75	−0.24	1.35
11	1′-$NHSO_2Me$,3′-Me	1.73	1.41	−0.14	1.52
12	1′-$NHSO_2Me$,3′−F	1.26	1.24	0.09	1.35
13	1′-$NHSO_2Me$,3′-NH_2[a]	1.71	0.18	−0.63	1.35
14	2′-NH_2	−0.04	−0.17	−0.16	1.00

[a] Data point not included in deriving equation.



Half-life ($T_{1/2}$) of 1′,2′,3′-X-substituted 9-aniline acridines exposed to thiols (Table 20)[8]

$$\log T_{1/2} = 1.48(\pm 0.46)\sigma + 2.99(\pm 0.83)B1_{3'} - 2.93 \quad (\pm 0.92) \quad (23)$$

$$n = 13,\ r^2 = 0.912,\ s = 0.234,\ q^2 = 0.793$$

outlier: 1′-$NHSO_2Me$,3′-NH_2

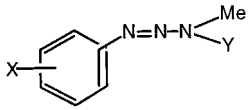
Equation 23 shows that electron-*attracting* substituents and bulky substituents in the 3′-position yield compounds that react more slowly (e.g., larger $T_{1/2}$). To look at this from our point of view multiply by −1 to obtain -1.48σ and −2.99 $B1'_3$ which shows that the aniline group is readily susceptible to displacement by nucleophilic reagents. Other nucleophiles also bring about displacement of the anilino moiety.[20] Thus, it appears (as with the aniline mustards) that there are many points in an animal where the acridines could react. However, in the above equation there are steric terms that indicate that the critical receptor has definite spacial features. Thus, it seems likely that the above nucleophilic reaction is occurring with macromolecules and probably with other nucleophiles such as glutathione. Also, DNA might be involved (eq 13). In any case, a polar binding site would appear to be involved. It has been suspected that this might be topoisomerase II.

Another consistent picture comes from the study of triazenes $X-C_6H_4N{=}NNMeY$ on cancer and mutagenesis (eqs 24−28).

Table 21. Mutagenicity of Triazines VI in Ames Test 30 Mutations/10^8 Bacteria (*S. typhimurium*)[21]

	substituents		log 1/*C*			
no.	X	Y	obsd	calcd (eq 24)	σ^+	log *P*
1	4-$CONH_2$	CMe_3[a]	3.83	6.26	−0.30	2.61
2	3,5-di-CN	H	3.46	3.50	1.12	2.18
3	4-SO_2NH_2	H	3.49	3.15	0.57	0.98
4	3-$CONH_2$	H	3.51	3.86	0.28	1.21
5	4-$CONH_2$	H	4.04	3.72	0.36	1.20
6	4-$CONH_2$	$CH_2CH{=}CH_2$	4.16	4.65	0.36	2.09
7	3-$NHCONH_2$	H	4.19	4.45	−0.03	1.29
8	4-CN	H	4.43	4.47	0.66	2.39
9	4-$COCH_3$	H	4.47	4.61	0.50	2.27
10	H	H	5.32	5.75	0.00	2.59
11	4-$CONH_2$	C_4H_9	5.41	5.03	0.36	2.46
12	4-$NHCONH_2$	H	5.59	5.73	−0.84	1.25
13	4-$NHCOCH_3$	H	5.83	5.64	−0.60	1.54
14	4-CF_3	H	5.99	5.91	0.61	3.70
15	3-CH_3	H	6.44	6.14	−0.07	2.85
16	4-Cl	H	6.48	6.34	0.11	3.33
17	4-CH_3	H	7.00	6.61	−0.31	2.93
18	4-C_6H_5	H	7.67	7.93	−0.18	4.40

[a] Data point not included in deriving equation.



VI

Mutagenicity of triazenes VI in Ames test 30 mutations/10^8 bacteria (S typhimurium) (Table 21)[21]

$$\log 1/C = -1.63(\pm 0.35)\sigma^+ + 1.04(\pm 0.17)\log P + 3.06(\pm 0.43) \quad (24)$$

$$n = 17,\ r^2 = 0.949,\ s = 0.315,\ q^2 = 0.929$$

outlier: X = 4-$CONH_2$, Y = CMe_3

Table 22. Thirty Percent Increase in Lifespan of Mouse with Sarcoma 180 by X-Triazenes VI[22]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 25)	σ
1	4-$CH_2CH_2CH_3$	3.56	3.50	−0.13
2	3-$NHCOCH_3$	3.45	3.26	0.21
3	4-C_6H_5	3.43	3.41	−0.01
4	H	3.42	3.41	0.00
5	3-CH_3	3.37	3.48	−0.10
6	3-SCH_3	3.33	3.30	0.15
7	4-COC_6H_5	3.16	3.11	0.43
8	4-F	3.24	3.37	0.06
9	3-CF_3	3.18	3.11	0.43
10	3-Cl	3.16	3.16	0.37
11	3-COOH	3.01	3.16	0.37
12	4-CN	2.91	2.96	0.66
13	4-CH=CHCOOH	2.79	2.79	0.90

30% increase in lifespan of mouse with sarcoma 180 by triazenes VI (Table 22)[22]

$$\log 1/C = -0.68(\pm 0.19)\sigma + 3.41(\pm 0.08) \quad (25)$$

$$n = 13,\ r^2 = 0.844,\ s = 0.094,\ q^2 = 0.802$$

Table 23. 80% Reduction of Tumor in BD2F1 Mice by 4-X-Triazenes VI[23]

		log 1/*C*			
no.	X	obsd	calcd (eq 26)	Clog *P*	σ
1	OH	5.49	5.26	1.92	−0.37
2	OCH_3	4.95	4.90	2.61	−0.27
3	CH_3	4.44	4.59	3.09	−0.17
4	$NHCOCH_3$	4.62	4.76	1.61	0.00
5	H	4.40	4.47	2.59	0.00
6	SCH_3	4.31	4.30	3.15	0.00
7	$CONH_2$	4.17	4.27	1.29	0.36
8	SO_2NH_2	4.00	3.99	0.96	0.60
9	CN	3.61	3.46	2.41	0.66
10	SO_2CH_3[a]	4.45	3.67	1.37	0.72
11	NO_2[a]	3.90	3.18	2.69	0.78

[a] Data points not included in deriving equation.

80% Reduction of tumor in BD2F1 mice by 4-X-triazenes VI (Table 23)[23]

$$\log 1/C = -1.61(\pm 0.40)\sigma - 0.30(\pm 0.19)\text{Clog } P + 5.24 (\pm 0.45) \quad (26)$$

$$n = 9,\ r^2 = 0.942,\ s = 0.151,\ q^2 = 0.828$$

outliers: 4-SO_2CH_3; 4-NO_2

Table 24. LD_{50} to Mice by 4-X-Triazenes VI[23]

		log 1/*C*			
no.	substituents	obsd	calcd (eq 27)	Clog *P*	σ
1	OH	4.37	4.20	1.92	−0.37
2	OCH_3	3.81	3.95	2.61	−0.27
3	CH_3	3.51	3.74	3.09	−0.17
4	$NHCOCH_3$	3.87	3.91	1.61	0.00
5	H	3.86	3.69	2.59	0.00
6	SCH_3	3.65	3.56	3.15	0.00
7	$CONH_2$[a]	3.17	3.63	1.29	0.36
8	COOH[a]	3.59	3.26	2.52	0.45
9	SO_2NH_2	3.40	3.47	0.96	0.60
10	CN	3.19	3.08	2.41	0.66
11	SO_2CH_3	3.21	3.26	1.37	0.72
12	NO_2	2.89	2.90	2.69	0.78

[a] Data points not included in deriving equation.

LD_{50} to mice by 4-X-triazenes VI (Table 24)[23]

$$\log 1/C = -0.98(\pm 0.29)\sigma - 0.22(\pm 0.17)\text{Clog } P + 4.27 (\pm 0.42) \quad (27)$$

$$n = 10,\ r^2 = 0.903,\ s = 0.151,\ q^2 = 0.815$$

outliers: 4-COOH; 4-$CONH_2$

Table 25. LD_{50} to Rats by X-Triazenes VI[24]

		log 1/*C*			
no.	substituents	obsd	calcd (eq 28)	σ^-	Clog *P*
1	H	2.54	2.59	0.00	2.59
2	4-Me[a]	2.62	2.77	−0.17	3.09
3	4-OMe	2.71	2.71	−0.26	2.61
4	4-F	2.71	2.67	−0.03	2.90
5	4-Cl	2.71	2.69	0.19	3.47
6	4-Br	2.73	2.69	0.25	3.62
7	4-I	2.68	2.74	0.27	3.88
8	4-NO_2	2.07	2.06	1.27	2.69

[a] Data point not included in deriving equation.

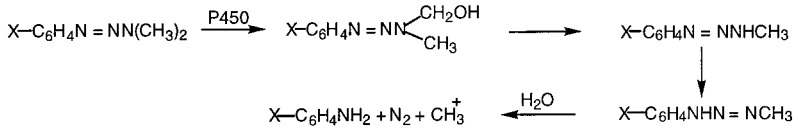
LD_{50} to rats by X-triazenes VI (Table 25)[24]

$$\log 1/C = -0.43(\pm 0.11)\sigma^- + 0.20(\pm 0.10)\text{Clog } P + 2.07 (\pm 0.32) \quad (28)$$

$$n = 7,\ r^2 = 0.973,\ s = 0.049,\ q^2 = 0.873$$

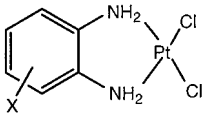
outlier: 4-Me

Scheme 1



In all of the above examples, we find negative σ terms (σ, σ^-, or σ^+). Since there is rather high collinearity among them, we do not always find σ^+ to be the parameter of choice.[9] In eq 24 there is a large positive log P term, and eq 28 also shows a small positive log P term. This is easily understood (see below) since the triazenes are not mutagenic unless they are activated by microsomes (S9). Presumably this occurs in animals via cytochrome P450. Scheme 1 shows the mechanism suggested.

It is the carbonium ion that attacks the DNA causing the mutagenesis. Mutagenicity and toxicity can be parallel processes related to the carbonium ions. A coefficient of about 1 with log P is found in a variety of compounds inducing mutagenesis in the Ames test (Table 31), since many compounds must be activated before they show activity. Why a positive hydrophobic term is lacking in eqs 26 and 27 for studies done on mice is not clear. It may be that the reaction perturbing the DNA is occurring in a polar region of the DNA and that the positive value of hydrophobicity in P450 activation is canceled in the DNA interaction. Possibly another enzyme is doing the activation.



VII

Table 26. Mutagenicity of Cis-platinum Analogs VII on *S. typhimurium* 30 Mutations/10^8 Bacteria[25]

		log 1/C		
no.	substituents	obsd	calcd (eq 29)	σ^-
1	4,5-di-OCH_3	4.64	5.07	−0.32
2	4,5-di-CH_3	4.99	4.11	−0.30
3	4-CH_3	5.60	5.45	−0.15
4	4-OC_2H_5	5.60	5.43	−0.16
5	4-OCH_3	5.65	5.43	−0.16
6	H	5.63	5.78	0.00
7	4,5(−CH=CH−CH=CH−)	5.92	5.87	0.04
8	4-Cl	6.94	6.41	0.28
9	4,5-di-Cl	6.89	7.03	0.56
10	4-$COOCH_3$	7.00	7.21	0.64
11	COC_6H_5	7.52	7.75	0.88
12	3,4,5-tri-Cl	7.73	7.66	0.84
13	4-NO_2	8.65	8.55	1.24

Mutagenicity of cis-platinum analogues VII on S. typhimurium 30 mutations/10^8 bacteria (Table 26)[25]

$$\log 1/C = 2.23(\pm 0.32)\sigma^- + 5.78(\pm 0.18) \quad (29)$$

$$n = 13,\ r^2 = 0.956,\ s = 0.260,\ q^2 = 0.940$$

Although σ gives almost as good a correlation ($r^2 = 0.934$), the collinearity between the two parameters is very high ($r^2 = 0.934$). What can be said is that electron withdrawal weakens the Pt−Cl bond so that nucleophilic displacement on DNA is the toxic event. Recent elegant studies on the binding of cis-platinum[26] show that the chlorines are displaced in the binding process that leads to mutagenesis. Although we have nothing directly comparable to compare with eq 29, the following example is of interest.[27]

$$X{-}C_6H_4NHCOCH_3 \xrightarrow[CH_3OH]{CH_3O^-} X{-}C_6H_4{-}NH_2 + CH_3COOMe$$

Table 27. Deacylation Rate of X−C_6H_4NHCOMe with OMe[27]

		log k		
no.	substituents	obsd	calcd (eq 30)	σ^-
1	4-H	−6.20	−6.33	0.00
2	3-SO_2CH_3	−5.60	−5.40	0.60
3	4-SO_2CH_3	−4.63	−4.70	1.05
4	3-CN	−5.55	−5.46	0.56
5	4-CN	−4.63	−4.93	0.90
6	3,4(−CH=CH−CH=CH−)	−6.23	−6.27	0.04
7	3-NO_2	−5.46	−5.23	0.71
8	4-NO_2[a]	−3.02	−4.40	1.24

[a] Data point not included in deriving equation.

Deacylation rate of X−C_6H_4NHCOMe with OMe (Table 27)[27]

$$\log k = 1.55(\pm 0.55)\sigma^- - 6.30(\pm 0.36) \quad (30)$$

$$n = 7,\ r^2 = 0.915,\ s = 0.209,\ q^2 = 0.847$$

outlier: 4-NO_2

Nucleophilic displacement by CH_3O^- shows a similar dependence on electron withdrawal by substituents.

A surprising result with the above cis-platinums VII is the following.

Table 28. Twenty-five Percent Increase in Lifespan of Mice with B-16 Melanoma[28]

		log 1/C			
no.	substituents	obsd	calcd (eq 31)	π	σ^-
1	4,5-di-Cl	3.61	3.80	1.42	0.56
2	4,5-(CH=CH−CH=CH)[a]	3.55	4.43	1.32	0.12
3	4-COC_6H_5	3.64	3.61	1.05	0.88
4	4-OCH_3[a]	4.51	5.74	−0.02	−0.26
5	4-NO_2	3.96	3.91	−0.28	1.27
6	4-Cl	4.93	4.71	0.71	0.19
7	4-Me	5.41	5.30	0.50	−0.17
8	4,5-di-Me	5.13	5.09	1.00	−0.24
9	H	5.13	5.39	0.00	0.00

[a] Data points not included in deriving equation.

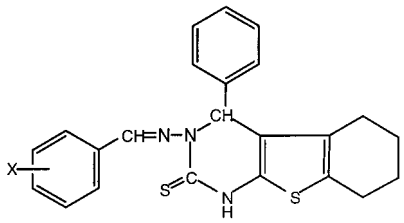
25% increase in lifespan of mice with B-16 melanoma (Table 28)[28]

$$\log 1/C = -1.30(\pm 0.41)\sigma^- - 0.61(\pm 0.39)\pi + 5.39(\pm 0.38) \quad (31)$$

$$n = 7,\ r^2 = 0.954,\ s = 0.209,\ q^2 = 0.845$$

outliers: 4,5(−CH = CHCH = CH-); 4-OCH_3

Hydrophobicity is of no value as in eq 31; in fact, π is of negative value. The electronic effect in eq 31 is the opposite of that in eq 29. This suggests that the 'curative' effect of the platinum compounds may be associated with a reaction other than that with DNA. It is noteworthy that the most widely used platinum drug, $(NH_2)_2Pt(Cl)_2$, has a very low log P value (-1.45).



VIII

Table 29. I_{50} HeLa Cells by Pyrimidines VIII[29]

		log 1/C		
no.	substituents	obsd	calcd (eq 32)	σ
1	H	6.61	6.75	0.00
2	4-F[a]	7.63	6.84	0.06
3	4-Cl	7.24	7.08	0.23
4	4-CN	7.63	7.68	0.66
5	4-OMe	6.39	6.37	−0.27
6	3-OMe	6.94	6.92	0.12

[a] Data point not included in deriving equation.

I_{50} HeLa cells by pyrimidines VIII (Table 29)[29]

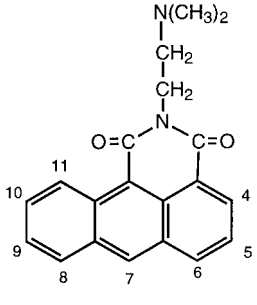
$$\log 1/C = 1.41(\pm 0.62)\sigma + 6.75(\pm 0.21) \quad (32)$$

$$n = 5,\ r^2 = 0.946,\ s = 0.132,\ q^2 = 0.863$$

outlier: 4-F

This result suggests that hydrolysis of the X−C_6H_4-CH=N− moiety in an aqueous phase could be involved or else reaction with some nucleophilic group might be possible. However, out of over 8300 QSAR for mechanistic organic chemistry, we have nothing with which to compare eq 32.

A recent extensive study of compounds by Remer's group[30] on a variety of cancer cells yielded QSAR that did not contain positive log P terms. In a few cases, log P terms were lacking; in the others, these terms were all negative. The following QSAR is illustrative.[31] The authors believe DNA to be the target.



IX

Table 30. I_{50} of Melanoma Cells (UACC375) by IX[31]

		log 1/C				
no.	substituents	obsd	calcd (eq 33)	Clog P	I	$B5_4$
1	4-Me	6.75	6.84	4.47	0	2.04
2	4-Cl	6.48	6.63	4.76	0	1.80
3	4-OH	5.12	5.49	3.85	1	1.93
4	4-OMe	6.74	6.84	4.19	0	3.07
5	4-$NH(CH_2)_2NMe_2$	6.41	6.23	4.23	0	5.21
6	3-Cl	7.11	6.89	4.70	0	1.00
7	8-OH	6.57	6.13	3.44	1	1.00
8	8-OMe	7.28	7.61	3.97	0	1.00
9	9-Cl	7.05	6.89	4.70	0	1.00
10	9-OH[a]	8.40	6.13	3.44	1	1.00
11	9-OMe[a]	6.79	7.61	3.97	0	1.00
12	10-Me	7.09	7.12	4.47	0	1.00
13	10-C_6H_5	5.73	5.77	5.86	0	1.00
14	10-CN	8.00	8.11	3.45	0	1.00
15	10-F	7.80	7.45	4.14	0	1.00
16	10-Cl	7.19	6.89	4.70	0	1.00
17	10-I	6.21	6.50	5.11	0	1.00
18	10-OH	5.92	6.13	3.44	1	1.00
19	10-OMe	7.28	7.46	4.12	0	1.00
20	10-OC_2H_5	7.11	6.95	4.65	0	1.00
21	10-NO_2	7.75	7.81	3.76	0	1.00
22	11-Cl[a]	5.69	6.89	4.70	0	1.00
23	11-OH	6.27	6.13	3.44	1	1.00

[a] Data points not included in deriving equation.

I_{50} of melanoma cells (UACC375) by IX (Table 30)[31]

$$\log 1/C = -0.97(\pm 0.24)\text{Clog } P - 1.99(\pm 0.37)I - 0.27(\pm 0.12)B5_4 + 11.7(\pm 1.12) \quad (33)$$

$$n = 20,\ r^2 = 0.898,\ s = 0.252,\ q^2 = 0.803$$

outliers: 9-OH; 9-OMe; 11-Cl

In this equation, I is an indicator variable for OH groups of which there are five examples. Its negative sign indicates that 4-OH, 8-OH, and 10-OH are less active than expected. Analogues with 9-OH and 11-OH are more active than predicted. Hydrogen bonding may be a problem, since 4-OMe, 8-OMe, 9-OMe, and 10-OMe are all well fit. Only two substituents in the 11 positions were tested, and both are poorly fit. It is assumed that IX analogues bind to DNA.

2. Mutagenesis

It is interesting that the above examples, except eq 24, have either no hydrophobic terms or a negative one. Equation 24 was introduced at that point for comparison with other activities of the phenyltriazenes.

A brief summary of mutagenic QSAR shown in Table 31 helps to orient our discussion of the subject of mutagenicity.[10c]

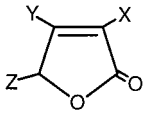
The results in Table 31 provide background for our discussion of the role of hydrophobicity in mutagenicity. The equations from which the coefficient with log P comes contain other terms, mostly molecular orbital in nature. What is of interest is that the compounds that require S9 for activation all have log P terms with coefficients near 1. The nitro compounds are an exception; they are activated by reduction by cellular cytosolic reductase (see section VII). The nitrofurans appear to be activated by an alternative mechanism.[32] The data on which example 12 is based are poor so that π, σ^*, or Es are highly collinear; hence, any one of the three gives a 'good' correlation.

Table 31.

	no. of compounds	type of compound	test[a]	coefficient with log *P*
1	188	aromatic and heteroaromatic nitro	TA98	0.65
2	117	aromatic and heteroaromatic nitro	TA100	1.10
3	88	aromatic and heteroaromatic amines + S9	TA98	1.08
4	67	aromatic and heteroaromatic amines + S9	TA100	0.92
5	21	$X-C_6H_4N=N-N(CH_3)R$ + S9	TA92	0.97
6	15	aromatic nitro	E. coli	1.07
7	21	quinolines + S9	TA100	1.14
8	12	$X-C_6H_4CH_2N(CH_3)N=O$ + S9	TA1535	0.92
9	40	nitrofurans	E. coli	1.00
10	20	nitrofurans	TA100	1.15
11	30	*N*-methyl-1, 2-aminobenzimidazoles + S9	TA98	0.96
12	15	$R_1OSO_2R_2$	TA100	1.10

[a] TA stands for *S. typhimurium* and the associated number for the type of bacteria that was used in the test. S9 represents the microsomal fraction used for activation to produce mutagenic activity.

The net lesson from Table 31 is that mutagenicity is often correlated with log *P* as an important parameter that may be involved with an activation step (examples where S9 is necessary) or possibly in the reaction with DNA. The uniformity of the coefficients in Table 31 is striking, indicating a common mechanism of activation. Equations 1−20 show that in examples where a chemical reaction with DNA *appears* to be occurring, a positive hydrophobic term is not significant.



X

Mutation rate for lactones X vs S. typhimurium (TA100)[33]

$$\log k = -6.50E_{\mathrm{LUMO}} - 6.24 \quad (34)$$

$$n = 58,\ r^2 = 0.925$$

For eq 34, *n* does not represent 58 different compounds but 10 compounds tested a number of times. Tuppurainen et al. also studied a set of these lactones on *S. typhimurium* TA100 from which eq 35 was derived (Table 32).[34]

Table 32. Mutagenicity of Lactones on *S. typhimurium* (TA 100)[34]

		log *k*		
no.	substituents	obsd	calcd (eq 35)	E_{LUMO}
1	3-Cl,4-$CHCl_2$,5-OH	8.75	8.27	−1.51
2	3-Cl,4-$CHCl_2$,5-OMe	8.65	7.32	−1.44
3	3-Cl,4-CH_2Cl,5-OH	6.36	5.58	−1.32
4	3-Cl,4-$CHCl_2$	5.18	5.27	−1.30
5	3,4-di-Cl,5-OH	4.09	4.56	−1.24
6	3-Cl,4-CH_2Cl	1.59	2.48	−1.10
7	4-CH_2Cl,5-OH	1.35	2.33	−1.08
8	3,4-di-Cl,5-OMe[a]	0.99	3.59	−1.17
9	3-Cl,4-Me,5-OC_2H_5	0.74	−1.28	−0.83
10	3-Cl,4-Me,5-OH	0.41	−0.09	−0.91
11	3,4-di-Cl	0.11	1.42	−1.02
12	3-Cl,5-OC_2H_5	−0.22	−0.69	−0.87
13	4-CH_2Cl	−1.19	−0.91	−0.85
14	3-Cl,5-OH	−1.60	0.60	−0.96
15	4-Me,5-OH	−3.51	−3.72	−0.65
16	4-CH_2OCOMe	−6.00	−5.33	−0.54
17	4-Me	−6.00	−7.11	−0.41

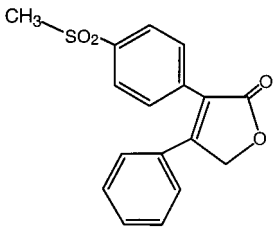
[a] Data point not included in deriving equation.

$$\log k = -14.0(\pm 2.0)E_{\mathrm{LUMO}} - 12.87(\pm 2.07) \quad (35)$$

$$n = 16,\ r^2 = 0.943,\ s = 1.12,\ q^2 = 0.927$$

outlier: 3,4-di-Cl, 5-OMe

The addition of a Clog *P* term to this equation makes no improvement. If the class of compounds X is mutagenic, one wonders why the new drug Vioxx, which is a COX-2 inhibitor, is not.



XI (Vioxx)

The fact that eqs 34 and 35 do not contain hydrophobic terms may be the answer. However, since the COX-2 inhibitor Vioxx inhibits an oxidoreductase that often operates via radical reactions[9] may explain why the unsaturated lactone ring is effective. A chemical reaction may be occurring via the 1,4-addition of a nucleophilic moiety to the lactone. However, we have nothing in our physical database with which to make a comparison.

Table 33. Mutagenicity of $X-C_6H_4-$ethylene oxide with *E. coli*[35]

		log *k*		
no.	substituents	obsd	calcd (eq 36)	σ^+
1	3,4-di-Me	2.09	2.13	−0.38
2	4-Me	2.07	2.00	−0.31
3	3-Me	1.56	1.53	−0.07
4	H	1.26	1.40	0.00
5	3-OMe	1.28	1.17	0.12
6	4-Br	1.08	1.11	0.15
7	3-Cl[a]	1.26	0.69	0.37

[a] Data point not included in deriving equation.

Mutagenicity of $X-C_6H_4-$ethylene oxide with E. coli (Table 33)[35]

$$\log k = -1.93(\pm 0.57)\sigma^+ + 1.40(\pm 0.12) \quad (36)$$

$$n = 6,\ r^2 = 0.956,\ s = 0.101,\ q^2 = 0.911$$

outlier: 3-Cl

An interesting comparison is the hepatotoxicity of $X-C_6H_4-CH{=}CH_2$ in mice.[36] *C* is the concentration

causing a 50% elevation in serum alanine transaminase (Table 34).[36]

Table 34. Hepatotoxicity of X−$C_6H_4CH=CH_2$ in Mice[36]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 37)	σ^+
1	H[a]	2.84	3.22	0.00
2	3-Me	3.22	3.26	−0.07
3	3-OMe	3.10	3.17	0.12
4	4-OMe	3.75	3.59	−0.78
5	4-NH_2	3.80	3.83	−1.30
6	H,β-Me	3.32	3.22	0.00
7	4-OMe,β-Me	3.47	3.59	−0.78

[a] Data point not included in deriving equation.

$$\log 1/C = -0.46(\pm 0.26)\sigma^+ + 3.22(\pm 0.18) \quad (37)$$

$$n = 6,\ r^2 = 0.862,\ s = 0.118,\ q^2 = 0.738$$

outlier: H

It was quite surprising that no hydrophobic term could be found for eq 37. The negative electronic term σ^+ suggests the possibility that the styrenes could be oxidized in the liver to epoxides that caused the toxicity according to eq 36.

The only equation from mechanistic organic chemistry that we have for comparison is the following for the reaction of X−$C_6H_4CH=CH_2$ with $Cl_3C^\bullet$ radicals in benzene (Table 35).[37]

Table 35. Rate of Reaction of X−$C_6H_4CH=CH_2$ with $Cl_3C^\bullet$ Radicals in Benzene[37]

		log k_{rel}		
no.	substituents	obsd	calcd (eq 38)	σ^+
1	4-Me	0.24	0.20	−0.31
2	3-Me	0.03	0.08	−0.07
3	H	0.00	0.05	0.00
4	3-OMe	0.02	−0.01	0.12
5	4-Cl	0.03	−0.01	0.11
6	3-Cl	−0.12	−0.13	0.37
7	3-CF_3	−0.21	−0.16	0.43
8	4-CN[a]	0.05	−0.28	0.66
9	3-NO_2	−0.28	−0.30	0.71
10	4-NO_2[a]	−0.06	−0.34	0.79

[a] Data points not included in deriving equation.

$$\log k_{rel} = -0.50(\pm 0.13)\sigma^+ + 0.05(\pm 0.04) \quad (38)$$

$$n = 8,\ r^2 = 0.937,\ s = 0.044,\ q^2 = 0.882$$

outliers: 4-CN; 4-NO_2

There are other examples of radical reactions of styrenes correlated by negative σ^+ terms.[9] The above equations are quite different from the toxicity of styrenes to *E. coli*[35] as illustrated by eq 39.

Table 36. LD_{30} of X-Styrene Oxides to *E. coli*[35]

		log 1/*C*			
no.	substituents	obsd	calcd (eq 39)	σ	Clog *P*
1	3,4-di-Me	2.82	2.80	−0.24	2.23
2	4-Me	2.43	2.50	−0.17	1.79
3	3-Me	2.55	2.56	−0.07	1.79
4	H	2.29	2.23	0.00	1.29
5	3-OMe	2.24	2.25	0.12	1.21
6	4-Br	3.10	3.02	0.23	2.15
7	3-Cl	2.92	2.99	0.37	2.00

LD_{30} of X-styrene oxides to E. coli (Table 36)[35]

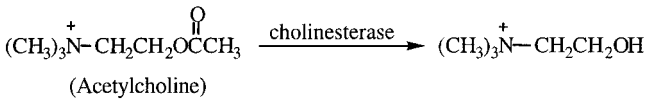
$$\log 1/C = 0.61(\pm 0.38)\sigma + 0.75(\pm 0.21)\text{Clog } P + 1.27(\pm 0.37) \quad (39)$$

$$n = 7,\ r^2 = 0.968,\ s = 0.073,\ q^2 = 0.887$$

The similarity of eqs 37 and 38 might imply that a radical reaction is involved in hepatotoxicity of styrenes. It is of special interest that eq 36 and especially eq 37 do not contain hydrophobic terms while eq 39 does. The small intercept in eq 39 and the coefficient with log *P* suggest that only nonspecific toxicity is involved (much smaller than that in eq 37). Also, the electronic term in eq 39 is positive. Obviously a much different mechanism is involved. Comparative QSAR works two ways: to show similarity and differences in mechanism.

IV. Toxicity of Phosphates as Cholinesterase Inhibitors

There has been enormous interest in the cholinesterase enzyme that was first started by the development of nerve gases during World War II, then continued in the search for insecticides, and today is associated with drugs for Alzheimer's disease.[38] Acetylcholine is crucial in the transmission of nerve impulses. The arrival of an impulse at a synaptic junction causes the release of acetylcholine into the synaptic cleft where it diffuses across to receptors. The interaction with receptors produces a depolarization of the postsynaptic membrane that propagates an impulse along the second nerve. The polarization is restored as the acetylcholine is hydrolyzed by cholinesterase.



(Acetylcholine)

Over the years, a large amount of work has been done on these enzymes. Currently, our database contains 134 QSAR and is still not complete. Depending on the particular esterase and the type of inhibitor, one may find QSAR with or without hydrophobic terms. A few examples have been summarized.[10d] At present, we are interested in the phosphate esters because they show a complete lack of dependence on hydrophobic interactions at the enzyme level and in the whole organism that can be related to simple chemical reactions.

There has been considerable interest in the past for the use of phosphates as pesticides. In the

following examples we find that positive hydrophobic terms are absent.

Table 37. LD_{50} for Mice by X−$C_6H_4OP(=S)(OMe)OC_6H_5$[39]

		log 1/C			
no.	substituents	obsd	calcd (eq 40)	σ^-	F_{ortho}
1	2,3-di-Cl	3.23	3.27	0.56	0.42
2	2,4-di-Cl	2.93	2.80	0.38	0.42
3	2,5-di-Cl	3.53	3.27	0.56	0.42
4	2,6-di-Cl	3.33	3.31	0.38	0.84
5	3,5-di-Cl	2.96	3.23	0.74	0.00
6	2,3,4-tri-Cl	3.81	3.77	0.75	0.42
7	2,3,5-tri-Cl	4.42	4.24	0.93	0.42
8	2,3,6-tri-Cl	4.27	4.28	0.75	0.84
9	2,4,5-tri-Cl	3.82	3.77	0.75	0.42
10	2,4,6-tri-Cl	3.60	3.81	0.57	0.84
11	3,4,5-tri-Cl	3.61	3.73	0.93	0.00
12	2,5-di-Cl,4-Br	3.76	3.93	0.81	0.42
13	2,5-di-Cl,4-I	3.91	3.98	0.83	0.42
14	4-NO_2	4.59	4.62	1.27	0.00
15	4-CN[a]	3.46	3.91	1.00	0.00
16	4-SO_2Me	4.48	4.26	1.13	0.00

[a] Data point not included in deriving equation.

LD_{50} for mice by X−$C_6H_4OP(=S)(OMe)OC_6H_5$ (Table 37)[39]

$$\log 1/C = 2.63(\pm 0.52)\sigma^- + 1.22(\pm 0.44)F_2 + 1.28(\pm 0.53) \quad (40)$$

$$n = 15,\ r^2 = 0.911,\ s = 0.168,\ q^2 = 0.884$$

outlier: 4-CN

Table 38. LD_{50} for Housefly by X−$C_6H_4OP(=O)(OR)_2$[40]

	substituents		log 1/C			
no.	R	X	obsd	calcd (eq 41)	σ	Clog P
1	Me	H	2.75	3.09	0.00	1.16
2	Me	3-Me	2.00	2.76	−0.07	1.66
3	Me	4-Me	1.99	2.47	−0.17	1.66
4	Me	4-OMe	2.00	2.29	−0.27	1.30
5	Me	3-Cl[a]	2.10	3.89	0.37	2.09
6	Me	4-Cl	2.60	3.49	0.23	2.09
7	Me	3-Br	4.00	3.91	0.39	2.24
8	Me	4-Br	3.53	3.45	0.23	2.24
9	Me	3-CN	4.99	4.70	0.56	1.11
10	Me	4-CN	4.84	4.98	0.66	1.11
11	Me	3-NO_2	4.90	5.05	0.71	1.38
12	Me	4-NO_2	5.10	5.25	0.78	1.38
13	C_2H_5	H	3.20	2.96	0.00	1.66
14	C_2H_5	4-Me	3.00	2.34	−0.17	2.15
15	C_2H_5	3-Cl	3.80	3.76	0.37	2.59
16	C_2H_5	4-Cl	3.72	3.36	0.23	2.59
17	C_2H_5	3-Br	4.11	3.78	0.39	2.74
18	C_2H_5	4-Br	4.06	3.32	0.23	2.74
19	C_2H_5	3-CN	5.00	4.56	0.56	1.61
20	C_2H_5	4-CN	5.10	4.85	0.66	1.61
21	C_2H_5	3-NO_2	5.10	4.92	0.71	1.88
22	C_2H_5	4-NO_2	5.20	5.12	0.78	1.88
23	C_2H_5	2,4-di-Cl	4.30	3.87	0.46	3.14
24	C_4H_9	H	2.50	2.47	0.00	3.49
25	C_4H_9	3-Me	2.00	2.14	−0.07	3.99
26	C_4H_9	4-Me	2.10	1.85	−0.17	3.99
27	C_4H_9	4-OMe	2.10	1.66	−0.27	3.63
28	C_4H_9	3-Cl	2.80	3.27	0.37	4.43
29	C_4H_9	4-Cl	2.50	2.87	0.23	4.43
30	C_4H_9	4-Br	2.95	2.83	0.23	4.58
31	C_4H_9	3-CN	4.00	4.07	0.56	3.44
32	C_4H_9	4-CN	4.01	4.36	0.66	3.44
33	C_4H_9	3-NO_2	4.21	4.43	0.71	3.71
34	C_4H_9	4-NO_2	4.38	4.63	0.78	3.71

[a] Data point not included in deriving equation.

LD_{50} for housefly by X−$C_6H_4OP(=O)(OR)_2$ (Table 38)[40]

$$\log 1/C = 2.84(\pm 0.41)\sigma - 0.27(\pm 0.13)\text{Clog } P + 3.40(\pm 0.39) \quad (41)$$

$$n = 33,\ r^2 = 0.883,\ s = 0.392,\ q^2 = 0.861$$

outlier: X = 3-Cl, R = CH_3

Table 39. LD_{50} for Fly by X−$C_6H_4OP(=O)(OMe)C_2H_5$[41]

		log 1/C		
no.	X	obsd	calcd (eq 42)	σ
1	4-OCH_3	2.57	2.37	−0.27
2	4-CH_3	2.66	2.65	−0.17
3	H	2.63	3.14	0.00
4	4-Cl	4.08	3.80	0.23
5	4-CN	5.27	5.03	0.66
6	4-SO_2CH_3	5.12	5.20	0.72
7	4-NO_2	5.24	5.38	0.78

LD_{50} for fly by X−$C_6H_4OP(=O)(OMe)C_2H_5$ (Table 39)[41]

$$\log 1/C = 2.87(\pm 0.72)\sigma + 3.14(\pm 0.36) \quad (42)$$

$$n = 7,\ r^2 = 0.954,\ s = 0.304,\ q^2 = 0.920$$

Table 40. LD_{50} for Thrip by X−$C_6H_4OP(=O)(OC_2H_5)_2$[42]

		log 1/C			
no.	substituents	obsd	calcd (eq 43)	σ^-	$B1_3$
1	4-NO_2	4.00	4.61	1.24	1.00
2	3-NO_2[a]	2.30	3.86	0.71	1.70
3	4-SO_2CH_3	4.00	4.09	1.05	1.00
4	3-$N(CH_3)_2$	1.00	0.99	−0.21	1.35
5	4-CN	4.70	3.95	1.00	1.00
6	3-OCH_3	1.70	1.89	0.12	1.35
7	4-OCH_3	0.00	0.48	−0.27	1.00
8	3-t-Bu	2.52	2.48	−0.12	2.60
9	4-t-Bu	1.00	0.67	−0.20	1.00
10	4-CHO[a]	1.30	4.31	1.13	1.00
11	4-COO^-	2.30	2.06	0.31	1.00

[a] Data points not included in deriving equation.

LD_{50} for thrip by X−$C_6H_4OP(=O)(OC_2H_5)_2$ (Table 40)[42]

$$\log 1/C = 2.74(\pm 0.73)\sigma^- - 1.00(\pm 0.85)B1_3 + 0.22(\pm 1.2) \quad (43)$$

$$n = 9,\ r^2 = 0.933,\ s = 0.478,\ q^2 = 0.840$$

outliers: 3-NO_2; 4-CHO

Table 41. LD_{50} for Rat by 4-X−$C_6H_4OP(=O)(OMe)C_2H_5$[41]

		log 1/C			
no.	substituents	obsd	calcd (eq 44)	σ	Clog P
1	4-Me	2.65	2.64	−0.17	2.05
2	4-Cl	3.38	3.43	0.23	2.40
3	4-CN	5.46	5.22	0.66	1.30
4	4-SO_2Me	5.54	5.62	0.57	0.33
5	4-NO_2	5.21	5.34	0.78	1.59

LD_{50} for rat by 4-X−C_6H_4O(P═O)(OMe)C_2H_5 (Table 41)[41]

$$\log 1/C = 2.54(\pm 1.37)\sigma - 0.64(\pm 0.67)\text{Clog } P + 4.39(\pm 1.47) \quad (44)$$

$$n = 5,\ r^2 = 0.988,\ s = 0.204,\ q^2 = 0.934$$

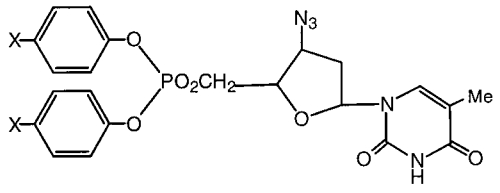
In all of the above examples, for a variety of organisms a large positive σ term appears. In two examples negative Clog P terms show that hydrophobicity has a deleterious effect. It is not clear why in two instances σ^- is the preferred parameter. However, there is rather high collinearity between the two parameters.

Equation 44 is based on too few data points; still its structure agrees with the other equations. This type of lateral support from mechanistic chemistry is as important as statistics. It is especially interesting that these equations on rats and mice do not contain positive log P terms, as one generally assumes that movement in the whole animal would be favored by an optimum log P. Equation 41, based on a relatively large number of data points, can be used to test this point. Adding a term in $(\log P)^2$ which would result in a parabola or including a bilinear term does not improve the equation. The other equations are based on too few data points to test this idea thoroughly.

In eq 40, F_2 represents the field/inductive parameter for ortho substituents.

Table 42. ED_{50} to Protect C8166 Cells from HIV by XII[43]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 45)	σ
1	NO_2	8.50	8.68	1.56
2	CN	8.50	8.34	1.32
3	SMe	6.40	6.47	0.00
4	CF_3	8.19	8.00	1.08
5	I	6.80	6.98	0.36
6	OMe	5.80	5.71	−0.54
7	H	6.50	6.47	0.00



XII

ED_{50} to protect C8166 cells from HIV by XII (Table 42)[43]

$$\log 1/C = 1.42(\pm 0.23)\sigma + 6.47(\pm 0.21) \quad (45)$$

$$n = 7,\ r^2 = 0.981,\ s = 0.170,\ q^2 = 0.961$$

This is a rather complicated structure. The relatively small σ term suggests a different mechanism of action, possibly simple binding without nucleophilic displacement. Still, nucleophilic displacement of one of the $-OC_6H_4X$ moieties is a possibility.

Table 43. I_{50} for Fly Cholinesterase by X−C_6H_4OP(═O)(Me)OC_2H_5[44]

		log 1/*C*			
no.	substituents	obsd	calcd (eq 46)	σ^-	Es_3
1	H	4.24	4.79	0.00	0.00
2	Me	4.16	4.34	−0.15	0.00
3	Cl	5.43	5.58	0.27	0.00
4	Br	5.58	5.61	0.28	0.00
5	OMe	3.88	4.31	−0.16	0.00
6	OEt	3.97	4.31	−0.16	0.00
7	CN	7.46	7.73	1.00	0.00
8	SMe	5.89	5.29	0.17	0.00
9	SOMe	7.07	6.61	0.62	0.00
10	SO_2Me	8.02	7.67	0.98	0.00
11	CO_2Me	7.22	6.67	0.64	0.00
12	Cl,3-Me	6.60	6.13	0.20	−1.24
13	CN,3-Me	7.60	8.28	0.93	−1.24
14	Cl,3-Et	7.00	6.23	0.22	−1.31
15	CN,3-Et	7.80	8.38	0.95	−1.31

I_{50} for fly cholinesterase by X−C_6H_4OP(═O)(Me)-OC_2H_5 (Table 43)[44]

$$\log 1/C = 2.94(\pm 0.74)\sigma^- - 0.61(\pm 0.55)Es_3 + 4.78(\pm 0.42) \quad (46)$$

$$n = 15,\ r^2 = 0.893,\ s = 0.528,\ q^2 = 0.815$$

Equations 43 and 44 show electronic terms similar to QSAR for the more complex systems.

Table 44. I_{50} of X−C_6H_4OP(═O)$(OC_2H_5)_2$ for Cholinesterase[45]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 47)	σ
1	2,4-di-NO_2[a]	8.52	11.41	1.56
2	2-NO_2	7.30	7.64	0.78
3	4-NO_2	7.59	7.64	0.78
4	4-CHO	6.82	5.90	0.42
5	4-CN	6.89	7.06	0.66
6	2,4,5-tri-Cl	8.22	7.88	0.83
7	2,4-di-Cl	6.30	6.09	0.46
8	2-Cl	4.70	4.98	0.23
9	4-Cl	4.52	4.98	0.23
10	H[a]	8.00	3.87	0.00
11	3-NO_2	7.30	7.30	0.71
12	4-Me	3.00	3.05	−0.17
13	3-OMe	3.89	4.45	0.12
14	4-OMe	3.00	2.56	−0.27
15	4-NMe_2[a]	6.40	−0.15	−0.83

[a] Data points not included in deriving equation.

I_{50} of X−C_6H_4OP(═O)$(OC_2H_5)_2$ for cholinesterase (Table 44)[45]

$$\log 1/C = 4.83(\pm 0.79)\sigma + 3.87(\pm 0.42) \quad (47)$$

$$n = 12,\ r^2 = 0.949,\ s = 0.443,\ q^2 = 0.928$$

outliers: H; 2,4-di-NO_2; 4-NMe_2

Table 45. Binding Affinity of 4-NO_2-X-$C_6H_3OP(=O)(OMe)_2$ for Fly Acetyl Cholinesterase[46]

		log $1/K_a$		
no.	substituents	obsd	calcd (eq 48)	σ_{meta}
1	H	5.54	5.62	0.00
2	3-F	6.50	6.58	0.34
3	3-Cl[a]	5.99	6.66	0.37
4	3-Br	6.78	6.72	0.39
5	3-I	6.71	6.61	0.35
6	3-CF_3	6.77	6.83	0.43
7	3-Me	5.48	5.42	−0.07

[a] Data point not included in deriving equation.

Binding affinity of 4-NO_2−X−$C_6H_3OP(=O)(OMe)_2$ for fly acetyl cholinesterase (Table 45)[46]

$$\log 1/K_a = 2.83(\pm 0.52)\sigma + 5.62(\pm 0.16) \quad (48)$$

$$n = 6,\ r^2 = 0.983,\ s = 0.091,\ q^2 = 0.959$$

outlier: 3-Cl

It is now of interest to compare the results with whole organisms with the one example we have from a simple chemical system.

Table 46. Alkaline Hydrolysis of X−$C_6H_4OP(=O)(OC_2H_5)_2$[47]

		log k		
no.	substituents	obsd	calcd (eq 49)	σ
1	4-Cl	−6.14	−6.14	0.23
2	4-NO_2	−4.41	−4.52	0.78
3	3-NO_2	−4.85	−4.73	0.71
4	4-H	−6.80	−6.81	0.00

Alkaline hydrolysis of X−$C_6H_4OP(=O)(OC_2H_5)_2$ (Table 46)[47]

$$\log k = 2.93(\pm 0.78)\sigma - 6.81(\pm 0.42) \quad (49)$$

$$n = 4,\ r^2 = 0.993,\ s = 0.118,\ q^2 = 0.971$$

The positive σ term is very similar to that seen in the above complex systems. Electron withdrawal favors nucleophilic attack by OH^-.

Except for eq 45, the above examples give a coherent picture of the toxicity of the phenyl phosphates from a simple example of mechanistic organic chemistry, to action on enzymes, and finally to toxicity in animals. The negative Es term in eq 46 means that the steric effect of substituents in the meta position increases activity since all Es values are negative. This agrees with eq 43, where *tert*-butyl is badly fit without the sterimol parameter B1.

V. Bacteria

Bacteria have been, as one might expect, one of the most studied test systems. Of 1775 QSAR on single-cell organisms in our current database, 649 are for bacteria. Bacteria vary enormously in their response to treatment with various organic compounds. It should be possible to begin to sort out some common reaction features. For example, we found years ago[2] in a modest study that Gram positive and Gram negative cells showed different optimum log P values. The optimum for Gram positive was about 6, while that for Gram negative was about 4.

1. Inhibition by Sulfonamides

In a classical study (1942), Bell and Robbin[48] showed for a very wide variety of sulfa drugs that a plot of pK_a vs potency yielded a more or less parabolic relationship. Later, Silipo and Vittoria[49] derived eq 50, showing that, in fact, the relationship was bilinear with respect to pK_a.

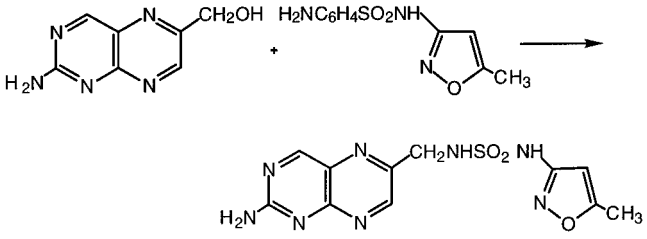
$$\log 1/C = 0.97(\pm 0.10)\mathrm{p}K_a - 1.56(\pm 0.14)\log(\beta \times 10^{\mathrm{p}Ka} + 1) + 0.56(\pm 0.55) \quad (50)$$

$$n = 87,\ r^2 = 0.878,\ s = 0.256$$

$$\text{ideal } \mathrm{p}K_a = 6.26 \log \beta = -6.05$$

The initial positive slope changed at 6.3 to a negative value of −0.59 (0.97 − 1.56 = −0.59). This nicely illustrates the value of the bilinear model vs the parabola.

It was soon discovered that the sulfa drugs inhibited the incorporation of *p*-aminobenzoic acid into folic acid by folate synthetase.[50] Indeed, it has been shown that folate synthetase can incorporate the drug sulfamethoxazole in pterin, thus completely blocking folate synthesis.



A huge amount of literature exists on the action of sulfa drugs on all kinds of bacteria. Our interest is in showing that the biological activity of the sulfas

does not depend on positive hydrophobic effects, but depends on electronic factors.

Table 47. Transport of X−$C_6H_4SO_2NH_2$ through Erythrocyte Membrane at pH 7.4[51]

		log $T_{1/2}$		
no.	substituents	obsd	calcd (eq 51)	σ^+
1	H[a]	−0.82	−1.37	0.00
2	4-NH_2	−0.75	−0.90	−1.30
3	4-Me[a]	−0.88	−1.26	−0.31
4	4-OH	−1.05	−1.04	−0.92
5	4-Cl	−1.16	−1.41	0.11
6	4-C_2H_5	−1.43	−1.26	−0.30
7	4-NO_2	−1.62	−1.66	0.79
8	2-NH_2	−1.02	−0.90	−1.30
9	2-NO_2	−1.66	−1.66	0.79
10	2,5-di-Me	−1.49	−1.23	−0.38
11	2-Me,4-NH_2	−0.77	−0.79	−1.61
12	3-Me,4-NH_2	−0.78	−0.88	−1.37

[a] Data points not included in deriving equation.

Transport of X−$C_6H_4SO_2NH_2$ through erythrocyte membrane at pH 7.4 (Table 47)[51]

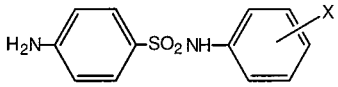
$$\log T_{1/2} = -0.36(\pm 0.14)\sigma^+ - 1.37(\pm 0.14) \quad (51)$$

$$n = 10,\ r^2 = 0.820,\ s = 0.160,\ q^2 = 0.754$$

outliers: H; 4-Me

It is of interest that hydrophobicity plays no role. Electron-releasing groups slow the rate of transport.

Compound XIII and its variations have received considerable attention as the following equation shows.



XIII

Table 48. I_{50} for *E. coli* Folate Sythetase by XIII[52]

		log 1/C		
no.	substituents	obsd	calcd (eq 52)	pK_a
1	H	4.30	4.43	9.10
2	4-OMe	4.12	4.35	9.34
3	4-Cl	4.46	4.60	8.56
4	4-I	4.70	4.72	8.17
5	2-Cl,4-OMe	4.72	4.52	8.81
6	3-CF_3	4.82	4.78	7.98
7	2-Cl	4.87	4.72	8.18
8	4-COMe	4.98	4.93	7.52
9	4-CN	5.15	4.98	7.36
10	4-NO_2	5.15	5.11	6.97
11	2-OMe,4-NO_2	5.22	5.01	7.27
12	2-Cl,4-NO_2	5.22	5.36	6.17
13	2-NO_2,4-CF_3	5.30	5.38	6.10
14	2-Br,4-NO_2	5.40	5.51	5.70

I_{50} for E. coli folate synthetase by XIII (Table 48)[52]

$$\log 1/C = -0.32(\pm 0.08)\mathrm{p}K_a + 7.33(\pm 0.61) \quad (52)$$

$$n = 14,\ r^2 = 0.865,\ s = 0.150,\ q^2 = 0.810$$

σ^- gives slightly poorer correlation:

$$\rho = 0.46,\ r^2 = 0.845$$

Table 49. Inhibition (MIC) by XIII of *E. coli*[53]

		log 1/C			
no.	substituents	obsd	calcd (eq 53)	pK_a	Clog P
1	4-NMe_2	4.35	4.42	9.46	1.87
2	2-OMe	4.45	4.46	9.43	1.74
3	2-OC_2H_5	4.35	4.26	9.60	2.27
4	4-OMe	4.47	4.52	9.34	1.74
5	4-OC_2H_5	4.49	4.53	9.21	2.27
6	4-Me	4.66	4.52	9.25	2.20
7	2-Me	4.46	4.54	9.34	1.64
8	3-Me	4.60	4.66	9.05	2.20
9	H	4.80	4.78	8.97	1.70
10	3-OC_2H_5	4.80	5.05	8.46	2.27
11	3-OMe	4.80	4.95	8.72	1.74
12	4-Cl	4.89	4.93	8.56	2.61
13	4-Br	4.89	5.12	8.24	2.76
14	2-Br	4.99	5.33	8.02	2.20
15	4-I	4.95	5.12	8.17	3.02
16	3-I	5.04	4.99	8.37	3.02
17	3-Cl	5.10	5.11	8.28	2.61
18	3-Br	4.95	5.07	8.31	2.76
19	3-NO_2	5.60	5.57	7.67	1.87
20	3-CF_3	5.25	5.25	7.98	2.93
21	4-CF_3	5.40	5.35	7.80	2.93
22	4-CN	6.00	5.73	7.36	1.59
23	4-$COCH_3$	5.70	5.68	7.52	1.50
24	4-NO_2	6.00	5.76	6.97	1.87
25	4-SO_2CH_3	5.85	5.90	7.30	0.55
26	2,3-di-Me	4.32	4.20	9.72	2.09
27	2-Me,5-Cl	4.80	4.64	9.00	2.55
28	2-Me,6-Cl	4.80	4.87	8.78	1.99
29	3,4-di-Cl	5.40	5.38	7.62	3.26
30	3,5-di-Cl	5.55	5.36	7.62	3.38
31	2-Cl,4-OMe	4.77	4.84	8.81	2.05
32	2-OMe,4-Cl	5.10	4.86	8.67	2.61
33	2-Cl,4-NO_2[a]	5.10	−0.74	6.17	2.08
34	2-Me,4-NO_2	5.55	5.77	6.98	1.81
35	2-Me,4-NO_2	5.41	5.65	6.79	2.64
36	2-Br,4-NO_2	5.64	5.49	5.70	2.23
37	4-NO_2,2-CF_3	5.32	5.46	5.90	2.85
38	2-Cl	5.55	5.32	8.08	2.05
39	2-I	5.68	5.33	7.99	2.36

[a] Data point not included in deriving equation.

Inhibition (MIC) by XIII of E. coli (Table 49)[53]

$$\log 1/C = 0.33(\pm 0.23)\mathrm{p}K_a - 1.04(\pm 0.30)\log(\beta \times 10^{\mathrm{p}Ka} + 1) - 0.15(\pm 0.10)\ \mathrm{Clog}\ P + 3.94(\pm 1.5) \quad (53)$$

$$n = 38,\ r^2 = 0.892,\ s = 0.170,\ q^2 = 0.862$$

$$\text{ideal } \mathrm{p}K_a = 6.9 \pm 0.40$$

outlier: 2-Cl, 4-NO_2

The optimum pK_a for eq 53 is in good agreement with that of eq 50. The different range in pK_a values accounts for the differences between eqs 50 and 53. No role for a positive hydrophobic term could be found in eq 53, so that we can conclude that the binding to the synthetase does not depend on hydrophobic interactions. In the case of eq 53 we see a very small negative log P term. One might assume that in crossing the cell membrane, hydrophobic character would be of assistance, but if it is, it is canceled with interaction with the enzyme.

Table 50. Growth Inhibition of *E. coli* Lyase Folate Synthetase by XIII[52]

		log 1/*C*				
no.	substituents	obsd	calcd (eq 54)	pK_a	Es_2	Clog *P*
1	H	4.79	4.86	9.20	0.00	1.70
2	4-OMe	4.46	4.78	9.34	0.00	1.74
3	4-Cl	4.88	4.85	8.56	0.00	2.61
4	4-I	4.95	4.89	8.17	0.00	3.02
5	2-Cl,4-OMe	4.79	4.42	8.81	−0.97	2.05
6	3-CF_3[a]	4.25	5.01	7.98	0.00	2.93
7	2-Cl	4.55	4.66	8.29	−0.97	2.05
8	4-$COCH_3$	5.70	5.74	7.52	0.00	1.50
9	4-CN	6.00	5.78	7.36	0.00	1.59
10	4-NO_2	6.00	5.87	6.97	0.00	1.87
11	2-OMe,4-NO_2	5.32	5.42	7.27	−0.55	1.91
12	2-Cl,4-NO_2[a]	4.96	5.67	6.17	−0.97	2.08
13	2-NO_2,4-CF_3	5.32	5.41	6.10	−1.01	2.85
14	2-Br,4-NO_2	5.63	5.74	5.70	−1.16	2.23
15	2-Cl,4-SO_2NH_2	6.07	6.05	6.51	−0.97	0.53

[a] Data points not included in deriving equation.

Growth inhibition of E. coli lyase folate synthetase by XIII (Table 50) [52]

$$\log 1/C = -0.48(\pm 0.13)\text{p}K_a + 0.53(\pm 0.30)Es_2 - 0.35(\pm 0.20)\text{Clog } P + 9.87(\pm 1.13) \quad (54)$$

$$n = 13,\ r^2 = 0.907,\ s = 0.201,\ q^2 = 0.785$$

outliers: 2-Cl, 4-NO_2; 3-CF_3

Ortho substituents appear to have a small negative effect as brought out by Es_2, and there is a small *negative* Clog *P* term but again no positive hydrophobic effect. pK_a give a slightly better correlation than σ^-.

Table 51. Inhibition (MIC) of *M. smegmatis* by XIII[53]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 55)	pK_a
1	4-$N(Me)_2$	4.54	4.44	9.46
2	2-OMe	4.52	4.46	9.43
3	2-OC_2H_5	4.48	4.36	9.60
4	4-OMe	4.49	4.46	9.43
5	4-OC_2H_5	4.51	4.59	9.21
6	4-Me	4.63	4.56	9.25
7	2-Me	4.49	4.51	9.34
8	3-Me	4.62	4.68	9.05
9	H	4.80	4.73	8.97
10	3-OC_2H_5	4.80	5.03	8.46
11	3-OMe	4.80	4.88	8.72
12	4-Cl	4.89	4.97	8.56
13	4-Br	4.89	5.16	8.24
14	2-Br	4.93	5.29	8.02
15	4-I	4.95	5.20	8.17
16	3-I	4.95	5.09	8.37
17	3-Cl	5.04	5.14	8.28
18	3-Br	4.93	5.10	8.34
19	3-NO_2	5.60	5.45	7.76
20	3-CF_3	5.02	5.32	7.98
21	4-CF_3	5.55	5.42	7.80
22	4-CN	5.92	5.68	7.36
23	4-$COCH_3$	5.70	5.59	7.52
24	4-NO_2	6.00	5.93	6.94
25	4-SO_2CH_3	5.77	5.72	7.30
26	2, 3-di-Me	4.50	4.29	9.72
27	2-Me, 5-Cl	4.80	4.71	9.00
28	2-Me, 6-Cl	4.80	4.84	8.78
29	3, 4-Cl	5.40	5.53	7.62
30	3, 5-Cl	5.55	5.53	7.62
31	2-Cl, 4-OMe	4.87	4.83	8.81
32	2-OMe, 4-Cl	5.10	4.91	8.67
33	2-Cl, 4-NO_2[a]	5.74	6.39	6.17
34	2-Me, 4-NO_2	6.16	5.91	6.98
35	2-NO_2, 4-Cl	5.92	6.02	6.79
36	2-Br, 4-NO_2	6.82	6.66	5.70
37	2-NO_2, 4-CF_3	6.30	6.43	6.10
38	4-NO_2, 2-CF_3[a]	5.62	6.55	5.90
39	2-Cl	5.55	5.26	8.08
40	2-I	5.38	5.31	7.99

[a] Data points not included in deriving equation.

Inhibition (MIC) of M. smegmatis by XIII (Table 51)[53]

$$\log 1/C = -0.59(\pm 0.06)\text{p}K_a + 10.04(\pm 0.47) \quad (55)$$

$$n = 38,\ r^2 = 0.926,\ s = 0.164,\ q^2 = 0.918$$

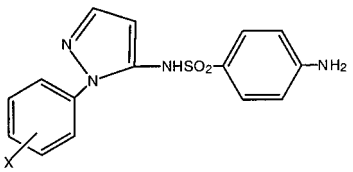
outliers: 2-Cl, 4-NO_2; 2-CF_3, 4-NO_2

Table 52. Inhibition (MIC) of *E. coli* by XIV[54]

		log 1/*C*			
no.	substituents	obsd	calcd (eq 56)	σ	CMR
1	H	6.10	5.95	0.00	8.54
2	3-$COOC_2H_5$	4.92	4.89	0.37	10.12
3	4-$COOC_2H_5$	4.80	4.93	0.45	10.12
4	2-Cl	5.40	5.69	0.23	9.03
5	3-Cl	5.70	5.77	0.37	9.03
6	4-Cl	5.70	5.69	0.23	9.03
7	2-OC_2H_5	4.92	4.95	−0.24	9.62
8	3-OC_2H_5	5.40	5.14	0.10	9.62
9	2-OMe	5.40	5.30	−0.27	9.16
10	3-OMe	5.70	5.52	0.12	9.16
11	2-NO_2	6.00	5.90	0.78	9.15
12	3-NO_2	5.82	5.86	0.71	9.15
13	4-NO_2	5.70	5.90	0.78	9.15
14	2-Me	5.40	5.48	−0.17	9.00
15	3-Me	5.70	5.54	−0.07	9.00
16	4-Me	5.70	5.48	−0.17	9.00
17	2-OH[a]	5.02	5.62	−0.37	8.69
18	4-OH[a]	5.17	5.62	−0.37	8.69
19	2-NH_2	4.99	5.28	−0.66	8.91
20	4-NH_2	5.19	5.28	−0.66	8.91

[a] Data points not included in deriving equation.

Inhibition (MIC) of E. coli by XIV (Table 52)[54]



XIV

$$\log 1/C = 0.57(\pm 0.22)\sigma - 0.81(\pm 0.23)\text{CMR} + 12.8(\pm 2.1) \quad (56)$$

$$n = 18,\ r^2 = 0.814,\ s = 0.177,\ q^2 = 0.734$$

outliers: 2-OH; 4-OH

In eqs 51−57, we find a reasonable agreement among the electronic terms. Recall that pK_a is the log of the reciprocal of the ionization constant. To place this in terms of ionization and σ constants, the sign must be changed.

The natriuretic action of sulfa drugs depends on electron withdrawal by substituents.

Table 53. Concentration of X−$C_6H_4SO_2NH_2$ Causing a 3-fold Increase in Na^+ Excretion in Rat[55]

		log 1/*C*			
no.	substituents	obsd	calcd (eq 57)	σ	$B1_3$
1	4-NHMe	2.70	2.79	−0.70	1.00
2	4-NH_2	2.80	2.82	−0.66	1.00
3	4-OMe	3.24	3.08	−0.27	1.00
4	4-Me	3.18	3.15	−0.17	1.00
5	3-Me	3.18	3.04	−0.07	1.52
6	H	3.16	3.27	0.00	1.00
7	4-Cl	3.30	3.43	0.23	1.00
8	4-Br	3.27	3.43	0.23	1.00
9	3-Cl	3.32	3.25	0.37	1.80
10	4-COMe	3.46	3.61	0.50	1.00
11	4-CN	4.02	3.72	0.66	1.00
12	3-NO_2	3.70	3.51	0.71	1.70
13	4-NO_2	3.85	3.80	0.78	1.00
14	3,4-di-Cl	3.27	3.40	0.60	1.80
15	3-NO_2,4-Cl[a]	3.32	3.67	0.94	1.70
16	3-CF_3,4-NO_2	3.60	3.76	1.21	1.99

[a] Data point not included in deriving equation.

Concentration of X−$C_6H_4SO_2NH_2$ causing 3-fold increase in the excretion from rat of Na^+(Table 53)[55]

$$\log 1/C = 0.68(\pm0.20)\sigma - 0.34(\pm0.29)B1_3 + 3.61(\pm0.35) \quad (57)$$

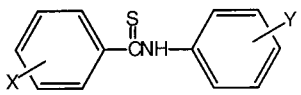
$$n = 15,\ r^2 = 0.827,\ s = 0.159,\ q^2 = 0.720$$

outlier: 3-NO_2, 4-Cl

There is a marginal steric effect of meta substituents. The one outlier might well have been expected since Cl ortho to NO_2 would be very sensitive to nucleophilic attack. The more acidic the sulfonamide, the more effective it is.

2. Inhibition by Thiobenzamides

Waisser and his associates investigated[56−58] thiobenzamides XV on various mycobacteria from which we have obtained the following results.



XV

Table 54. MIC of XV with *M. Avium*[56]

	substituents		log 1/*C*			
no.	X	Y	obsd	calcd (eq 58)	σ_X	σ_Y
1	H	3-F	3.30	3.49	0.00	0.34
2	3-Cl	3-F	3.90	3.96	0.37	0.34
3	4-Cl	3-F	3.60	3.78	0.23	0.34
4	4-NO_2	3-F[a]	3.90	4.47	0.78	0.34
5	4-Me	3-F	3.30	3.28	−0.17	0.34
6	4-OMe	3-F	3.30	3.15	−0.27	0.34
7	3-Br	3-F	4.22	3.98	0.39	0.34
8	H	4-F[a]	3.60	3.02	0.00	0.06
9	3-Cl	4-F	3.60	3.49	0.37	0.06
10	4-Cl	4-F	3.30	3.31	0.23	0.06
11	4-NO_2	4-F	3.90	4.00	0.78	0.06
12	4-Me	4-F	2.70	2.81	−0.17	0.06
13	4-OMe	4-F	2.70	2.68	−0.27	0.06
14	3-Br	4-F	3.60	3.51	0.39	0.06

[a] Data points not included in deriving equation.

MIC of XV with M. avium (Table 54)[56]

$$\log 1/C = 1.26(\pm0.31)\sigma_X + 1.67(\pm0.70)\sigma_Y + 2.92(\pm0.18) \quad (58)$$

$$n = 12,\ r^2 = 0.915,\ s = 0.147,\ q^2 = 0.852$$

outliers: X=4-NO_2, Y = 3-F; X = H, Y = 4-F

Table 55. MIC of XV with *M. Tuberculosis*[56]

	substituents		log 1/*C*			
no.	X	Y	obsd	calcd (eq 59)	σ^+_X	σ_Y
1	H	3-F	4.22	4.01	0.00	0.34
2	3-Cl	3-F	4.22	4.35	0.37	0.34
3	4-Cl	3-F	4.22	4.11	0.11	0.34
4	4-NO_2	3-F	4.52	4.73	0.79	0.34
5	4-Me	3-F	3.60	3.73	−0.31	0.34
6	4-OMe	3-F	3.30	3.31	−0.78	0.34
7	3-Br	3-F	4.52	4.37	0.39	0.34
8	H	4-F	3.60	3.57	0.00	0.06
9	3-Cl	4-F	3.90	3.91	0.37	0.06
10	4-Cl	4-F	3.90	3.67	0.11	0.06
11	4-NO_2	4-F	4.22	4.29	0.79	0.06
12	4-Me	4-F[a]	2.70	3.29	−0.31	0.06
13	4-OMe	4-F	2.70	2.87	−0.78	0.06
14	3-Br	4-F	3.90	3.93	0.39	0.06

[a] Data point not included in deriving equation.

MIC of XV with M. tuberculosis (Table 55)[56]

$$\log 1/C = 0.91(\pm0.20)\sigma^+_X + 1.58(\pm0.69)\sigma_Y + 3.48(\pm0.18) \quad (59)$$

$$n = 13,\ r^2 = 0.923,\ s = 0.156,\ q^2 = 0.864$$

outlier: X = 4-Me, Y = 4-F

Table 56. MIC of XV with *M. fortuitum*[56]

	substituents		log 1/*C*			
no.	X	Y	obsd	calcd (eq 60)	σ_X	σ_Y
1	H	3-F	3.60	3.53	0.00	0.34
2	3-Cl	3-F	3.90	3.88	0.37	0.34
3	4-Cl	3-F[a]	3.30	3.75	0.23	0.34
4	4-NO_2	3-F	3.90	4.27	0.78	0.34
5	4-Me	3-F	3.30	3.37	−0.17	0.34
6	4-OMe	3-F	3.30	3.28	−0.27	0.34
7	3-Br	3-F	4.22	3.90	0.39	0.34
8	H	4-F[a]	3.60	2.99	0.00	0.06
9	3-Cl	4-F	3.60	3.34	0.37	0.06
10	4-Cl	4-F	3.30	3.21	0.23	0.06
11	4-NO_2	4-F	3.90	3.73	0.78	0.06
12	4-Me	4-F	2.70	2.83	−0.17	0.06
13	4-OMe	4-F	2.70	2.74	−0.27	0.06
14	3-Br	4-F	3.00	3.36	0.39	0.06

[a] Data points not included in deriving equation.

MIC of XV with M. fortuitum (Table 56)[56]

$$\log 1/C = 0.95(\pm0.42)\sigma_X + 1.93(\pm1.11)\sigma_Y + 2.87(\pm0.29) \quad (60)$$

$$n = 12,\ r^2 = 0.810,\ s = 0.237,\ q^2 = 0.637$$

outliers: X = 4-Cl, Y = 3-F; X = H, Y = 4-F

Table 57. MIC of *M. kansasii* with XV[56]

	substituents		log 1/*C*			
no.	X	Y	obsd	calcd (eq 61)	σ_X	σ_Y
1	H	3-F	3.90	3.73	0.00	0.34
2	3-Cl	3-F	4.22	4.28	0.37	0.34
3	4-Cl	3-F	4.22	4.07	0.23	0.34
4	4-NO_2	3-F[a]	4.22	4.88	0.78	0.34
5	4-Me	3-F	3.30	3.47	−0.17	0.34
6	4-OMe	3-F	3.30	3.33	−0.27	0.34
7	3-Br	3-F	4.22	4.30	0.39	0.34
8	H	4-F	3.60	3.19	0.00	0.06
9	3-Cl	4-F	3.60	3.74	0.37	0.06
10	4-Cl	4-F	3.60	3.54	0.23	0.06
11	4-NO_2	4-F	4.22	4.35	0.78	0.06
12	4-Me	4-F	2.70	2.94	−0.17	0.06
13	4-OMe	4-F	2.70	2.79	−0.27	0.06
14	3-Br	4-F	3.90	3.77	0.39	0.06

[a] Data point not included in deriving equation.

MIC of M. kansasii with XV (Table 57)[56]

$$\log 1/C = 1.48(\pm 0.40)\sigma_X + 1.90(\pm 0.88)\sigma_Y + 3.08(\pm 0.22) \quad (61)$$

$$n = 13,\ r^2 = 0.889,\ s = 0.197,\ q^2 = 0.820$$

outlier: X = 4-NO_2, Y = 3-F

Comparison of the parameters for the four equations shows good agreement. Possibly using an EC_{50} as the end point instead of MIC would have yielded better QSAR. Only one series (*M. tuberculosis*) has a significantly different intercept, indicating that it is more sensitive than the others that have surprisingly close intercepts. One compound, X = H, Y = 4-F, is an outlier in two of the four examples. There is no obvious reason for this.

Of the three electronic parameters (σ, σ^+, σ^-) that we investigated for both X and Y, only in one instance (eq 59) did a term other than σ appear. We have no idea as to why σ^+ appears in only this example. An earlier study by Waisser[57] on a large set of data could not be correlated with satisfactory equations.

One study of X−$C_6H_4C(=S)NH_2$ on rats yields a result of interest.

Table 58. Induction of Serum Alaninamino Transferase in Rats by a Dose of 0.76 mmol/kg[58]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 62)	σ
1	H	0.55	0.43	0.00
2	3-Br	−0.14	−0.23	0.39
3	4-Br	−0.33	−0.17	0.23
4	3-Cl	−0.15	−0.24	0.37
5	4-Cl	−0.12	−0.17	0.23
6	3,4-di-Cl	−0.06	0.15	0.60
7	3,5-di-Cl	0.78	0.69	0.74
8	3-OMe[a]	0.48	0.04	0.12
9	3-Me[a]	1.20	0.74	−0.07
10	4-Me	1.19	1.27	−0.17
11	3-NO_2	0.40	0.56	0.71
12	4-NO_2	1.03	0.89	0.78
13	4-SMe	0.45	0.43	0.00

[a] Data points not included in deriving equation.

Induction of serum alaninamino transferase in rats by a dose of 0.76 mmol/kg (Table 58)[58]

$$\log 1/C = -3.97(\pm 0.86)\sigma + 5.84(\pm 1.2)\sigma^2 + 0.43(\pm 0.15) \quad (62)$$

$$n = 11,\ r^2 = 0.941,\ s = 0.142,\ q^2 = 0.878$$

outliers: 3-OMe; 3-Me

The induction of the enzyme is a measure of liver toxicity. Thiobenzamides are known to produce a variety of toxic reactions.[59,60] Equation 62 implies that either electron-withdrawing or -releasing substituents promote toxicity. The minimum activity occurs at $\sigma \sim 0.4$.

Hanzlik and co-workers[61] studied the action of 4-X−$C_6H_4(C{=}S)NH_2$ congeners on rats and showed that for a small number (3 or 4) of substituents toxicity is correlated with σ with a negative slope (ρ). For hepatotoxicity in rats estimated by plasma glutamic pyruvate transanimase, $\rho = -1.40$. The most electron-attracting substituent studied was 4-CF_3 ($\sigma = 0.54$). There was no evidence for a hydrophobic effect. The above results suggest that two types of toxicity are involved. There is no doubt that there is more than one way for the thioamides to produce toxic effects.

Turning now to our physical database, we find the following examples of interest.

Table 59. Ionization of X−$C_6H_4C(=S)NH_2$ in DMSO−10% Ethanol[62]

		pK_a		
no.	substituents	obsd	calcd (eq 63)	σ
1	H	12.85	12.73	0.00
2	4-Me	13.00	12.91	−0.17
3	4-Cl	12.46	12.49	0.23
4	4-NMe_2	13.50	13.61	−0.83
5	4-OMe	13.05	13.02	−0.27
6	4-NO_2	11.84	11.91	0.78
7	4-Br	12.46	12.49	0.23

Ionization of X−$C_6H_4C(=S)NH_2$ in DMSO−10% ethanol (Table 59)[62]

$$pK_a = -1.06(\pm 0.19)\sigma + 12.73(\pm 0.09) \quad (63)$$

$$n = 7,\ r^2 = 0.976,\ s = 0.091,\ q^2 = 0.924$$

Table 60. Ionization of X−$C_6H_4SO_2NH_2$ in Water at 20 °C[63]

		pK_a			
no.	substituent	obsd	calcd (eq 64)	σ^-	F_2
1	4-NH_2	10.48	10.39	−0.63	0.00
2	4-OMe	10.17	10.15	−0.26	0.00
3	4-Me	10.11	10.09	−0.17	0.00
4	3-Me	10.06	10.03	−0.07	0.00
5	H	9.95	9.99	0.00	0.00
6	4-Cl	9.88	9.87	0.19	0.00
7	4-Br	9.87	9.83	0.25	0.00
8	3-Cl	9.80	9.75	0.37	0.00
9	4-COMe	9.66	9.46	0.84	0.00
10	4-CN	9.26	9.35	1.00	0.00
11	3-NO_2	9.42	9.54	0.71	0.00
12	4-NO_2	9.04	9.18	1.27	0.00
13	3,4-di-Cl	9.60	9.63	0.56	0.00
14	3-NO_2, 4-Cl	9.34	9.42	0.90	0.00
15	3-CF_3, 4-NO_2	9.09	8.91	1.70	0.00
16	2-Me	9.93	10.19	−0.17	0.00
17	2-Cl	9.58	9.55	0.19	0.42
18	2-NO_2	8.67	8.69	1.27	0.65

Ionization of X−$C_6H_4SO_2NH_2$ in water at 20 °C (Table 60)[63]

$$pK_a = -0.63(\pm0.09)\sigma^- - 0.76(\pm0.32)F_2 + 9.99(\pm0.07) \quad (64)$$

$$n = 18,\ r^2 = 0.954,\ s = 0.105,\ q^2 = 0.931$$

Note: 4-NHMe omitted for lack of a σ^- value.

F is the field/inductive parameter that often is essential for ortho substituents in addition to the normal σ_P value.

Table 61. Ionization of X−$C_6H_4SO_2NH$−C_6H_4−Y in Aqueous 23.4% Alcohol at 20 °C[64]

	substituent		pK_a			
no.	X	Y	obsd	calcd (eq 65)	σ_X	σ_Y
1	H	H	9.10	9.03	0.00	0.00
2	H	4-OMe	9.42	9.69	0.00	−0.27
3	H	4-Me	9.35	9.45	0.00	−0.17
4	H	4-F	8.90	8.89	0.00	0.06
5	H	4-Cl	8.47	8.48	0.00	0.23
6	H	4-Br	8.50	8.48	0.00	0.23
7	H	3-Br	8.25	8.09	0.00	0.39
8	H	3-NO_2	7.50	7.31	0.00	0.71
9	3-NO_2	H	7.93	7.82	0.71	0.00
10	3-NO_2	4-OMe	8.44	8.47	0.71	−0.27
11	3-NO_2	4-Me	8.27	8.23	0.71	−0.17
12	3-NO_2	4-F	7.85	7.67	0.71	0.06
13	3-NO_2	4-Cl	7.51	7.26	0.71	0.23
14	3-NO_2	4-Br	7.42	7.26	0.71	0.23
15	4-Cl	H	8.75	8.64	0.23	0.00
16	4-Cl	4-OMe	9.19	9.30	0.23	−0.27
17	4-Cl	4-Me	9.02	9.05	0.23	−0.17
18	4-Cl	4-F	8.61	8.50	0.23	0.06
19	4-Cl	4-Cl	8.30	8.08	0.23	0.23
20	4-Cl	4-Br	8.24	8.08	0.23	0.23
21	4-Cl	3-NO_2	7.19	6.92	0.23	0.71
22	4-F	H	8.85	8.93	0.06	0.00
23	4-F	4-OMe	9.32	9.59	0.06	−0.27
24	4-F	4-Me	9.20	9.34	0.06	−0.17
25	4-F	4-F	8.73	8.79	0.06	0.06
26	4-F	4-Cl	8.41	8.37	0.06	0.23
27	4=F	4-Br	8.38	8.37	0.06	0.23
28	4-F	3-NO_2	7.27	7.21	0.06	0.71
29	4-Me	4-OMe	9.80	9.98	−0.17	−0.27
30	4-Me	4-Me	9.65	9.74	−0.17	−0.17
31	4-Me	H	9.34	9.33	−0.17	0.00
32	4-Me	4-F	9.23	9.18	−0.17	0.06
33	4-Me	4-Cl	8.78	8.77	−0.17	0.23
34	4-Me	3-NO_2	7.80	7.60	−0.17	0.71
35	4-NH_2	H	10.29	10.16	−0.66	0.00
36	4-NH_2	4-Me	10.53	10.58	−0.66	−0.17
37	4-NH_2	3-Me	10.44	10.33	−0.66	−0.07
38	4-NH_2	4-Cl	9.76	9.61	−0.66	0.23
39	H	4-NO_2	6.66	7.14	0.00	0.78
40	3-NO_2	4-NO_2	5.51	5.93	0.71	0.78
41	4-Cl	4-NO_2	6.24	6.75	0.23	0.78
42	4-F	4-NO_2[a]	6.45	7.00	0.06	0.78
43	4-Me	4-NO_2[a]	6.78	7.44	−0.17	0.78

[a] Data points not included in deriving equation.

Ionization of X−$C_6H_4SO_2NH$−C_6H_4−Y in aqueous 23.4% alcohol at 20 °C (Table 61)[64]

$$pK_a = -1.71(\pm0.16)\sigma_X - 2.42(\pm0.19)\sigma_Y + 9.03(\pm0.07) \quad (65)$$

$$n = 41,\ r^2 = 0.970,\ s = 0.190,\ q^2 = 0.963$$

outliers: X=4-F, Y = 4-NO_2; X = 4-Me, Y = 4-NO_2

Table 62. Ionization of X−$C_6H_4NHSO_2$−C_6H_4−NH_2 in Water at 25 °C[65]

		pK_a		
no.	substituent	obsd	calcd (eq 66)	σ^-
1	3,5-di-NO_2	6.19	6.46	1.42
2	3-NO_2, 5-Cl	6.92	7.04	1.08
3	4-NO_2	6.97	6.72	1.27
4	3-NO_2, 4-Cl	7.16	7.28	0.94
5	4-CN	7.36	7.18	1.00
6	4-SO_2NH_2	7.45	7.28	0.94
7	3,5-di-Cl	7.54	7.63	0.74
8	3-NO_2	7.67	7.68	0.71
9	4-COMe	7.61	7.40	0.87
10	3-SO_2NH_2	7.81	8.10	0.46
11	3-CN	7.83	7.93	0.56
12	3-Cl	8.28	8.26	0.37
13	3-COMe	8.34	8.24	0.38
14	4-Cl	8.56	8.57	0.19
15	3-OMe	8.72	8.68	0.12
16	H	8.97	8.89	0.00
17	3-Me	9.05	9.01	−0.07
18	4-Me	9.25	9.18	−0.17
19	4-OMe	9.34	9.33	−0.26
20	3-NMe_2	9.01	9.16	−0.16
21	4-NMe_2[a]	9.46	10.31	−0.83

[a] Data point not included in deriving equation.

Ionization of X−$C_6H_4NHSO_2$−C_6H_4−NH_2 in water at 25 °C (Table 62)[65]

$$pK_a = -1.71(\pm0.15)\sigma^- + 8.89(\pm0.10) \quad (66)$$

$$n = 20,\ r^2 = 0.972,\ s = 0.153,\ q^2 = 0.963$$

outlier: 4-$N(CH_3)_2$

Table 63. Oxidation Potential of X−$C_6H_4C(=S)NH_2$ in Acetonitrile[59]

		E_1		
no.	substituent	obsd	calcd (eq 67)	σ
1	4-OMe	1.06	1.07	−0.27
2	4-Me	1.12	1.10	−0.17
3	H	1.15	1.15	0.00
4	4-Cl	1.21	1.23	0.23
5	4-CF_3	1.34	1.33	0.54

Oxidation potential of X−$C_6H_4C(=S)NH_2$ in acetonitrile (Table 63)[59]

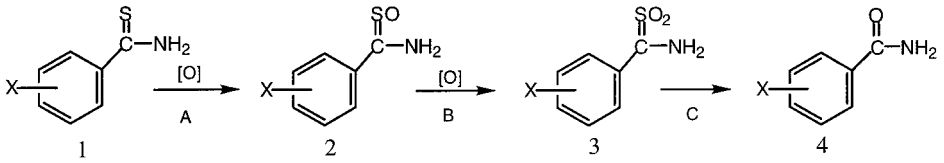
$$E_1 = 0.32(\pm0.07)\sigma + 1.15(\pm0.02) \quad (67)$$

$$n = 5,\ r^2 = 0.985,\ s = 0.015,\ q^2 = 0.951$$

Table 64. Alkaline Solvolysis in Methanol of X−$C_6H_4CSN(Me)C_6H_4$−Y[66]

	substituent		log k_2			
no.	X	Y	obsd	calcd (eq 68)	σ_X	σ^-_Y
1	4-OMe	4-NO_2	−1.37	−1.53	−0.27	1.27
2	4-Me	4-NO_2	−1.34	−1.36	−0.17	1.27
3	H	4-NO_2	−1.18	−1.06	0.00	1.27
4	4-Cl	4-NO_2	−0.70	−0.67	0.23	1.27
5	3-Br	4-NO_2	−0.57	−0.40	0.39	1.27
6	3-NO_2	4-NO_2	0.01	0.15	0.71	1.27
7	4-NO_2	4-NO_2	0.08	0.28	0.78	1.27
8	4-NO_2	4-Me	−2.58	−2.72	0.78	−0.17
9	4-NO_2	H	−2.37	−2.36	0.78	0.00
10	4-NO_2	4-Br	−1.90	−1.84	0.78	0.25
11	4-NO_2	3-Cl	−1.82	−1.60	0.78	0.37
12	4-NO_2	3-NO_2	−0.66	−0.89	0.78	0.71
13	4-NO_2	3,5-di-NO_2	0.99	0.59	0.78	1.42

Scheme 2



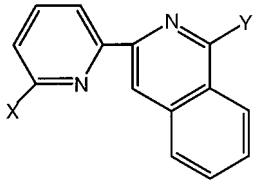
Alkaline Solvolysis in Methanol of X−C_6H_4CS−N(Me)−C_6H_4−Y (Table 64)[66]

$$\log k_2 = 1.72(\pm 0.38)\sigma_X + 2.08(\pm 0.27)\sigma^-_Y - 3.70(\pm 0.39) \quad (68)$$

$$n = 13,\ r^2 = 0.968,\ s = 0.202,\ q^2 = 0.940$$

The thiobenzamides appear to undergo the following metabolic pathway.[59] Some evidence for this is that 4-methylthiobenzamide has been shown to be converted in rat plasma to structures 2 and 4 of Scheme 2.[67] These results of Hanzlik's group, to some degree, parallel those of eq 62 in that electron-releasing groups can increase toxicity. The limited range of σ examined leaves one in doubt as to the parabolic relationship. Of course, a negative ρ is what would be expected for the first two steps in Scheme 2 (i.e., electron-releasing substituents would promote oxidation). Why do electron-attracting elements increase toxicity? The final step to a benzamide is more complex. The hydrolysis that occurs in step C suggests nucleophilic attack by water. Other nucleophiles such as the −SH in glutathione could be involved leading to toxicity. The electron-withdrawing substituents would inhibit the oxidation steps. As eq 68 shows, reaction with a nucleophile is promoted by substituents having positive σ values. In examples 58−61, the positive ρ suggests that the road to toxicity is via nucleophilic attack on the C(=S)NH_2 moiety. The oxidation track of Scheme 2 would be favored by substituents with negative σ values. The direct attack on the thioamide would be favored by electron-withdrawing groups. However, eq 62 suggests two mechanisms for toxicity in the liver. One promoted by electron-attracting groups and one by electron-releasing groups.

3. Miscellaneous Inhibitors



XVI

Table 65. MIC of *Mycoplasma gallisepticum* by XVI[68]

	substituents		log 1/*C*			
no.	X	Y	obsd	calcd (eq 69)	σ^+_X	F_X
1	H	H[a]	4.60	6.62	0.00	0.00
2	Cl	H	4.92	5.18	0.11	0.42
3	NH_2	H[a]	5.80	7.07	−1.30	0.08
4	OMe	H	6.10	6.09	−0.78	0.29
5	Me	H	6.70	6.76	−0.31	0.01
6	C_2H_5	H	6.70	6.78	−0.30	0.00
7	C_3H_7	H	7.00	6.75	−0.29	0.01
8	C_6H_5	H	6.22	6.32	−0.18	0.12
9	H	Me	6.40	6.62	0.00	0.00
10	Cl	Me	5.47	5.18	0.11	0.42
11	NH_2	Me	7.00	7.07	−1.30	0.08
12	Me	Me	7.00	6.76	−0.31	0.01

[a] Data points not included in deriving equation.

MIC of Mycoplasma gallisepticum by XVI (Table 65)[68]

$$\log 1/C = -0.55(\pm 0.42)\sigma^+_X - 3.28(\pm 1.0)F_X + 6.62(\pm 0.28) \quad (69)$$

$$n = 10,\ r^2 = 0.921,\ s = 0.223,\ q^2 = 0.814$$

outliers: X = H, Y = H; X = NH_2, Y = H

Equation 69 is similar to eq 70 for the ionization of 2-X-pyridines (Table 66)[69]

Table 66. Ionization of 2-X-Pyridines[69]

		pK_a			
no.	substituent	obsd	calcd (eq 70)	σ^+	F
1	H	5.17	5.46	0.00	0.00
2	2-Me	5.94	5.71	−0.31	0.01
3	2-C_2H_5	5.97	5.80	−0.30	0.00
4	2-C_3H_7	5.97	5.69	−0.29	0.01
5	2-OMe	3.06	3.38	−0.78	0.29
6	2-OC_2H_5	3.47	3.73	−0.81	0.26
7	2-NH_2	6.71	6.13	−1.30	0.08
8	2-NHCOMe	4.09	2.97	−0.60	0.31
9	2-N(C_2H_5)$_2$	7.32	7.73	−2.07	0.01
10	2-F	−0.44	0.93	−0.07	0.45
11	2-Cl	0.72	1.03	0.11	0.42
12	2-Br	0.90	0.68	0.15	0.45
13	2-I	1.82	1.00	0.14	0.42
14	2-NO_2	−2.20	−2.10	0.79	0.65
15	2-C_6H_5	4.48	4.44	−0.18	0.12
16	2-$CH_2C_6H_5$	5.13	6.19	−0.28	−0.04
17	2-CH=CH_2	4.98	4.31	−0.16	0.13

$$pK_a = -1.15(\pm 0.66)\sigma^+ - 10.24(\pm 2.01)F + 5.46(\pm 0.67) \quad (70)$$

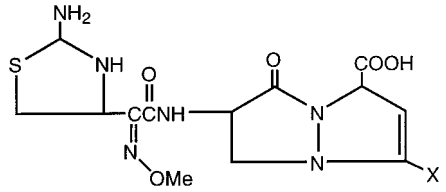
$$n = 17,\ r^2 = 0.945,\ s = 0.679,\ q^2 = 0.923$$

Equation 69 shows that electron-releasing substituents increase potency, and eq 70 shows that such substituents increase pK_a (i.e., basicity).

Table 67. MIC for Miscellaneous 10 Different Types of Bacteria by XVII[70]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 71)	σ^2
1	COOMe	1.05	1.34	0.20
2	PO_3Me	1.66	1.02	0.28
3	H	2.32	2.18	0.00
4	CF_3[a]	1.87	0.97	0.29
5	$PO_3C_2H_5$[a]	2.29	0.69	0.36
6	COMe	0.39	1.14	0.25
7	COC_6H_5	1.00	1.41	0.19
8	C_6H_5	2.41	2.17	0.00
9	2-thienyl	2.41	2.16	0.00
10	CH_2OCOMe	2.41	2.16	0.00
11	CONHMe	1.99	1.64	0.13
12	$COOC_3H_7$	1.35	1.34	0.20
13	$COOC_2H_5$	1.26	1.34	0.20
14	COOH	1.78	2.18	0.00
15	$COCH_2F$[a]	1.66	0.15	0.49
16	$CONHC_6H_5$	1.35	1.58	0.14
17	$COOC_6H_5$	1.84	1.34	0.20
18	COC_2H_5	0.63	1.22	0.23
19	CN	−0.03	0.38	0.44
20	SO_2Me	−0.39	0.04	0.52
21	SMe[a]	−2.26	2.18	0.00
22	$SO_2C_6H_5$	0.03	0.27	0.46
23	$SO_2C_2H_5$	−0.21	−0.27	0.59
24	$COCF_3$[a]	2.41	−0.47	0.64
25	SO_2NMe_2	0.39	0.43	0.42
26	$NHCO_2Me$	2.41	2.06	0.03
27	S-thiadiazole	1.81	2.17	0.00
28	S-tetrazole-1-Me	2.05	2.17	0.00
29	CH=NOMe	1.87	1.80	0.09
30	$CH{=}NOCH_2CH_2C_6H_5$	1.81	1.80	0.09
31	2-pyridyl	2.11	2.14	0.01
32	4-pyridyl	2.20	2.04	0.03
33	$CH{=}NOCH_2CH{=}CH_2$	1.87	1.80	0.09
34	$CH{=}CH_2$	2.38	2.17	0.00
35	SO_2-di-Me-isooxazole	0.27	−0.27	0.59
36	$SO_2CH_2CH_2NHCOMe$	0.27	−0.27	0.59

[a] Data points not included in deriving equation.



XVII

MIC for miscellaneous 10 different types of bacteria by XVII (Table 67)[70]

$$\log 1/C = -4.12(\pm 0.67)\sigma^2 + 2.18(\pm 0.18) \quad (71)$$

$$n = 31,\ r^2 = 0.846,\ s = 0.358,\ q^2 = 0.821$$

outliers: CF_3; $PO_3C_2H_5$; $COCH_2F$; SMe; $COCF_3$

The correlation is not particularly good because of the necessity to drop five data points. This may be, in part, due to the use of a mixture of bacteria. No steric effect could be found for X using B1. The optimum value of σ is about 0. There are few values below 0 (one side of the parabola is essentially empty), so that this area was not well explored. Up to a point, electron-attracting groups are obviously bad. This suggests that increased ionization is deleterious. It is surprising that the author did not explore groups such as OCH_3 or NMe_2. No evidence could be found for a role for hydrophobicity.

VI. Phenols

A very interesting example of comparative QSAR comes from Harada et al.[71] They investigated the toxicity (I_{50}) of substituted anilines to mouse embryo fibroblast cells. From their data we formulated the following equation (Table 68).

Table 68. IC_{50} of Substituted Anilines to Mouse Embryo Fibroblast Cells[71]

		log 1/*C*			
no.	substituents	obsd	calcd (eq 72)	σ^+	Clog *P*
1	H[a]	2.73	3.91	0.00	0.92
2	2-NO_2	3.28	3.26	0.79	1.80
3	3-NO_2	3.44	3.45	0.71	1.26
4	4-NO_2	3.49	3.41	0.79	1.26
5	2-NH_2	4.85	4.91	−1.30	−0.31
6	3-NH_2[a]	3.92	4.34	−0.16	−0.31
7	4-NH_2	4.68	4.91	−1.30	−0.31
8	2-Me	3.83	3.93	−0.31	1.36
9	3-Me	3.72	3.80	−0.07	1.41
10	4-Me	3.70	3.92	−0.31	1.41
11	2-OMe	4.13	4.22	−0.78	1.18
12	3-OMe	3.52	3.82	0.12	1.00
13	4-OMe	4.55	4.27	−0.78	1.00
14	2-Cl	3.68	3.57	0.11	1.91
15	3-Cl	3.41	3.44	0.37	1.91
16	4-Cl	3.89	3.57	0.11	1.91
17	2-OH	4.82	4.45	−0.92	0.62
18	3-OH	4.08	4.04	0.12	0.25
19	4-OH	4.70	4.56	−0.92	0.25
20	4-C_2H_5	3.64	3.76	−0.30	1.94
21	4-C_3H_7	3.46	3.60	−0.29	2.47

[a] Data points not included in deriving equation.

$$\log 1/C = -0.50(\pm 0.19)\sigma^+ - 0.29(\pm 0.16)\text{Clog } P + 4.17(\pm 0.23) \quad (72)$$

$$n = 19,\ r^2 = 0.877,\ s = 0.196,\ q^2 = 0.836$$

outliers: H; 3-NH_2

The authors used two terms, E_{HOMO} and E_{LUMO}, in place of σ^+ to obtain essentially the same result ($r^2 = 0.863$). We find H and 3-NH_2 to be outliers, as did the authors.

This result plus two studies from the EPA began to awaken our interest[7] in phenols and anilines QSAR having terms in $-\sigma^+$.

Phenols causing maldevelopment of rat embryos in vitro[7]

$$\log 1/C = -0.60\sigma^+ + \text{const.} \quad (73)$$

Three examples of eq 73 were obtained from experiments with different end points.[7] The correlations were not particularly sharp ($r^2 = 0.8$), and this is not surprising considering the problem of quantitatively defining maldevelopment of rat embryo (e.g., tail deformation). However, the agreement among the three types of experiments is surprisingly good. The spread in log *P* values was not great, which could account for the lack of hydrophobic terms. Another experiment by an EPA group[72] also pointed in the same direction.

Table 69. IC_{50} for DNA Replication by Phenols in Chinese Hamster Ovary Cells V79[72]

		log 1/C			
no.	substituents	obsd	calcd (eq 74)	σ^+	CMR
1	2,4-di-NH_2	5.15	5.26	−2.60	3.58
2	4-NH_2	4.74	4.67	−1.30	3.21
3	2-NH_2	4.72	4.67	−1.30	3.21
4	4-NHMe	4.66	4.58	−1.81	3.67
5	4-Me	3.82	3.84	−0.31	3.31
6	3-NH_2	3.72	3.82	−0.16	3.21
7	4-NHCOMe	3.70	3.17	−0.60	4.17
8	4-OH[a]	3.30	4.61	−0.92	3.00
9	2-NHCOMe	2.68	3.17	−0.60	4.17
10	2,6-di-Me,4-NHCOMe	2.66	2.68	−1.22	5.10
11	H[a]	2.62	4.08	0.00	2.84

[a] Data points not included in deriving equation.

I_{50} for DNA replication by phenols in chinese hamster ovary cells V79 (Table 69)[72]

$$\log 1/C = -0.74(\pm 0.34)\sigma^+ - 1.02(\pm 0.41)\mathrm{CMR} + 6.98(\pm 0.16) \quad (74)$$

$$n = 9,\ r^2 = 0.915,\ s = 0.305,\ q^2 = 0.849$$

outliers: H; 4-OH

Again, not a sharp correlation but in line with the rat embryo results. The 4-OH congener, hydroquinone, is easily oxidized to quinone, which has its own type of toxicity.

At this point, a search of the literature on radical reactions in organic and biochemistry uncovered 25 examples of •H abstraction from simple phenols by various radicals. Twenty-three of these QSAR had negative σ^+ terms.[9] Besides these straight chemical reactions, a number of biochemical processes with such terms are known.[9] These results induced us to initiate work on rapidly growing cells using phenols as inhibitors. The logic behind the use of leukemia cells was that fast growing cells (like those of rat embryos or human embryos) produce large amounts of ROS (reactive oxygen species) that could convert phenols to radicals that could attack DNA. Our first results yielded the following equation.[73]

I_{50} for leukemia cells by phenols and estrogens

$$\log 1/C = -0.83(\pm 0.18)\sigma^+ - 0.74(\pm 0.28)(\sigma^+)^2 + 0.56(\pm 0.15)\log P - 0.45(\pm 0.21)\log(\beta \times 10^{\log P}+1) + 2.70(\pm 0.26) \quad (75)$$

$$n = 39,\ r^2 = 0.913,\ s = 0.229,\ q^2 = 0.895$$

optimum $\log P = -0.18$

outliers: 4-C_2H_5, 3-NH_2

$$\log \beta = -2.28$$

These days, in which few seem to be concerned about mechanism, many would be satisfied with this result as it covers simple phenols up to nonylphenol. Also well correlated are the estrogenic phenols, bisphenol A, estradiol, and diethylstilbestrol (DES). However, it is hard to interpret an inverted parabolic σ^+ relationship coupled with more typical bilinear terms for log *P*. After considerable thought and experimenting with the data, we found that two different types of toxicity are involved and split the data as follows to yield a far more satisfying result.[73]

I_{50} for leukemia cells by phenols with electron-withdrawing substituents[73]

$$\log 1/C = 0.62(\pm 0.16)\log P + 2.35(\pm 0.31) \quad (76)$$

$$n = 15,\ r^2 = 0.845,\ s = 0.232,\ q^2 = 0.800$$

outlier: 3-OH

I_{50} for leukemia cells by phenols with electron-releasing substituents[73]

$$\log 1/C = -1.58(\pm 0.26)\sigma^+ + 0.21(\pm 0.06)\log P + 3.10(\pm 0.24) \quad (77)$$

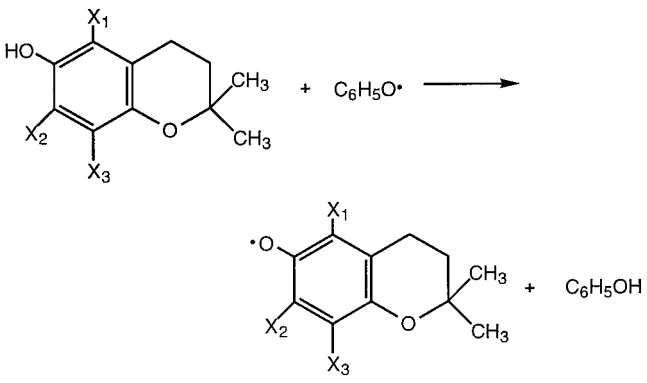
$$n = 23,\ r^2 = 0.898,\ s = 0.191,\ q^2 = 0.868$$

omitted: 3-NH_2, 4-$NHCOCH_3$

Equation 76 is very similar to scores of QSAR describing nonspecific toxicity to all sorts of biological systems. We believe that the ROS (or possibly an enzyme) that abstracts •H from the phenolic OH is a weak one (possibly superoxide) whose action is blocked by electron-withdrawing substituents (eq 76) but promoted by electron-releasing substituents that can assist radical formation. After finding that the environmental estrogens octyl and nonyl phenols were well fit by eq 77, bisphenol A, estradiol, and diethylstilbestrol were tested and found to conform to eq 77. An example that illustrates our thinking from mechanistic organic chemistry is QSAR 78 from the data of Mukai et al. (Table 70).[74]

Table 70. Rate of Radical Reaction with α-Tocopherol Analogs[74]

		log k			
no.	compounds	obsd	calcd (eq 78)	σ	B1, X_3
1	A-TOC-model	3.62	3.67	−0.41	1.52
2	B-TOC-model	3.35	3.32	−0.24	1.52
3	G-TOC-model	3.32	3.32	−0.24	1.52
4	D-TOC-model	3.00	2.98	−0.07	1.52
5	TOC-model-1	2.61	2.68	0.00	1.00
6	TOC-model-2	3.13	3.09	−0.20	1.00
7	TOC-model-3	3.30	3.37	−0.34	1.00
8	TOC-model-4	3.28	3.29	−0.30	1.00
9	TOC-model-5	3.45	3.29	−0.30	1.00
10	TOC-model-6	3.37	3.43	−0.37	1.00



$$\log k = -2.01(\pm 0.49)\sigma + 0.30(\pm 0.24)\mathrm{B1,X_3} + 2.38(\pm 0.32) \quad (78)$$

$$n = 10,\ r^2 = 0.935,\ s = 0.080,\ q^2 = 0.860$$

In this equation, $B1,X_3$ is the sterimol parameter for substituents X_3. Its positive coefficient suggests that substituents in this position, along with the 2-methyl groups, shield the ring oxygen from hydrogen bonding with the aqueous solvent and thus free the π electrons for radical stabilization. It is of interest that diorthosubstitution ($X_1 + X_2$) does not require a steric parameter.

It was also found that the phenolic activity on leukemia cells could be well fit by using the HOMO−LUMO gap parameter[75] yielding a slightly better correlation than eq 77 and having an equivalent coefficient with log P as eq 77.[75] The next step was to use MO-calculated relative ($H = 0$) homolytic bond dissociation energies (BDE) for the following type of reaction (Table 71).[76]

$$\mathrm{X{-}C_6H_4OH + C_6H_5O^{\bullet} \rightarrow X{-}C_6H_4O^{\bullet} + C_6H_5OH}$$

$$\log 1/C = -0.19(\pm 0.02)\mathrm{BDE} + 0.21(\pm 0.03)\log P + 3.11(\pm 0.10) \quad (79)$$

$$n = 52,\ r^2 = 0.920,\ s = 0.202,\ q^2 = 0.909$$

This equation is satisfying from a number of viewpoints. The log P coefficient and the intercept are the same as those in eq 77. BDE is better than σ^+ in eq 77 (in part, this is due to the fact that σ^+ had to be estimated for the complex phenols in Table 71), and of course, BDE speaks directly to the role of phenoxy radicals as illustrated in eq 78. This correlation covers a number of ortho-substituted phenols as well as three more estrogens: estriol, equilin, equilenin. It is of *particular interest* for this review that molecules containing an ortho substituent did not require a log P or a steric parameter value to fit eq 79 (i.e., log P was set to zero) yet they are well fit by eq 79.

This is well established by eq 80.[76] QSAR for ortho-substituted phenols acting on L1210 cells (data in Table 71)

$$\log 1/C = -0.17(\pm 0.03)\mathrm{BDE} + 3.18(\pm 0.16) \quad (80)$$

$$n = 14,\ r^2 = 0.936,\ s = 0.191,\ q^2 = 0.915$$

The slope and intercept as well as the quality of fit are very close to eq 79, and adding a term in log P or a steric parameter does not improve the result.

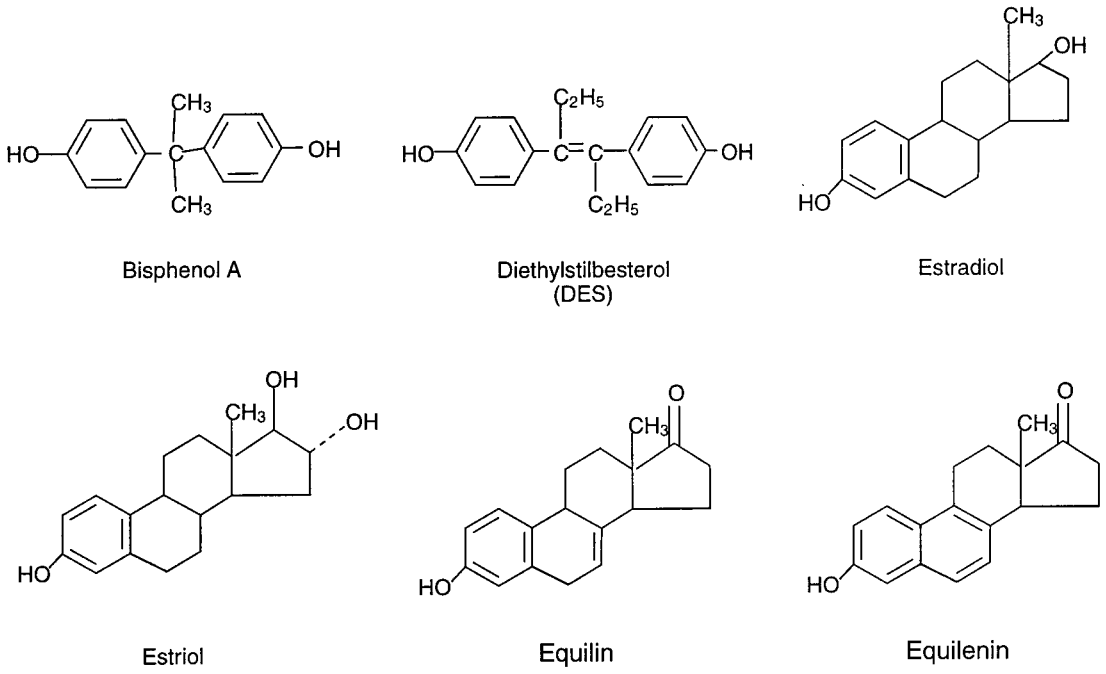
Since the phenols with electron-releasing functions are estrogenic (cause malformation of the fetus[77]) and are also carcinogenic,[78,79] we assume that they are converted to radicals, by the ROS from fast growing cells, that attack the DNA. This is a two-step process: the first step being governed by σ^+ or BDE and the second step being under the influence of a hydropho-

Table 71. I_{50} Activity of Phenols against L1210 Leukemia Cells[76]

		log 1/C			
no.	substituents	obsd	calcd (eq 79)	log P	BDE
1	4-OMe	4.48	4.49	1.34	−5.97
2	4-OC_2H_5	4.64	4.65	1.81	−6.28
3	4-OC_3H_7	4.85	4.74	2.33	−6.17
4	4-OC_4H_9	5.20	4.86	2.90	−6.22
5	4-OC_6H_{13}	5.50	5.14	4.22	−6.21
6	H	3.27	3.41	1.47	0.00
7	4-NO_2[a]	3.45	2.66	1.91	4.52
8	4-Cl[a]	4.29	3.90	2.39	−1.61
9	4-I	3.86	4.08	2.91	−2.01
10	4-CHO	3.08	2.91	1.35	2.55
11	4-F	3.83	3.82	1.77	−1.86
12	4-NH_2	5.09	4.86	0.04	−9.39
13	4-OH	4.59	4.39	0.59	−6.24
14	4-Me	3.85	3.97	1.94	−2.50
15	4-C_2H_5	3.86	4.06	2.47	−2.35
16	4-NHCOMe[a]	3.73	4.00	0.51	−4.22
17	4-CN[a]	3.44	3.05	1.60	2.10
18	4-OC_6H_5	4.97	4.68	3.35	−4.73
19	bisphenolA	4.07	4.30	3.32	−2.70
20	4-Br[a]	4.20	3.95	2.59	−1.63
21	4-CMe_3	4.09	4.29	3.31	−2.66
22	3-NO_2[a]	3.48	2.94	2.00	3.14
24	3-NHCOMe	2.65	2.76	0.73	2.67
25	3-Cl[a]	3.87	3.37	2.50	1.39
26	3-CMe_3	3.88	3.74	3.05	−0.02
27	3-Me	3.54	3.65	1.96	−0.74
28	3-OMe	3.71	3.67	1.58	−1.29
29	3-NMe_2[a]	4.11	3.71	1.56	−1.49
30	3-C_2H_5	3.71	3.66	2.40	−0.27
31	3-Br[a]	3.82	3.46	2.63	1.02
32	3-CN	3.11	2.88	1.70	3.12
33	3-F	3.46	3.35	1.93	0.83
34	3-OH	3.46	3.36	0.80	−0.45
35	3-NH_2[a]	4.11	3.42	0.21	−1.46
36	2-Me	3.52	3.66	0.00	−3.01
37	2-Cl	3.22	3.06	0.00	0.25
38	2-F	3.20	3.03	0.00	0.42
39	2-OMe	3.78	3.72	0.00	−3.29
40	2-C_2H_5	3.75	3.31	0.00	−1.10
41	2-OH	4.92	4.99	0.00	−10.17
42	2-OH,4-Me	5.03	5.33	0.00	−12.00
43	2-NH_2	5.16	5.30	0.00	−11.82
44	2-CN[a]	3.30	2.49	0.00	3.31
45	2-NO_2[a]	3.34	1.06	0.00	11.01
46	2-Br[a]	3.44	2.95	0.00	0.83
47	2-CMe_3	4.00	3.81	0.00	−3.78
48	4-C_3H_7	4.04	4.19	3.00	−2.47
49	4-C_4H_9	4.33	4.33	3.64	−2.50
50	4-C_5H_{11}	4.47	4.42	4.06	−2.53
51	4-C_8H_{17}	4.62	4.76	5.68	−2.55
52	4-$CONH_2$[a]	2.48	2.94	0.33	1.24
53	4-SO_2NH_2	2.50	2.94	0.06	0.95
54	4-C_7H_{15}	4.49	4.66	5.15	−2.60
55	4-C_9H_{19}	4.75	4.86	6.21	−2.48
56	diethyl stilbesterol	4.68	4.65	5.07	−2.63
57	β-estradiol	4.34	4.28	4.01	−1.83
58	etoposide[a]	6.81	3.56	0.60	−1.77
59	caffeic acid[a]	4.32	5.32	1.13	−10.67
60	quercetin[a]	4.00	5.27	2.06	−9.36
61	estrone[a]	-	3.99	3.13	−1.28
62	equilin	4.10	3.99	2.90	−1.52
63	estriol	4.01	3.84	2.45	−1.19
64	equilenin	4.60	4.43	3.12	−3.65
65	2-naphthol	3.82	4.28	2.70	−3.28
66	2-I[a]	3.95	3.18	0.00	−0.41
67	2-SMe	3.70	3.67	0.00	−3.03
68	2-$CHMe_2$	3.50	3.63	0.00	−2.84
69	2-CH_2CHMe_2	3.90	3.73	0.00	−3.36
70	2-CH_2OH	2.70	3.00	0.00	0.59
71	2-C_3H_7	3.49	3.56	0.00	−2.45
72	2-CF_3[a]	3.22	2.67	0.00	2.35
73	2-$NHCONH_2$[a]	3.50	4.95	0.00	−9.95
74	2-OC_2H_5	3.25	3.51	0.00	−2.20

[a] Data points not included in deriving equation.

Chart 1



bic interaction (except for ortho-substituted phenols). The para substituents seem to contact a large hydrophobic region since the phenols of Chart 1 as well as octyl and nonyl phenol are all well fit by eq 79. What is surprising about the ortho-substituted phenols is that substituents cause no steric effects. Trying steric terms in eq 80 did not improve the result. It would seem that a very slight nudge by the ortho group produces a QSAR that lacks a hydrophobic term or that the DNA could be hit in another position. The nature of the hydrophobic binding surface is hard to picture. We have observed that entities binding to a more or less flat surface produce QSAR with log P or π coefficients of about 0.5, while engulfment into a crevice or pocket yields values of about 1.[3] It may be that the character of our surface is more significant than its shape. Ortho-substituted phenols are not the only substances yielding a QSAR without a hydrophobic term. A study of a set of thiophenols acting on the leukemia cells yields a QSAR with only a negative σ^+ term.[80] We are now exploring other potential radical-forming functions. A few years ago, we could not understand why phenol was not mutagenic in the Ames test or carcinogenic while simply adding a 4-OMe function yielded a carcinogenic substance.[79] This is now clear since 4-OCH_3 has a large negative σ^+ of -0.72. Equation 79 now helps us understand why the drug Premarin can cause cancer in postmenopausal women. The amount of female hormones in a woman must somehow be controlled or detoxified or cancer may result. No doubt the elements in the body that control ROS radicals keep things under control. A proper diet rich in antioxidants would also seem to help. Strange as it may seem, the study of phenols acting on cancer cells may open a path for better understanding of two important classes of toxicity.

The kind of toxicity we are considering does not show up even with phenols containing strong electron-releasing substituents in short-term whole animal tests.

Table 72. LD_{50} of Phenols to Mice[81]

		log 1/C		
no.	substituents	obsd	calcd (eq 81)	Clog P
1	H	2.41	2.40	1.48
2	4-Cl	2.59	2.85	2.49
3	2-Cl	2.74	2.70	2.16
4	2,4-di-Cl	3.03	3.06	2.96
5	2-Br	2.69	2.79	2.36
6	2-C_2H_5	2.85	2.86	2.50
7	4-C_2H_5	2.95	2.86	2.50
8	4-NO_2	2.60	2.57	1.85
9	4-I	3.15	3.03	2.90
10	2,4-di-Me	2.82	2.84	2.47
11	3,5-di-Me	2.89	2.84	2.47
12	4-C_6H_5	3.10	3.24	3.36
13	2-F	2.32	2.51	1.72
14	4-F	2.56	2.59	1.92
15	2-Me	2.64	2.62	1.97
16	2-Br,4-Me	2.98	3.01	2.85
17	4-C_3H_7	3.24	3.09	3.03
18	4-CMe_3	3.28	3.21	3.30
19	2-CMe_3	3.26	3.12	3.10
20	2-SC_4H_9	3.37	3.35	3.62
21	4-SC_4H_9	3.35	3.35	3.62
22	2-CMe_3,4-Me[a]	3.06	3.34	3.60
23	4-CMe_3,2-Me	3.31	3.34	3.60
24	4-Br	2.79	2.92	2.64
25	2-Cl,4-NO_2[a]	3.34	2.78	2.33
26	3-OH	2.10	2.10	0.81
27	4-OMe	2.67	2.44	1.57
28	2-NO_2	2.57	2.57	1.85

[a] Data points not included in deriving equation.

LD_{50} of phenols to mice (Table 72)[81]

$$\log 1/C = 0.45(\pm 0.06)\text{Clog } P + 1.74(\pm 0.16) \quad (81)$$

$$n = 26,\ r^2 = 0.905,\ s = 0.107,\ q^2 = 0.890$$

outliers: 2-CMe_3, 4-Me; 2-Cl, 4-NO_2

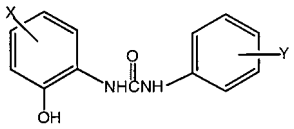
In the above equation, derived from data of Biagi et

Table 73. I_{50} of Peroxidation of Lipids by XVIII[82]

	substituents		log 1/C				
no.	X	Y	obsd	calcd (eq 82)	σ^+	I_{COOR}	$F_{X,2}$
1	4-OMe	H	6.37	6.35	−0.78	0.00	0.00
2	3-OMe	H	5.22	5.27	0.12	0.00	0.00
3	2-OMe	H	5.55	5.53	−0.78	0.00	0.29
4	4-OC_8H_{17}	H	6.43	6.39	−0.81	0.00	0.00
5	4-SMe	H	6.09	6.14	−0.60	0.00	0.00
6	2-Me,4-OMe	H	6.41	6.70	−1.09	0.00	0.01
7	2-C_2H_5,4-OMe	H	6.55	6.71	−1.08	0.00	0.00
8	2-CMe_3,4-OMe	H	6.85	6.72	−1.04	0.00	−0.02
9	2-C_8H_{17},4-OMe	H	6.36	6.73	−1.07	0.00	−0.01
10	2,4-di-OMe	H	6.60	6.46	−1.56	0.00	0.29
11	2-OC_8H_{17},4-OMe	H	6.52	6.50	−1.59	0.00	0.29
12	2-OMe,4-OC_8H_{17}	H	6.48	6.50	−1.59	0.00	0.29
13	2,3,4-tri-OMe	H	6.19	6.32	−1.44	0.00	0.29
14	4-OMe	3-CF_3	6.52	6.35	−0.78	0.00	0.00
15	4-OMe	3-COOH	5.00	5.05	−0.78	1.00	0.00
16	4-OMe	4-Me	6.51	6.35	−0.78	0.00	0.00
17	4-OMe	4-CH=CHCOOH	5.19	5.05	−0.78	1.00	0.00
18	4-OMe	4-Cl	6.36	6.35	−0.78	0.00	0.00
19	4-OMe	4-OMe	6.23	6.35	−0.78	0.00	0.00
20	4-OMe	4-$OCH_2CO_2C_2H_5$	4.95	5.05	−0.78	1.00	0.00
21	2-CMe_3,4-OMe	4-NMe_2	6.89	6.72	−1.04	0.00	−0.02
22	2-CMe_3, 4-OMe	4-$O(CH_2)_3N(C_4H_9)_2$	6.85	6.72	−1.04	0.00	−0.02
23	2-CMe_3,4-OMe	2,6-di-$CHMe_2$	6.80	6.72	−1.04	0.00	−0.02
24	2-CMe_3, 4-OMe	2,4-di-F	6.82	6.72	−1.04	0.00	−0.02

al.,[81] both electron-attracting substituents (4-NO_2) and electron-releasing substituents (4-OH, 4-OMe) are well fit. Nor does the σ^+ type of toxicity show up in cells such as *T. pyriformis* (a protozoa) that is often used to assess the toxicity of xenobiotics. The toxicity we are considering is that mediated by damaged DNA which may be slow to appear in whole organisms. In the case of *T. pyriformis*, some other type of toxicity (e.g., membrane deformation) may take precedence.

Another σ^+ action of phenols coming from a study by Nakao et al.[82] is of interest. They studied the antioxidant activity of XVIII.



XVIII

Activity was defined as the ability to inhibit lipid peroxidation in homogenized rat brain. The lipid peroxidation level in the incubated homogenate was measured as the amount of malonaldehyde formed by peroxidation of unsaturated lipids (IC_{50}). The authors derived[82] an equation with a rather unusual electronic parameter. We have reformulated[83] their results using σ^+ to obtain eq 82 (Table 73).[82]

$$\log 1/C = -1.20(\pm 0.23)\sigma^+ - 2.85(\pm 0.68)F_{X,2} - 1.31(\pm 0.20)I_{COOR} + 5.42(\pm 0.21) \quad (82)$$

$$n = 24,\ r^2 = 0.944,\ s = 0.153,\ q^2 = 0.926$$

outlier: one example where the OH in XVIII was converted to OCH_3

$F_{X,2}$ is the field/inductive parameter for ortho substituents (ortho to the OH). This type of parametrization has often been found useful for ortho substitution where σ or σ^+ is the normal para value.[84] F accounts for the extra electronic effect of substituents being close to the reaction center. The indicator variable I takes the value of 1 for three examples where there was a substituent on the Y ring. Equation 82 suggests that the HO of XVIII donates $^\bullet$H to inhibit lipid peroxidation. No doubt this occurs by breaking the radical chain progress.

$$ROO^\bullet + RH \rightarrow ROOH + R^\bullet$$

$$R^\bullet + O_2 \rightarrow ROO^\bullet$$

Again, we see in QSAR 82 no hydrophobic term. The authors supplied us with a set of XVIII derivatives to test in our system (L1210 cells), and we found no significant correlation[85] which brings out the difference in the two systems. Their equation had $r^2 = 0.902$; including the point that we omitted, ours had $r^2 = 0.944$. The conclusion from eq 82 is that in our leukemia cells, lipid peroxidation is not a factor to be considered.

VII. Aromatic Nitro Compounds

The aromatic nitro group is one of the most commonly studied substituents in SAR work. In our current database of 7300 sets, 1821 contain one or more aromatic nitro derivatives. This is despite the fact that the nitro function is one of the most slippery to deal with. It activates halogens so that they easily undergo nucleophilic displacement. Worse yet, it is readily reduced in vivo to hydroxylamine, which can yield nitrenium derivatives (e.g., $C_6H_5-NHOSO_3^-$). Equation 83 was derived from data of Tatsumi et al.[86]

Table 74. Reduction of X−$C_6H_4NO_2$ by Xanthine Oxidase[86]

		log *k*			
no.	substituents	obsd	calcd (eq 83)	σ^-	$B5_2$
1	4-NH_2	1.36	1.16	−0.63	1.00
2	4-OMe	1.42	1.53	−0.26	1.00
3	4-OH	1.46	1.42	−0.37	1.00
4	4-SH	1.46	1.93	0.15	1.00
5	4-Me	1.46	1.61	−0.17	1.00
6	4-SO_3-[a]	1.58	2.35	0.58	1.00
7	H	1.68	1.78	0.00	1.00
8	4-C_6H_5	1.78	1.80	0.02	1.00
9	4-CH_2Cl	1.80	1.90	0.12	1.00
10	4-CH_2OH	1.89	1.86	0.08	1.00
11	4-COO^-	1.90	2.09	0.31	1.00
12	4-Cl	2.20	1.97	0.19	1.00
13	4-Br	2.23	2.03	0.25	1.00
14	4-SO_2NH_2[a]	2.25	2.71	0.94	1.00
15	4-CN	2.68	2.77	1.00	1.00
16	4-$CONH_2$	2.71	2.38	0.61	1.00
17	4-COOMe	2.72	2.52	0.75	1.00
18	4-NO2	2.80	3.03	1.27	1.00
19	4-COMe	2.82	2.61	0.84	1.00
20	4-CHO	2.84	2.79	1.03	1.00
21	4-COC_6H_5	2.85	2.60	0.83	1.00
22	3-Cl	1.84	2.15	0.37	1.00
23	2-Cl	1.64	1.69	0.19	1.80
24	3-CHO	2.16	2.13	0.35	1.00
25	2-CHO[a]	1.92	2.32	1.03	2.36
26	3-NO_2	2.29	2.48	0.71	1.00
27	2-NO_2	2.53	2.53	1.27	2.44
28	3-NH_2	1.80	1.62	−0.16	1.00
29	2-NH_2	0.85	0.82	−0.63	1.97

[a] Data points not included in deriving equation.

Reduction rate of X−$C_6H_4NO_2$ by xanthine oxidase (Table 74)[86]

$$\log k = 0.98(\pm 0.16)\sigma^- - 0.35(\pm 0.23)B5_2 + 2.13(\pm 0.27) \quad (83)$$

$$n = 26,\ r^2 = 0.884,\ s = 0.201,\ q^2 = 0.865$$

outliers: 4-SO_3^-; 4-SO_2NH_2; 2-CHO

No hydrophobic term occurs in eq 83. The negative sterimol parameter applies to ortho substituents.

The above reduction rate can be compared with eq 84 for the radical reduction rate of aromatic nitro compounds.

Table 75. Reduction of 4-X−$C_6H_4NO_2$ by $CH_3C^{\bullet}HOH$ in N_2O-Saturated Aqueous Solution[87]

		log *k*		
no.	X	obsd	calcd (eq 84)	σ^-
1	NO_2	9.38	9.33	1.27
2	CN	9.08	9.10	1.00
3	SO_2NH_2	8.90	9.05	0.94
4	CHO	9.26	9.13	1.03
5	CF_3	8.63	8.81	0.65
6	COMe	9.00	8.97	0.84
7	CO_2Me	8.93	8.89	0.75
8	SO_3^-	8.78	8.75	0.58
9	$CONH_2$	8.63	8.77	0.61
10	CO_2^-	8.77	8.52	0.31
11	H[a]	8.52	8.26	0.00
12	Me	8.18	8.11	−0.17
13	OMe	8.04	8.04	−0.26
14	OH	7.85	7.94	−0.37

[a] Data point not included in deriving equation.

Reduction of 4-X−$C_6H_4NO_2$ by $CH_3C^{\bullet}HOH$ in N_2O saturated aqueous solution (Table 75)[87]

$$\log k = 0.85(\pm 0.15)\sigma^- + 8.26(\pm 0.11) \quad (84)$$

$$n = 13,\ r^2 = 0.932,\ s = 0.125,\ q^2 = 0.911$$

outlier: H

A radical reduction has also been shown with X−$C_6H_4NO_2$ with aqueous pyrimidine plus H_2O_2 (Table 76).[88]

Table 76. Radical Reduction of X−$C_6H_4NO_2$ with Aqueous Pyrimidine Plus H_2O_2[88]

		log *k*		
no.	substituent	obsd	calcd (eq 85)	σ^-
1	NO_2	1.66	1.39	1.27
2	CN	1.08	1.11	1.00
3	SO_2NH_2	0.83	1.04	0.94
4	COMe	0.86	0.94	0.84
5	COOMe	0.81	0.84	0.75
6	$CONH_2$	0.68	0.70	0.61
7	Cl	0.34	0.26	0.19
8	SO_3^-	0.59	0.67	0.58
9	CH_2OH	0.15	0.14	0.08
10	H	0.08	0.06	0.00
11	Me	−0.05	−0.12	−0.17
12	OMe	−0.16	−0.22	−0.26
13	NH_2	−0.68	−0.61	−0.63

$$\log k = 1.05(\pm 0.13)\sigma^- + 0.06(\pm 0.09) \quad (85)$$

$$n = 13,\ r^2 = 0.965,\ s = 0.120,\ q^2 = 0.944$$

omitted: SO_3H and CH═NOH, for lack of σ^- values

Table 77. Hydrogenation of X−$C_6H_4NO_2$ in Dioxan with Pt-Coated Silica Gel[89]

		log *k*		
no.	substituent	obsd	calcd (eq 86)	σ^-
1	4-COMe	1.56	1.57	0.84
2	4-Cl	1.10	1.03	0.19
3	H[a]	1.55	0.88	0.00
4	4-Me	0.79	0.74	−0.17
5	4-OMe	0.49	0.66	−0.26
6	4-NH_2	0.42	0.36	−0.63

[a] Data point not included in deriving the equation.

Hydrogenation of X−$C_6H_4NO_2$ in Dioxan with Pt coated silica gel (Table 77)[89]

$$\log k = 0.83(\pm 0.33)\sigma^- + 0.87(\pm 0.16) \quad (86)$$

$$n = 5,\ r^2 = 0.955,\ s = 0.115,\ q^2 = 0.908$$

outlier: H

Equations 83−86 suggest a common mechanism of radical reduction that is quite similar to the following in vivo reactions.

Thus, the rate of catalytic hydrogenation also falls in line with the other radical mechanisms. We also have examples of reduction in chemical systems correlated by σ^+, no doubt a collinearity problem. It is noteworthy, however, that all of the bio QSAR are

correlated by σ^-. Some discussion of the lack of importance of hydrophobic effects in the toxicity of aromatic nitro compounds has been reported.[86] Despite a large amount of work on the toxicity of aromatic nitro compounds, studies of carefully selected sets with simple substitution are lacking.

Equations 87 and 88 from studies by Zhao et al. are of particular interest.[90]

Table 78. Toxicity to Photobacterium Phosphoreum by Aromatic Nitro Compounds[91]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 87)	σ^-
1	1-NO_2,3,4-di-Cl	4.12	4.47	1.65
2	1-NO_2,3-Cl,4-F	3.68	4.14	1.43
3	1-NO_2,4-Cl	3.94	4.18	1.46
4	1-NO_2,3-Cl	4.05	4.18	1.46
5	1-NO_2,4-Br	4.68	4.28	1.52
6	1,3-di-NO_2,4-Br[a]	5.00	6.20	2.79
7	1,4-di-NO_2	5.84	5.82	2.54
8	1,3-di-NO_2[a]	4.93	5.82	2.54
9	1,2-di-NO_2	6.03	5.82	2.54
10	NO_2	3.82	3.90	1.27
11	1-Me,4-NO_2	3.90	3.64	1.10
12	1-Me,3-NO_2	3.74	3.64	1.10
13	1-Me,2-NO_2	3.91	3.64	1.10

[a] Data points not included in deriving equation.

EC_{50} toxicity to Photobacterium phosphoreum by aromatic nitro compounds (Table 78)[91]

$$\log 1/C = 1.52(\pm 0.41)\sigma^- + 1.97(\pm 0.66) \quad (87)$$

$$n = 11,\ r^2 = 0.888,\ s = 0.294,\ q^2 = 0.846$$

outliers: 1,3-di-NO_2, 4-Br; 1,3-di-NO_2

Table 79. Acute Toxicity of Aromatic Nitro Compounds to Fathead Minnows[92]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 88)	σ^-
1	3,4-di-Cl[a]	4.12	4.66	0.56
2	4-Cl	3.94	4.13	0.19
3	3-Cl	4.05	4.39	0.37
4	4-Br[a]	4.68	4.21	0.25
5	3-NO_2,4-Br	5.00	5.24	0.96
6	4-NO_2	5.84	5.69	1.27
7	3-NO_2	4.93	4.88	0.71
8	2-NO_2	6.03	5.69	1.27
9	H	3.82	3.85	0.00
10	2-Me,5-NO_2	4.49	4.63	0.54
11	2-Me,3-NO_2	4.44	4.63	0.54
12	4-Me	3.90	3.61	−0.17
13	3-Me	3.74	3.75	−0.07
14	2-Me	3.91	3.61	−0.17

[a] Data points not included in deriving equation.

LC_{50} 96 h acute toxicity of aromatic nitro compounds to fathead minnows (Table 79)[92]

$$\log 1/C = 1.44(\pm 0.31)\sigma^- + 3.85(\pm 0.21) \quad (88)$$

$$n = 12,\ r^2 = 0.914,\ s = 0.242,\ q^2 = 0.866$$

outliers: 3,4-di-Cl; 4-Br

The shape of these two equations resembles eq 85 and 86, as does eq 89.

Table 80. Toxicity of Nitrobenzenes to *Daphnia magna*[90]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 89)	σ^-
1	1-NO_2,3,4-di-Cl	4.23	4.24	1.65
2	1-NO_2,3-Cl,4-F	4.01	4.02	1.43
3	1-NO_2,4-Cl	3.98	4.05	1.46
4	1-NO_2,3-Cl	3.92	4.05	1.46
5	1-NO_2,4-Br[a]	4.72	4.11	1.52
6	1,3-di-NO_2,4-Br	5.45	5.35	2.79
7	1,4-di-NO_2	5.12	5.11	2.54
8	1,3-di-NO_2[a]	4.20	5.11	2.54
9	1,2-di-NO_2	5.07	5.11	2.54
10	1-NO_2	3.53	3.86	1.27
11	1-Me,4-NO_2[a]	4.33	3.70	1.10
12	1-Me,3-NO_2	3.82	3.70	1.10
13	1-Me,2-NO_2	4.04	3.70	1.10

[a] Data points not included in deriving equation.

I_{50} toxicity of nitrobenzenes to Daphnia magna (Table 80)[90]

$$\log 1/C = 0.98(\pm 0.22)\sigma^- + 2.62(\pm 0.41) \quad (89)$$

$$n = 10,\ r^2 = 0.927,\ s = 0.186,\ q^2 = 0.888$$

outliers: 1-NO_2, 4-Br; 1-Me, 4-NO_2; 1,3-di-NO_2

Table 81. LD_{50} of X−C_6H_4−NO_2 to Fathead Minnow[93]

		log 1/*C*			
no.	substituent	obsd	calcd (eq 90)	σ^-	L_3
1	2-Me	3.57	3.74	−0.17	2.06
2	3-Me	3.63	3.58	−0.07	2.87
3	4-Me	3.76	3.74	−0.17	2.06
4	2-NO_2	5.45	5.32	1.27	2.06
5	3-NO_2	4.38	4.25	0.71	3.44
6	4-NO_2	5.22	5.32	1.27	2.06
7	2-NO_2,3-Me	5.01	4.98	1.20	2.87
8	2-Me,5-NO_2	3.75	4.06	0.54	3.44
9	3-Me,4-NO_2	5.15	4.98	1.20	2.87
10	2-Me,3-NO_2	3.99	4.06	0.54	3.44
11	2-NO_2,5-Me	5.08	5.25	1.20	2.06
12	3-NO_2,5-Me	3.91	4.17	0.64	3.44
13	3,5-di-NO_2	5.29	5.03	1.42	3.44
14	3-Cl	3.94	3.85	0.37	3.52
15	H[a]	3.02	3.92	0.00	2.06
16	2-NH_2	3.70	3.23	−0.63	2.06
17	2-NH_2,5-NO_2	4.07	4.01	0.08	2.06
18	4-OH	3.36	3.52	−0.37	2.06
19	4-F	3.70	3.89	−0.03	2.06

[a] Data point not included in deriving equation.

LD_{50} of X−$C_6H_4NO_2$ to fathead minnow (Table 81)[93]

$$\log 1/C = 1.10(\pm 0.18)\sigma^- - 0.33(\pm 0.18)L_3 + 4.61(\pm 0.46) \quad (90)$$

$$n = 18,\ r^2 = 0.923,\ s = 0.211,\ q^2 = 0.881$$

outlier: H

Table 82. LD_{50} of $X-C_6H_4-NO_2$ to *Cyprinus carpio* (fish)[93]

		log 1/*C*				
no.	substituents	obsd	calcd (eq 91)	σ^-	$B5_3$	$B5_5$
1	4-Me	3.53	3.67	−0.17	1.00	1.00
2	2-NO_2	5.31	5.16	1.27	1.00	1.00
3	3-NO_2	4.07	4.13	0.71	2.44	1.00
4	4-NO_2	5.17	5.16	1.27	1.00	1.00
5	2-Me, 5-NO_2	3.83	3.96	0.54	2.44	1.00
6	2-Me, 3-NO_2	3.96	3.96	0.54	2.44	1.00
7	4-Cl	3.79	4.04	0.19	1.00	1.00
8	3-Cl	3.80	3.98	0.37	1.80	1.00
9	H[a]	3.12	3.84	0.00	1.00	1.00
10	3,4-di-Cl	4.48	4.18	0.56	1.80	1.00
11	2,5-di-Cl	4.54	4.66	0.56	1.00	1.80
12	2-Cl	3.79	4.04	0.19	1.00	1.00
13	3-NO_2, 4-Cl	5.35	5.19	0.90	1.00	2.44
14	2-NH_2[a]	3.93	3.19	−0.63	1.00	1.00
15	3-NH_2	3.35	3.38	−0.16	1.97	1.00
16	4-NH_2	3.48	3.19	−0.63	1.00	1.00
17	2-NH_2, 5-NO_2	4.25	4.34	0.08	1.00	2.44
18	2-OH	3.58	3.46	−0.37	1.00	1.00
19	3-OH	3.90	3.68	0.12	1.93	1.00

[a] Data points not included in deriving equation.

LD_{50} of $X-C_6H_4NO_2$ to Cyprinus carpio (fish) (Table 82)[93]

$$\log 1/C = 1.04(\pm 0.21)\sigma^- - 0.31(\pm 0.19)B5_3 + 0.29(\pm 0.23)B5_5 + 3.86(\pm 0.47) \quad (91)$$

$$n = 17,\ r^2 = 0.922,\ s = 0.197,\ q^2 = 0.871$$

outliers: H; 2-NH_2

Table 83. Binding of Nitrobenzenes to Hemoglobin in Wistar Rats[94]

		log HBI			
no.	substituents	obsd	calcd (eq 92)	σ^-	Clog *P*
1	4-Me	−0.37	−0.32	−0.17	2.38
2	4-C_2H_5	−0.92	−0.78	−0.19	2.91
3	4-C_6H_5[a]	2.25	0.23	0.02	3.77
4	H	1.78	1.22	0.00	1.89
5	4-F[a]	1.60	0.92	−0.03	2.03
6	4-Cl	2.33	2.17	0.19	2.60
7	4-Br	2.35	2.52	0.25	2.75
8	2-Me	−0.14	−0.27	−0.17	2.30
9	2-C_2H_5	−0.59	−0.73	−0.19	2.83
10	3-Me	0.01	0.41	−0.07	2.38
11	3,5-di-Me	−0.20	−0.40	−0.14	2.88
12	2-Cl[a]	0.32	2.30	0.19	2.40
13	3-Cl[a]	1.73	3.48	0.37	2.60
14	3-Cl, 4-F[a]	1.00	3.18	0.34	2.74
15	2,4-di-F	0.36	0.79	−0.06	1.87

[a] Data points not included in deriving equation.

Binding of nitrobenzenes to hemoglobin in wistar rats (Table 83)[94]

$$\log \text{HBI} = 7.28(\pm 1.69)\sigma^- - 0.60(\pm 0.70)\text{Clog } P + 2.36(\pm 1.74) \quad (92)$$

$$n = 10,\ r^2 = 0.940,\ s = 0.340,\ q^2 = 0.861$$

outliers: 4-C_6H_5; 4-F; 2-Cl; 3-Cl; 3-Cl, 4-F

Note: log HBI is the hemoglobin binding index.

Equations 87−91 present a uniform picture that is in line with eqs 83−85. Equation 92 is poor since five compounds had to be omitted. It is of interest that all attempts to find a positive hydrophobic effect were unsuccessful. The Clog *P* term is of marginal value and is in fact negative. The electronic term is interesting in that σ^- is essential. Using σ instead gives a much poorer correlation ($r^2 = 0.780$). Equation 92 may be of help in further such studies. Lymphocytes follow a pattern with the normal dependence on σ^-.

Table 84. I_{50} for Chromosome Aberration by Aromatic Nitro Compounds in Human Lymphocytes[95]

		log 1/*C*				
no.	substituents	obsd	calcd (eq 93)	I	σ^-	$B1_2$
1	3-NH_2	2.23	2.68	0	−0.16	1.00
2	4-OH	3.12	2.91	0	−0.37	1.00
3	4-Me	2.83	2.69	0	−0.17	1.00
4	4-NH_2[a]	4.03	3.18	0	−0.63	1.00
5	3-Cl,4-F	2.15	2.15	0	0.34	1.00
6	3-Cl,4-NH_2	3.06	2.79	0	−0.26	1.00
7	3-NO_2	4.89	4.93	1	0.71	1.00
8	4-NO_2	4.43	4.34	1	1.27	1.00
9	2-NO_2	3.67	3.90	1	1.27	1.70
10	2-Me,5-NO_2	5.03	4.79	1	0.54	1.52
11	2-Me	2.40	2.37	0	−0.17	1.52
12	3-Me	2.39	2.59	0	−0.07	1.00
13	2-NH_2,5-NO_2	5.32	5.38	1	0.08	1.35
14	2-Br,5-NO_2	4.17	4.07	1	0.96	1.95
15	2-OH,5-NO_2	5.13	5.11	1	0.34	1.35
16	H	2.15	2.51	0	0.00	1.00
17	3-Cl	2.47	2.12	0	0.37	1.00
18	2-Me,3-NO_2	4.66	4.79	1	0.54	1.52

[a] Data point not included in deriving equation.

I_{50} for chromosome aberration by aromatic nitro compounds in human lymphocytes (Table 84)[95]

$$\log 1/C = -1.06(\pm 0.40)\sigma^- + 3.18(\pm 0.44)I - 0.63(\pm 0.54)B1_2 + 3.14(\pm 0.60) \quad (93)$$

$$n = 17,\ r^2 = 0.965,\ s = 0.246,\ q^2 = 0.947$$

outlier: 4-NH_2

Adding a hydrophobic term to eq 93 does not improve it. The indicator variable *I* takes the value of 1 for dinitro congeners. These are exceptionally active.

Table 85. Two-Day I_{50} of Monosubstituted Nitrobenzenes to *T. pyriformis*[96]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 94)	Clog *P*
1	H	3.35	3.47	1.89
2	2-NH_2[a]	3.08	3.42	1.80
3	2-OH	3.77	3.45	1.85
4	2-Me	3.48	3.71	2.30
5	2-Cl	3.68	3.77	2.40
6	2-Br	3.86	3.86	2.55
7	2-CN[a]	4.08	2.96	1.02
8	2-CH_2OH	2.85	2.82	0.77
9	2-COOH[a]	1.36	3.11	1.27
10	2-C_6H_5	4.30	4.22	3.17
11	2-$CONH_2$	2.28	2.28	−0.14
12	2-CHO	3.17	3.41	1.78
13	2-NO_2[a]	4.25	3.32	1.63
14	3-NH_2	3.03	3.10	1.26
15	3-OH	3.51	3.45	1.85
16	3-Me	3.57	3.76	2.38
17	3-Cl	3.84	3.89	2.60
18	3-Br	4.22	3.97	2.75
19	3-CN	3.45	3.14	1.32
20	3-CH_2OH	2.78	2.86	0.85
21	3-COOH[a]	1.91	3.44	1.84
22	3-C_6H_5	4.57	4.57	3.77
23	3-$CONH_2$	2.81	2.81	0.76
24	3-CHO	3.14	3.25	1.50
25	3-NO_2[a]	3.76	3.32	1.63
26	3-OMe	3.67	3.60	2.10
27	3-COMe	3.32	3.24	1.49

[a] Data points not included in deriving equation.

Two-day I_{50} of monosubstituted nitrobenzenes to T. pyriformis (Table 85)[96]

$$\log 1/C = 0.59(\pm 0.08)\text{Clog } P + 2.37(\pm 0.17) \quad (94)$$

$$n = 21,\ r^2 = 0.922,\ s = 0.158,\ q^2 = 0.911$$

outliers: 2-NO_2; 3-NO_2; 2-NH_2; 2-CN; 2-COOH; 3-COOH

The dinitro compounds are more active than predicted as is the 2-CN compound. Of course, the two COOH groups are partially ionized and not expected to fit.

Table 86. MIC of Nitrobenzenes for Yeast, *S. cerevisiae*[97]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 95)	Mlog *P*
1	H	4.01	4.04	1.85
2	2-Cl	4.65	4.68	2.52
3	3-Cl	4.64	4.63	2.47
4	4-Cl	4.65	4.55	2.39
5	4-Br[a]	5.13	4.70	2.55
6	2-Me	4.52	4.47	2.30
7	3-Me	4.52	4.58	2.42
8	4-Me	4.50	4.53	2.37
9	3,4-di-Cl	5.20	5.24	3.12
10	2,4-di-Cl	5.24	5.21	3.09

[a] Data point not included in deriving equation.

MIC of nitrobenzenes for yeast, S. cerevisiae (Table 86)[97]

$$\log 1/C = 0.94(\pm 0.12)\text{Mlog } P + 2.30(\pm 0.30) \quad (95)$$

$$n = 9,\ r^2 = 0.981,\ s = 0.055,\ q^2 = 0.970$$

outlier: 4-Br

Equations 94 and 95 bring out a very important point. They suggest that in these examples only hydrophobicity counts and that the results of eq 83−85 do not apply. Only nonspecific toxicity is involved for yeast and protozoa. There are hundreds of such nonspecific examples, such as the following classic study by Klarmann et al. [98]

Table 87. Growth Inhibition of *M. tuberculosis* by Phenols[98]

		log 1/*C*		
no.	substituents	obsd	calcd (eq 96)	log *P*
1	4-Br	1.94	1.94	2.59
2	4-Br,2-Me	2.35	2.33	3.09
3	4-Br,2-Et	2.70	2.73	3.59
4	4-Br,2-Pr	3.18	3.12	4.09
5	4-Br,2-Bu	3.76	3.52	4.59
6	4-Br,2-amyl	3.99	3.91	5.09
7	4-Br,2-sec-amyl	3.54	3.75	4.89
8	4-Br,2-hexyl	4.26	4.30	5.59
9	4-Br,2-cyclohexyl	3.75	3.92	5.10
10	2-Br	1.78	1.75	2.35
11	2-Br,4-*tert*-amyl	3.39	3.25	4.25
12	2-Br,4-hexyl	4.11	4.11	5.35
13	2-Br,4-C_3H_7,3,5-di-Me	3.69	3.72	4.85
14	H	0.95	1.05	1.46

Growth inhibition of M. tuberculosis by phenols (Table 87)[98]

$$\log 1/C = 0.79(\pm 0.06)\log P - 0.10(\pm 0.25) \quad (96)$$

$$n = 14,\ r^2 = 0.986,\ s = 0.122,\ q^2 = 0.982$$

Thus, we see that the nitro group can cause problems in the construction of a data set for a QSAR analysis. It is often included since synthesis may be easy and it is a strong electron-attracting substituent. A better substituent of this type would be CN. Also, one must be careful in composing a set of nitro compounds. Dinitro derivatives are often outliers. Conjugated nitro plus halogen compounds also cause difficulties.

VIII. Acetophenones

A nice set of comparative examples comes from the reduction of acetophenones.

Table 88. Rate of Reduction of X−C_6H_4COMe by Amino Acid Reductase from Rabbit Kidney[99]

		log *k*			
no.	substituents	obsd	calcd (eq 97)	σ^+	Es_4
1	H	1.07	1.18	0.00	1.24
2	4-$COCH_3$	2.60	2.51	0.50	−1.28
3	4-NO_2	2.94	2.90	0.79	−1.28
4	4-$NHCOCH_3$	0.59	0.55	−0.60	0.63
5	3-OCH_3	1.63	1.25	0.05	1.24
6	3-NO_2	1.97	2.07	0.67	1.24
7	4-CH_3[a]	1.63	1.10	−0.31	0.00
8	4-OCH_3	0.20	0.29	−0.78	0.69
9	4-CF_3	2.50	2.63	0.61	−1.16
10	3-CH_3	0.97	1.09	−0.07	1.24

[a] Data point not included in deriving equation.

Rate of reduction of X−C_6H_4COMe by amino acid reductase from rabbit kidney (Table 88)[99]

$$\log k = 1.33(\pm 0.35)\sigma^+ - 0.27(\pm 0.17)Es_4 + 1.51(\pm 0.18) \quad (97)$$

$$n = 9,\ r^2 = 0.970,\ s = 0.191,\ q^2 = 0.943$$

outlier: 4-Me

Table 89. Reduction of X−C_6H_4COMe by Di-*tert*-butyl Peroxide in 2-Butanol[100]

		log k_{rel}		
no.	substituent	obsd	calcd (eq 98)	σ^+
1	3-CF_3	0.69	0.72	0.52
2	4-Cl	0.48	0.25	0.11
3	H	0.00	0.12	0.00
4	3-Me	−0.07	0.04	−0.07
5	4-Me	−0.23	−0.24	−0.31
6	4-OMe	−0.77	−0.79	−0.78
7	2,4-di-Me[a]	−0.74	0.12	0.00
8	2,4,6-tri-Me[a]	−1.30	0.12	0.00

[a] Data points not included in deriving equation.

Reduction of X−C_6H_4COMe by di-tert-butyl peroxide in 2-butanol (Table 89)[100]

$$\log k_{rel} = 1.16(\pm 0.41)\sigma^+ + 0.12(\pm 0.17) \quad (98)$$

$$n = 6,\ r^2 = 0.940,\ s = 0.143,\ q^2 = 0.902$$

outliers: ortho-substituted congeners; 2,4-di-Me; 2,4,6-tri-Me

The results from these two QSAR studies imply a radical mechanism of reduction.[9]

IX. Benzaldehydes

Reduction rates of benzaldehydes to benzyl alcohols.

Table 90. Reduction of X−C_6H_4CHO by Horse Liver Alcohol Dehydrogenase[101]

		log *k*		
no.	substituents	obsd	calcd (eq 99)	σ^+
1	4-NO_2[a]	1.81	2.83	0.79
2	4-Cl	1.90	2.05	0.11
3	H	1.99	1.92	0.00
4	Me	1.58	1.57	−0.31
5	OMe	1.18	1.03	−0.78
6	NMe_2	−0.10	−0.02	−1.70

[a] Data point not included in deriving equation.

Reduction of X−C_6H_4CHO by horse liver alcohol dehydrogenase (Table 90) [101]

$$\log k = 1.14(\pm 0.29)\sigma^+ + 1.92(\pm 0.25) \quad (99)$$

$$n = 5,\ r^2 = 0.981,\ s = 0.136,\ q^2 = 0.891$$

outlier: 4-NO_2

That the 4-NO_2 is an outlier as is to be expected from what we have learned about the behavior of aromatic NO_2 groups.

Table 91. Reduction of X−C_6H_4CHO by Human Kidney Aldehyde Reductase[102a]

		log k_{cat}/K_m		
no.	substituents	obsd	calcd (eq 100)	σ^+
1	4-NO_2	1.59	1.61	0.79
2	4-COO^-[a]	1.75	0.05	−0.02
3	4-Br	0.60	0.38	0.15
4	H	−0.10	0.09	0.00
5	4-F	−0.16	−0.05	−0.07
6	4-Me	−0.42	−0.51	−0.31

[a] Data point not included in deriving equation.

Reduction of X−C_6H_4CHO by human kidney aldehyde reductase (Table 91)[102a]

$$\log k_{cat}/K_m = 1.92(\pm 0.72)\sigma^+ + 0.09(\pm 0.28) \quad (100)$$

$$n = 5,\ r^2 = 0.960,\ s = 0.188,\ q^2 = 0.923$$

outlier: 4-COO^-

Table 92. Reduction of X−C_6H_4CHO by Alcohol Yeast Dehydrogenase[102b]

		log *k*		
no.	substituent	obsd	calcd (eq 100a)	σ^+
1	4-Br	0.48	0.41	0.15
2	4-Cl	0.30	0.32	0.11
3	H	−0.08	0.08	0.00
4	4-Me	−0.41	−0.59	−0.31
5	4-OMe	−1.68	−1.62	−0.78

Reduction of X−C_6H_4CHO by alcohol yeast dehydrogenase (Table 92)[102b]

$$\log k = 2.18\ (\pm 0.62)\sigma^+ + 0.084(\pm 0.24) \quad (100a)$$

$$n = 5,\ r^2 = 0.976,\ s = 0.152,\ q^2 = 0.915$$

Table 93. Reduction of X−C_6H_4CHO by Bovine Brain Aldehyde Reductase[102c]

		log k_{cat}		log $1/K_m$		
no.	substituent	obsd	calcd (eq 100b)	obsd	calcd (eq 100c)	σ^+
1	4-NO_2	1.85	1.76	5.22	5.36	0.79
2	3-Cl	1.64	1.58	5.15	5.01	0.37
3	4-COOH[a]	1.63	1.60	5.40	5.05	0.42
4	4-CN	1.56	1.70	5.30	5.25	0.66
5	3-OMe	1.51	1.47	4.57	4.79	0.12
6	H	1.36	1.42	4.77	4.69	0.00
7	4-Me	1.27	1.29	4.70	4.43	−0.31
8	4-OMe	1.10	1.08	3.85	4.03	−0.78

[a] Data point not included in deriving equation.

Reduction of X−C_6H_4CHO by bovine brain aldehyde reductase (Table 93)[102c]

$$\log k_{cat} = 0.43(\pm 0.17)\sigma^+ + 1.42(\pm 0.09) \quad (100b)$$

$$n = 7,\ r^2 = 0.898,\ s = 0.087,\ q^2 = 0.787$$

outlier: 4-COOH

$$\log 1/K_m = 0.85(\pm 0.39)\sigma^+ + 4.69(\pm 0.20) \quad (100c)$$

$$n = 7,\ r^2 = 0.864,\ s = 0.203,\ q^2 = 0.679$$

outlier: 4-COOH

In the case of eqs 100b and 100c, a reasonable correlation is not obtained with log k_{cat}/K_m. Equation 100 is similar to eq 99 (note confidence limits and σ^+); however, in the case of eq 100, 4-NO_2 is well fit.

The biological reduction QSAR can now be compared with one from mechanistic organic chemistry.

Table 94. Reduction in Dodecane of X−C_6H_4CHO by B-Octyl-9-borabicyclo[3.3.1]nonane(9-BBN)[103]

		log k_{rel}		
no.	substituent	obsd	calcd (eq 101)	σ^+
1	4-NO_2	0.83	0.82	0.79
2	4-CN	0.71	0.69	0.66
3	4-Cl	0.08	0.12	0.11
4	H	0.00	0.01	0.00
5	4-Me	−0.33	−0.31	−0.31
6	4-OMe	−0.75	−0.79	−0.78
7	4-NMe_2	−1.75	−1.74	−1.70

Reduction in dodecane of X−C_6H_4CHO by B-octyl-9-borabicyclo[3.3.1]nonan (9-BBN) (Table 94)[103]

$$\log k_{rel} = 1.03(\pm 0.04)\sigma^+ + 0.01(\pm 0.03) \quad (101)$$

$$n = 7,\ r^2 = 0.999,\ s = 0.032,\ q^2 = 0.998$$

The authors of eq 101 suggest that the mechanism first involves the addition of H^-. That this is reasonable for an anionic moiety can be seen from the following example.

Table 95. Addition of CN to X−C_6H_4CHO in Aqueous Solution at 25 °C[104]

		log k		
no.	substituent	obsd	calcd (eq 102)	σ^+
1	4-OMe	1.56	1.52	−0.78
2	4-Me	1.99	2.04	−0.31
3	H	2.32	2.38	0.00
4	3-OMe	2.46	2.51	0.12
5	4-Cl	2.56	2.50	0.11
6	3-Br	2.85	2.80	0.39

Addition of CN^- to X−C_6H_4CHO in aqueous solution at 25 °C (Table 95)[104]

$$\log k = 1.10(\pm 0.18)\sigma^+ - 2.38(\pm 0.07) \quad (102)$$

$$n = 6,\ r^2 = 0.986,\ s = 0.061,\ q^2 = 0.950$$

The value of ρ^+ in eq 102 is similar to those in eqs 97−101. The mechanism of attack that occurs by H^- with eqs 99 and 100 is not known, but it would be reasonable to assume addition of H^-. The same could be said for the reduction of the acetophenones. However, available data supports a radical mechanism[9] as for the acetophenones (eq 98).

X. Aromatic Amines

Aromatic amines provide examples without positive hydrophobic terms in the QSAR. An example is eq 72, which can be compared with eqs 103−109.

Table 96. Radical Oxidation of 4-X−$C_6H_4NH_2$ by Borate Radicals in Aqueous Solution[105,106]

		log k_2		
no.	substituent	obsd	calcd (eq 103)	σ^+
1	H	8.52	8.51	0.00
2	Cl	8.33	8.42	0.11
3	Br[a]	8.23	8.39	0.15
4	NO_2	7.88	7.85	0.79
5	F	8.61	8.57	−0.07
6	CH_3	8.79	8.77	−0.31

[a] Data point not included in deriving equation.

Rate of radical oxidation of 4-X−$C_6H_4NH_2$ by borate radicals in aqueous solution (Table 96)[105,106]

$$\log k_2 = -0.84(\pm 0.24)\sigma^+ + 8.51(\pm 0.09) \quad (103)$$

$$n = 5,\ r^2 = 0.977,\ s = 0.062,\ q^2 = 0.863$$

outlier: 4-Br

Table 97. Oxidation of X−C_6H_4 NH_2 by Vanadium V in 30% Acetic Acid−Water[107]

		log k_2		
no.	substituent	obsd	calcd (eq 104)	σ^+
1	H	0.47	0.58	0.00
2	2-Cl	0.17	0.22	0.11
3	3-Cl	−0.35	−0.65	0.37
4	4-Cl	0.18	0.22	0.11
5	4-NO_2	−1.87	−2.03	0.79
6	2-NO_2	−2.47	−2.03	0.79
7	3-NO_2	−1.61	−1.77	0.71

Oxidation of X−$C_6H_4NH_2$ by vanadium V in 30% acetic acid−water (Table 97)[107]

$$\log k_2 = -3.31(\pm 0.79)\sigma^+ + 0.58(\pm 0.40) \quad (104)$$

$$n = 7,\ r^2 = 0.958,\ s = 0.263,\ q^2 = 0.916$$

Equation 104 is of interest although we cannot say that a radical mechanism similar to eqs 102 and 103 is occurring. What we do know is that weak radicals produce QSAR with larger ρ^+ values than strong radicals.[9] There are a few examples of cytochrome *c* peroxidase acting on anilines that show no dependence on hydrophobicity.

Table 98. Oxidation of 4-X−C_6H_4−NH_2 by Cytochrome *c* Peroxidase from *E. coli* Plus H_2O_2[108]

		log k_2		
no.	substituents	obsd	calcd (eq 105)	σ^+
1	H	1.10	1.09	0.00
2	3-Cl	−0.25	0.04	0.37
3	3-OMe[a]	1.58	0.75	0.12
4	3-Me	1.31	1.29	−0.07
5	4-Cl	1.06	0.78	0.11
6	4-Me	2.09	1.98	−0.31
7	4-OMe	3.23	3.32	−0.78
8	4-OH	3.68	3.72	−0.92

[a] Data point not included in deriving equation.

Oxidation of 4-X−$C_6H_4NH_2$ by cytochrome c peroxidase from E. coli plus H_2O_2 (Table 98)[108]

$$\log k_2 = -2.86(\pm 0.43)\sigma^+ + 1.09(\pm 0.21) \quad (105)$$

$$n = 7,\ r^2 = 0.983,\ s = 0.193,\ q^2 = 0.962$$

outlier: 3-OMe

Table 99. Oxidation of X−C_6H_4−NH_2 by Cytochrome *c* Peroxidase W51F Plus H_2O_2[108]

		log k_2		
no.	substituents	obsd	calcd (eq 106)	σ^+
1	H	3.06	3.14	0.00
2	3-Cl	2.37	2.55	0.37
3	3-OMe	3.04	2.95	0.12
4	3-Me	3.26	3.26	−0.07
5	4-Cl[a]	3.56	2.97	0.11
6	4-Me	4.08	3.64	−0.31
7	4-OMe	4.08	4.39	−0.78
8	4-OH	4.67	4.62	−0.92

[a] Data point not included in deriving equation.

Oxidation of X−$C_6H_4NH_2$ by cytochrome c peroxidase W 51F plus H_2O_2 (Table 99)[108]

$$\log k_2 = -1.60(\pm 0.58)\sigma^+ + 3.14(\pm 0.29) \quad (106)$$

$$n = 7,\ r^2 = 0.909,\ s = 0.263,\ q^2 = 0.829$$

outlier: 4-Cl

Table 100. Oxidation of X−C_6H_4−NH_2 by Cytochrome *c* Peroxidase W51A Plus H_2O_2[108]

		log k_2		
no.	substituents	obsd	calcd (eq 107)	σ^+
1	H	2.93	3.07	0.00
2	3-Cl	2.16	2.29	0.37
3	3-OMe	3.00	2.82	0.12
4	3-Me	3.19	3.21	−0.07
5	4-Cl[a]	3.55	2.84	0.11
6	4-Me	4.01	3.72	−0.31
7	4-OMe	4.32	4.70	−0.78
8	4-OH	5.20	5.00	−0.92

[a] Data point not included in deriving equation.

Oxidation of X−$C_6H_4NH_2$ by cytochrome c peroxidase W 51A plus H_2O_2 (Table 100)[108]

$$\log k_2 = -2.10(\pm 0.58)\sigma^+ + 3.07(\pm 0.29) \quad (107)$$

$$n = 7,\ r^2 = 0.945,\ s = 0.263,\ q^2 = 0.873$$

outlier: 4-Cl

Since σ^+ is the parameter of choice, we believe it is likely that a radical mechanism is involved.[9]

Table 101. Oxidation of X−C_6H_4−NH_2 to X−C_6H_4N═O by Chloroperoxidase from Soil Fungus[109]

		log V_{max}/K_m			
no.	substituents	obsd	calcd (eq 108)	MR	σ^+
1	H	3.26	3.35	0.10	0.00
2	4-F	3.61	3.48	0.09	−0.07
3	4-Me	3.22	3.40	0.57	−0.31
4	4-Cl	2.63	2.66	0.60	0.11
5	4-Br	2.65	2.30	0.89	0.15
6	4-Et	2.84	2.91	1.03	−0.30
7	4-I	1.78	1.80	1.39	0.14
8	3,4-di-Cl	1.25	1.43	1.20	0.48
9	4-$CHMe_2$	2.48	2.40	1.50	−0.28

Oxidation of X−$C_6H_4NH_2$ to X−C_6H_4N═O by chloroperoxidase from soil fungus (Table 101)[109]

$$\log V_{max}/K_m = -1.67(\pm 0.64)\sigma^+ - 1.02(\pm 0.32)\mathrm{MR} + 3.46(\pm 0.31) \quad (108)$$

$$n = 9,\ r^2 = 0.950,\ s = 0.192,\ q^2 = 0.883$$

In the above example, MR pertains to the whole molecule.

Another surprising in vivo study is the following.

Table 102. Hemoglobin Binding of X−$C_6H_4NH_2$ in Wistar Rats[94]

		log HBI				
no.	substituents	obsd	calcd (eq 109)	σ	F_2	$B1_3$
1	4-Me	0.63	0.83	−0.17	0.00	1.00
2	4-C_2H_5	0.76	0.91	−0.15	0.00	1.00
3	4-C_6H_5[a]	2.54	1.41	−0.01	0.00	1.00
4	H	1.34	1.45	0.00	0.00	1.00
5	4-F	1.52	1.66	0.06	0.00	1.00
6	4-Cl	2.76	2.28	0.23	0.00	1.00
7	4-Br	2.53	2.28	0.23	0.00	1.00
8	2-Me	0.60	0.76	−0.17	0.01	1.00
9	2-C_2H_5	0.71	0.91	−0.15	0.00	1.00
10	2,4-di-Me	0.36	0.15	−0.34	0.01	1.00
11	3,6-di-Me	0.04	0.08	−0.34	0.02	1.00
12	3-Me	0.69	0.28	−0.07	0.00	1.52
13	3,4-di-Me	−0.16	−0.33	−0.24	0.00	1.52
14	3,5-di-Me[a]	1.15	0.03	−0.14	0.00	1.52
15	2,4,6-tri-Me	−0.70	−0.53	−0.51	0.02	1.00
16	2-Cl	−0.30	−0.68	0.23	0.42	1.00
17	2,4-di-Cl	−0.22	0.15	0.46	0.42	1.00
18	3-Cl	1.10	1.37	0.37	0.00	1.80
19	3-Cl-4-F	1.49	1.59	0.43	0.00	1.80
20	2,4-di-F[a]	1.51	−1.29	0.12	0.45	1.00

[a] Data points not included in deriving equation.

Hemoglobin binding of X−$C_6H_4NH_2$ in Wistar rats (Table 102)[94]

$$\log \text{HBI} = 3.60(\pm 0.69)\sigma - 7.04(\pm 1.39)F_2 - 1.76(\pm 0.63)B1_3 + 3.20(\pm 0.78) \quad (109)$$

$$n = 17,\ r^2 = 0.924,\ s = 0.290,\ q^2 = 0.821$$

outliers: 3,5-di-Me; 2,4-di-F; 4-C_6H_5

Like eq 92, there is no positive dependence on hydrophobicity. An odd feature of eq 109 is the positive σ term seemingly in opposition to the negative F term of the ortho substituents.

XI. Aromatic Tellurium Compounds

An unusual reaction is the inhibition of lipid peroxidation by tellurium compounds.

Table 103. Inhibition of Lipid Peroxidation by Rat Liver Microsomes by X−C_6H_4−Te−C_6H_4−X[110]

		log 1/C		
no.	substituents	obsd	calcd (eq 110)	σ^+
1	4-NMe_2	7.52	7.50	−1.70
2	4-NH_2	7.22	7.32	−1.30
3	4-NHC_6H_5	7.26	7.37	−1.40
4	4-OMe	7.19	7.09	−0.78
5	4-OH	7.30	7.15	−0.92
6	4-C_6H_5[a]	7.10	6.81	−0.18
7	4-Me	7.00	6.87	−0.31
8	H	6.73	6.73	0.00
9	4-Br	6.66	6.66	0.15
10	4-Cl[a]	6.92	6.68	0.11
11	4-F	6.60	6.76	−0.07
12	4-CF_3	6.38	6.45	0.61
13	4-NO_2	6.43	6.37	0.79

[a] Data points not included in deriving equation.

Inhibition of lipid peroxidation by rat liver microsomes by X−C_6H_4−Te−C_6H_4-X (Table 103)[110]

$$\log 1/C = -0.46(\pm 0.09)\sigma^+ + 6.73(\pm 0.09) \quad (110)$$

$$n = 11,\ r^2 = 0.931,\ s = 0.109,\ q^2 = 0.904$$

outliers: 4-Cl; 4-C_6H_5

Table 104. Singlet-Oxygen Quenching by Competitive Inhibition of the Oxidation of 1,3-Diphenylisobenzofuran in Aqueous 10% Methanol by X−C_6H_4−Te−C_6H_4−X[111]

		log k		
no.	X	obsd	calcd (eq 111)	σ^+
1	4-NMe_2	−5.32	−5.29	−3.40
2	4-NH_2	−5.45	−5.51	−2.60
3	4-OH	−5.75	−5.72	−1.84
4	4-OMe	−5.80	−5.80	−1.56
5	H	−6.14	−6.22	0.00
6	4-F	−6.28	−6.19	−0.14
7	3-OMe	−6.14	−6.29	0.24
8	4-Cl	−6.42	−6.28	0.22
9	3-Cl	−6.43	−6.43	0.74
10	H,4-COMe[a]	−6.66	−6.36	0.50

[a] Data point not included in deriving equation.

Singlet-oxygen quenching by competitive inhibition of the oxidation of 1,3-diphenylisobenzofuran in aqueous 10% methanol by X−C_6H_4−Te−C_6H_4−X (Table 104)[111]

$$\log k = -0.27(\pm 0.06)\sigma^+ - 6.22(\pm 0.09) \quad (111)$$

$$n = 9,\ r^2 = 0.952,\ s = 0.100,\ q^2 = 0.926$$

outlier: H,4-COMe

Again, we believe that the negative σ^+ term implies a radical reaction,[9] and again, we see no role for hydrophobicity in eqs 110 and 111.

XII. Stilbenes

Table 105. Mutagenesis of Salmonella TA100 by H_2N−C_6H_4CH=CHC_6H_4−X[112]

		log k			
no.	substituents	obsd	calcd (eq 112)	σ^+	Clog P
1	4′-OMe[a]	3.08	4.34	−0.78	3.13
2	4′-Me	4.03	4.01	−0.31	3.71
3	3′-NH_2	4.48	4.51	−0.16	1.98
4	4′-H	4.00	4.07	0.00	3.21
5	3′-OMe	4.06	4.06	0.12	3.13
6	4′-Cl	3.84	3.81	0.11	3.92
7	3′-Cl	3.71	3.73	0.37	3.92
8	3′-CN	4.23	4.08	0.56	2.64
9	4′-CN[a]	3.36	4.04	0.66	2.64
10	4′-NO_2	3.80	3.90	0.79	2.95

[a] Data points not included in deriving equation.

Mutagenesis of Salmonella TA100 by H_2N−C_6H_4CH=CHC_6H_4−X (Table 105)[112]

$$\log k = -0.31(\pm 0.24)\sigma^+ - 0.32(\pm 0.13)\text{Clog } P + 5.09(\pm 0.44) \quad (112)$$

$$n = 8,\ r^2 = 0.902,\ s = 0.092,\ q^2 = 0.780$$

outliers: 4′-OMe; 4′-CN

Table 106. Reaction of X−C_6H_4CH=CHC_6H_5 with $^{\bullet}SCH_2COOH$ at 105 °C[113]

		log k_{rel}		
no.	substituent	obsd	calcd (eq 113)	σ^+
1	3,4-di-OMe[a]	0.72	0.27	−0.66
2	4-OMe	0.30	0.31	−0.78
3	4-Me	0.11	0.12	−0.31
4	3,5-di-Me	0.11	0.06	−0.14
5	H	0.00	0.00	0.00
6	4-Br	−0.10	−0.06	0.15

[a] Data point not included in deriving equation.

Reaction of X−C_6H_4CH=CHC_6H_5 with $^{\bullet}SCH_2COOH$ at 105 °C (Table 106)[113]

$$\log k_{rel} = -0.40(\pm 0.18)\sigma^+ - 0.001(\pm 0.07) \quad (113)$$

$$n = 5,\ r^2 = 0.944,\ s = 0.041,\ q^2 = 0.828$$

outlier: 3,4-di-OMe

Neither eq 112 nor 113 are very good, but they do support each other in that σ^+ is involved. This harks back to eqs 36 and 37. The styrenes of eq 37 behave similar to the stilbenes, and both may be oxidized in vivo to epoxides that produce the final result.

XIII. Oxidation of X–$C_6H_4SCH_3$

Oxidation of phenyl methyl sulfides has been a popular object for study, especially by physical organic chemists. Unfortunately, most studies are based on rather few data points with little or no attention to the collinearity among σ, σ^+, and σ^-.

Table 107. Oxidation of X−C_6H_4SMe with Soybean Sulfoxidase[114]

		log V_{max}		
no.	substituents	obsd	calcd (eq 115)	σ^+
1	4-NH_2	0.70	0.75	−1.30
2	4-OMe	0.56	0.41	−0.78
3	4-Me	−0.07	0.11	−0.31
4	4-Br	−0.09	−0.20	0.15
5	4-NO_2	−0.64	−0.61	0.79

Oxidation of X−C_6H_4SMe with soybean sulfoxidase (Table 107)[114]

$$\log 1/K_m = 0.43(\pm 0.23)\sigma^+ - 2.15(\pm 0.18) \quad (114)$$

$$n = 5,\ r^2 = 0.920,\ s = 0.119,\ q^2 = 0.816$$

$$\log V_{max} = -0.65(\pm 0.29)\sigma^+ - 0.10(\pm 0.23) \quad (115)$$

$$n = 5,\ r^2 = 0.944,\ s = 0.148,\ q^2 = 0.890$$

$$\log V_{max}/K_m = -0.22(\pm 0.49)\sigma^+ - 2.24(\pm 0.39) \quad (116)$$

$$n = 5,\ r^2 = 0.406,\ s = 0.251,\ q^2 = -0.198$$

In the binding step ($1/K_m$) the positive ρ value would suggest that oxidation is inhibited. The negative ρ in eq 115 would suggest a radical mechanism. It is not surprising that eq 116 is so poor: on adding eqs 114 and 115, the positive and negative coefficients of σ^+ almost annihilate each other. Jackknifing out one datapoint does little to improve it nor does using a $(\sigma^+)^2$ term.

Table 108. Oxidation of X−$C_6H_4SCH_3$ to R Form of Sulfoxide by Cytochrome P450−Terp[115]

		log %		
no.	substituents	obsd	calcd (eq 117)	σ^+
1	OMe	1.30	1.36	−0.78
2	Me	1.00	0.92	−0.31
3	H	0.70	0.64	0.00
4	Cl	0.48	0.54	0.11
5	CN	0.00	0.03	0.66

Oxidation of X−$C_6H_4SCH_3$ to R form of sulfoxide by cytochrome P450−Terp (Table 108)[115]

$$\log \% = -0.93(\pm 0.23)\sigma^+ + 0.64(\pm 0.11) \quad (117)$$

$$n = 5,\ r^2 = 0.983,\ s = 0.075,\ q^2 = 0.943$$

Table 109. Oxidation of X−$C_6H_4SCH_3$ to Sulfoxide by *Mortierella isabellina* 1757 [116]

		log k_{rel}			
no.	substituents	obsd	calcd (eq 118)	σ^+	$B1_4$
1	H	0.00	0.06	0.00	1.00
2	4-Me	−0.35	−0.22	−0.31	1.52
3	4-C_2H_5	−0.32	−0.22	−0.30	1.52
4	4-F	−0.06	−0.16	−0.07	1.35
5	4-Cl[a]	−0.14	−0.52	0.11	1.80
6	4-Br	−0.63	−0.63	0.15	1.95
7	4-NO_2	−0.56	−0.61	0.79	1.70
8	4-OMe	0.14	0.01	−0.78	1.35

[a] Data point not included in deriving equation.

Oxidation of X−$C_6H_4SCH_3$ to sulfoxide by Mortierella isabellina 1757 (Table 109)[116]

$$\log k_{rel} = -0.24(\pm 0.31)\sigma^+ - 0.69(\pm 0.50)B1_4 + 0.75(\pm 0.76) \quad (118)$$

$$n = 7,\ r^2 = 0.882,\ s = 0.122,\ q^2 = 0.627$$

outlier: 4-Cl

Equation 118 is not very satisfactory (note confidence limits on parameters of eq 118), although it does indicate a weak dependency on σ^+.

Table 110. Oxidation of X−C_6H_4SMe by Horseradish Peroxidase[117]

		logV_{max}		
no.	substituents	obsd	calcd (eq 119)	σ^+
1	4-$OCHMe_2$	1.38	1.39	−0.85
2	4-OMe	1.29	1.29	−0.78
3	4-Me	0.61	0.59	−0.31
4	H	0.11	0.13	0.00

Oxidation of X−C_6H_4SMe by horseradish peroxidase (Table 110)[117]

$$\log V_{max} = -1.48(\pm 0.13)\sigma^+ + 0.13(\pm 0.08) \quad (119)$$

$$n = 4,\ r^2 = 0.999,\ s = 0.021,\ q^2 = 0.995$$

Considering now our physical database, we find 18 studies on the oxidation of methylphenyl sulfides. Of these, 10 are based on σ^+. The following are representative examples.

Table 111. Oxidation of X−$C_6H_4SCH_3$ to X−C_6H_4SOMe by $CH_3CONHCl$ in 50% Acetic Acid[118]

		log k			
no.	substituent	obsd	calcd (eq 120)	$B1_2$	σ^+
1	H	2.03	2.12	1.00	0.00
2	4-Me	2.48	2.65	1.00	−0.31
3	4-OMe	3.40	3.44	1.00	−0.78
4	4-F	2.32	2.24	1.00	−0.07
5	4-Cl	2.05	1.94	1.00	0.11
6	4-Br	1.93	1.87	1.00	0.15
7	4-NO_2	0.98	0.79	1.00	0.79
8	4-COMe	1.43	1.28	1.00	0.50
9	4-COOMe	1.46	1.30	1.00	0.49
10	4-NH_2	4.71	4.32	1.00	−1.30
11	3-Me	2.23	2.24	1.00	−0.07
12	3-OMe	1.99	1.92	1.00	0.12
13	3-NH_2	2.27	2.39	1.00	−0.16
14	3-Cl	1.46	1.50	1.00	0.37
15	3-Br	1.42	1.47	1.00	0.39
16	3-I	1.52	1.53	1.00	0.35
17	3-NO_2	0.65	0.93	1.00	0.71
18	3-COOMe	1.33	1.52	1.00	0.36
19	2-Me[a]	1.73	2.08	1.52	−0.31
20	2-OMe	2.93	3.06	1.35	−0.78
21	2-NO_2	0.07	0.02	1.70	0.79
22	2-COOMe	0.63	0.60	1.64	0.49
23	2-NH_2	3.75	3.94	1.35	−1.30
24	2-Cl	0.88	1.06	1.80	0.11
25	2-Br	0.82	0.83	1.95	0.15
26	2-I	0.82	0.63	2.15	0.14
27	2-CN	0.31	0.35	1.60	0.66

[a] Data point not included in deriving equation.

Oxidation of X−$C_6H_4SCH_3$ to X−C_6H_4SOMe by $CH_3CONHCl$ in 50% acetic acid (Table 111)[118]

$$\log k = -1.70(\pm 0.11)\sigma^+ - 1.10(\pm 0.18)B1_2 + 3.22(\pm 0.23) \quad (120)$$

$$n = 26,\ r^2 = 0.981,\ s = 0.157,\ q^2 = 0.971$$

outlier: 2-CH_3

The sterimol parameter shows that ortho substituents hinder the reaction. The use of *N*-chloroacetamide suggests a radical mechanism since there are a variety of haloamides producing radical reactions with various substrates.[9]

Table 112. Oxidation of X−C_6H_4SMe to X−C_6H_4SOMe with Oxochromium(V) in 20% Aqueous Acetonitrile[119]

		log k		
no.	substituents	obsd	calcd (eq 121)	σ^+
1	H	0.59	0.80	0.00
2	4-OMe	1.90	1.95	−0.78
3	4-Me	1.38	1.26	−0.31
4	4-C_2H_5	1.27	1.24	−0.30
5	4-$CHMe_2$	1.32	1.21	−0.28
6	3-Me	0.99	0.90	−0.07
7	4-F	0.81	0.90	−0.07
8	3-OMe	0.60	0.62	0.12
9	4-Cl	0.55	0.63	0.11
10	4-Br	0.56	0.57	0.15
11	3-Cl	0.47	0.25	0.37
12	4-COOH	0.06	0.17	0.42
13	4-COMe	0.03	0.06	0.50
14	4-NO_2	−0.34	−0.38	0.79

Oxidation of X−C_6H_4SMe to X−C_6H_4SOMe with oxochromium V in 20% aqueous acetonitrile (Table 112)[119]

$$\log k = -1.48(\pm 0.18)\sigma^+ + 0.80(\pm 0.07) \quad (121)$$

$$n = 14,\ r^2 = 0.966,\ s = 0.117,\ q^2 = 0.956$$

Table 113. Oxidation of X−C_6H_4SMe to X−C_6H_4SOMe with Phenyliodoso Diacetate in 5% Aqueous Acetonitrile[120]

		log k_2		
no.	substituent	obsd	calcd (eq 122)	σ^+
1	H[a]	−2.10	−2.30	0.00
2	4-OMe	−1.58	−1.57	−0.78
3	4-Me	−2.00	−2.01	−0.31
4	4-$CHMe_2$	−2.05	−2.04	−0.28
5	3-Me	−2.22	−2.23	−0.07
6	4-Br	−2.25	−2.44	0.15
7	4-F	−2.31	−2.23	−0.07
8	3-OMe	−2.38	−2.41	0.12
9	4-Cl	−2.41	−2.40	0.11
10	3-Cl	−2.70	−2.65	0.37
11	4-COMe	−2.91	−2.77	0.50
12	4-NO_2	−2.99	−3.04	0.79

[a] Data point not included in deriving equation.

Oxidation of X−C_6H_4SMe to X−C_6H_4SOMe with phenyliodoso diacetate in 5% aqueous acetonitrile (Table 113)[120]

$$\log k_2 = -0.94(\pm 0.15)\sigma^+ - 2.30(\pm 0.06) \quad (122)$$

$$n = 11,\ r^2 = 0.959,\ s = 0.088,\ q^2 = 0.942$$

outlier: H

Table 114. Oxidation of X−C_6H_4SMe with Peroxydisulfate in 50% Aqueous Ethanol[121]

		log k_2		
no.	substituent	obsd	calcd (eq 123)	σ^+
1	4-OMe	−1.90	−1.86	−0.78
2	4-Me	−2.19	−2.16	−0.31
3	4-$CHMe_2$	−2.23	−2.18	−0.28
4	4-F	−2.25	−2.32	−0.07
5	3-Me	−2.30	−2.32	−0.07
6	H	−2.34	−2.36	0.00
7	3-OMe	−2.36	−2.44	0.12
8	4-Cl	−2.40	−2.44	0.11
9	4-Br	−2.42	−2.46	0.15
10	3-Cl	−2.65	−2.61	0.37
11	4-COMe	−2.77	−2.69	0.50
12	4-NO_2	−2.90	−2.88	0.79
13	4-COOH[a]	−2.94	−2.64	0.42

[a] Data point not included in deriving equation.

Oxidation of X−C_6H_4SMe with peroxydisulfate in 50% aqueous ethanol (Table 114)[121]

$$\log k_2 = -0.65(\pm 0.09)\sigma^+ - 2.36(\pm 0.04) \quad (123)$$

$$n = 12,\ r^2 = 0.964,\ s = 0.054,\ q^2 = 0.947$$

outlier: 4-COOH

The slopes of the above reactions differ considerably as do the biological oxidations of the phenylmethyl sulfides. We believe that eq 120 is of the most interest because it suggests a radical reaction.[9] Only eq 119 has a ρ^+ value approaching that of eq 120.

Four examples of the chemical oxidation are best correlated by σ. The following two are representative.

Table 115. Oxidation of X−C$_6$H$_4$SMe to X−C$_6$H$_4$SOMe by *N*-Bromoacetamide in 20% Aqueous Acetonitrile[122]

		log k_2		
no.	substituent	obsd	calcd (eq 124)	σ
1	4-OMe	−0.50	−0.71	−0.27
2	4-Me	−1.01	−0.95	−0.17
3	3-Me	−1.38	−1.19	−0.07
4	H	−1.45	−1.36	0.00
5	3-OMe	−1.49	−1.65	0.12
6	4-Cl	−1.95	−1.92	0.23
7	4-COMe	−2.68	−2.56	0.50
8	4-NO$_2$	−3.14	−3.24	0.78

Oxidation of X−C$_6$H$_4$SMe to X−C$_6$H$_4$SOMe by N-bromoacetamide in 20% aqueous acetonitrile (Table 115)[122]

$$\log k_2 = -2.40(\pm 0.40)\sigma - 1.36(\pm 0.15) \quad (124)$$

$$n = 8,\ r^2 = 0.973,\ s = 0.154,\ q^2 = 0.945$$

Using σ^+ in place of σ yields a QSAR with $r^2 = 0.943$ and slope of −1.75, very similar to QSAR 120.

Table 116. Oxidation of X−C$_6$H$_4$SME to X−C$_6$H$_4$SOMe by Chromium(VI) in 50% Aqueous Acetic Acid[123]

		log k_2		
no.	substituent	obsd	calcd (eq 125)	σ
1	H	−1.51	−1.48	0.00
2	4-OMe	−0.70	−0.91	−0.27
3	4-Me	−1.23	−1.12	−0.17
4	4-CHMe$_2$	−1.28	−1.16	−0.15
5	3-Me	−1.48	−1.33	−0.07
6	4-F	−1.59	−1.60	0.06
7	3-OMe	−1.67	−1.73	0.12
8	4-Cl	−1.85	−1.96	0.23
9	4-Br	−1.89	−1.96	0.23
10	3-Cl	−2.18	−2.26	0.37
11	4-COOH	−2.53	−2.43	0.45
12	4-COMe	−2.52	−2.53	0.50
13	4-NO$_2$	−3.16	−3.12	0.78

Oxidation of X−C$_6$H$_4$SMe to X−C$_6$H$_4$SOMe by chromium VI in 50% aqueous acetic acid (Table 116)[123]

$$\log k_2 = -2.11(\pm 0.23)\sigma - 1.48(\pm 0.08) \quad (125)$$

$$n = 13,\ r^2 = 0.974,\ s = 0.110,\ q^2 = 0.961$$

With σ^+ in place of σ, $r^2 = 0.953$ and slope = −1.58. Four examples are best correlated by σ^-.

Table 117. Oxidation of X−C$_6$H$_4$SMe to X−C$_6$H$_4$SOMe by NaIO$_4$ in 50% Aqueous Ethanol[124]

		log k_2		
no.	substituent	obsd	calcd (eq 126)	σ^-
1	4-OMe	−1.05	−1.20	−0.26
2	H	−1.42	−1.45	0.00
3	4-COO$^-$	−1.78	−1.75	0.31
4	3-OMe	−1.59	−1.57	0.12
5	4-Cl	−1.66	−1.63	0.19
6	3-Cl	−1.95	−1.81	0.37
7	4-COOH	−2.13	−2.19	0.77
8	4-COOMe	−2.15	−2.17	0.75
9	3-NO$_2$	−2.31	−2.13	0.71
10	4-NO$_2$	−2.52	−2.67	1.27

Oxidation of X−C$_6$H$_4$SMe by NaIO$_4$ in 50% aqueous ethanol (Table 117)[124]

$$\log k_2 = -0.96(\pm 0.19)\sigma^- - 1.45(\pm 0.12) \quad (126)$$

$$n = 10,\ r^2 = 0.941,\ s = 0.115,\ q^2 = 0.878$$

Using σ^+ in place of σ^-, $r^2 = 0.910$ and $\rho = -0.94$

Table 118. Oxidation of X−C$_6$H$_4$SMe with Bromate in 40% Aqueous Acetic Acid[125]

		log k		
no.	substituent	obsd	calcd (eq 127)	σ^-
1	4-OMe	1.85	2.01	−0.26
2	4-Me	1.89	1.84	−0.17
3	H	1.64	1.53	0.00
4	4-F	1.58	1.58	−0.03
5	4-Cl	1.13	1.18	0.19
6	4-Br	1.13	1.07	0.25
7	4-COMe	0.08	−0.03	0.84
8	4-COOH	0.04	0.10	0.77
9	4-NO$_2$	−0.89	−0.82	1.27

Oxidation of X−C$_6$H$_4$SMe with bromate in 40% aqueous acetic acid (Table 118)[125]

$$\log k = -1.85(\pm 0.15)\sigma^- + 1.53(\pm 0.09) \quad (127)$$

$$n = 9,\ r^2 = 0.991,\ s = 0.096,\ q^2 = 0.985$$

With σ^+, $r^2 = 0.810$, $s = 0.455$, and $q^2 = 0.446$. The 4-OMe derivative is very badly fit.

It is of interest that all of the biological QSAR for the oxidation of phenylmethyl sulfides are best correlated by σ^+, but the chemical oxidations are varied. No doubt the various oxidizing agents play a significant role. Also, the collinearity problem is something that chemists often gave little consideration to. What can be said is that electron-releasing substituents invariably promote oxidation. Oxidation of benzenethiols has received much less attention.

Table 119. Haematin-Catalyzed Oxidation of X−C$_6$H$_4$-SH[126]

		log k		
no.	substituent	obsd	calcd (eq 128)	σ^+
1	4-NH$_2$	1.41	1.30	−1.30
2	2-NH$_2$	1.21	1.30	−1.30
3	4-Me	0.49	0.51	−0.31
4	H	0.23	0.26	0.00
5	4-NO$_2$	−0.35	−0.38	0.79

Haematin-catalyzed oxidation of X−C_6H_4SH (Table 119)[126]

$$\log k = -0.80(\pm 0.16)\sigma^+ + 0.26(\pm 0.14) \quad (128)$$
$$n = 5,\ r^2 = 0.989,\ s = 0.087,\ q^2 = 0.964$$

Table 120. Haematin-Catalyzed Oxidation of X−C_6H_4SH[126]

		log k		
no.	substituent	obsd	calcd (eq 129)	σ^+
1	4-NH_2	1.41	1.30	−1.30
2	2-NH_2	1.21	1.30	−1.30
3	4-Me	0.49	0.51	−0.31
4	H	0.23	0.27	0.00
5	4-NO_2	−0.32	−0.36	0.79

Haematin-catalyzed oxidation of X−C_6H_4SH (Table 120)[126]

$$\log k = -0.79(\pm 0.16)\sigma^+ + 0.27(\pm 0.15) \quad (129)$$
$$n = 5,\ r^2 = 0.988,\ s = 0.091,\ q^2 = 0.959$$

We could find nothing published to compare with eqs 128 and 129. However, from work in progress in our laboratory, testing thiophenols on L1210 cells we find no hydrophobic effect and $\rho^+ = -0.96$.[127] No hydrophobic effect was detected with the leukemia cells. The negative σ^+ terms suggest a radical reaction similar to the phenols. It is much easier to abstract •H from SH than from OH; hence, we would expect a smaller value of ρ^+.

XIV. Phenylacetylenes

Table 121. Oxidation of X−$C_6H_4C{\equiv}CH$ to Phenylacetic Acid by P450 from Rat Liver[128]

		log V_{max}		
no.	substituent	obsd	calcd (eq 130)	σ^+
1	4-Me	0.88	0.98	−0.31
2	H	0.74	0.68	0.00
3	4-Cl	0.40	0.57	0.11
4	4-NO_2	−0.05	−0.09	0.79
5	2-Me	1.15	0.98	−0.31

Oxidation of X−$C_6H_4C{\equiv}CH$ to phenylacetic acid by P450 from rat liver (Table 121)[128]

$$\log V_{max} = -0.98(\pm 0.56)\sigma^+ + 0.68(\pm 0.23) \quad (130)$$
$$n = 5,\ r^2 = 0.912,\ s = 0.158,\ q^2 = 0.681$$

The slope of eq 130 is a bit different[9] from that obtained by the authors.[128]

Table 122. Epoxidation of X−$C_6H_4C{\equiv}CH$ by Perbonzoic Acid in Benzene[129]

		log k_{rel}		
no.	substituent	obsd	calcd (eq 131)	σ^+
1	4-OMe	1.01	1.05	−0.78
2	4-Me	0.43	0.40	−0.31
3	H	0.00	−0.03	0.00
4	4-Cl	−0.17	−0.18	0.11
5	3-Br	−0.58	−0.58	0.40
6	3-NO_2	−0.97	−0.95	0.67

Epoxidation of X−$C_6H_4C{\equiv}CH$ by perbenzoic acid in benzene (Table 122)[129]

$$\log k_{rel} = -1.37(\pm 0.07)\sigma^+ - 0.03(\pm 0.03) \quad (131)$$
$$n = 6,\ r^2 = 0.999,\ s = 0.029,\ q^2 = 0.994$$

The similarity in the slopes of the two equations would suggest that epoxidation is the initial rate-limiting step in both equations.

XV. Oxidation of Toluenes

There are many examples of radical abstraction of •H from toluenes with negative σ^+ terms ranging from −2.70 to −0.38 depending on the type of radical employed and the solvent.[9] We have found only one weak biological example.

Table 123. Hydroxylation of 4-X−$C_6H_4CH_3$ by Microsomal P450 LM2[130]

		log k_{cat}/K_m			
no.	substituent	obsd	calcd (eq 132)	σ^+	MR
1	I	6.22	6.21	0.13	1.39
2	Me	5.25	5.40	−0.31	0.57
3	Br	5.71	5.51	0.15	0.89
4	H	4.56	4.53	0.00	0.10
5	Cl	5.01	5.14	0.11	0.60
6	F	4.70	4.59	−0.08	0.10
7	CN	4.71	4.79	0.66	0.63
8	NO_2[a]	4.14	4.85	0.79	0.74

[a] Data point not included in deriving equation.

Hydroxylation of X−$C_6H_4CH_3$ by microsomal P450 LM2 (Table 123)[130]

$$\log k_{cat}/K_m = -0.71(\pm 0.62)\sigma^+ + 1.37(\pm 0.41)\mathrm{MR} + 4.39(\pm 0.29) \quad (132)$$
$$n = 7,\ r^2 = 0.956,\ s = 0.157,\ q^2 = 0.907$$
$$\text{outlier: 4-}NO_2$$

Correlation with log k_{cat} yields a stronger σ^+ term [−0.85(±0.57)] and a weaker MR term [0.60(±0.35)]. There is significant collinearity between MR and log P ($r^2 = 0.729$). A study with a better set of substituents is called for, since only one electron-releasing substituent (CH_3) was considered.

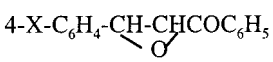
XVI. Epoxides

One can search our present large database in a variety of ways to look for similarities. The following example with chalcone epoxides illustrates the point.[131]

Table 124. I_{50} of Murine Epoxidase Hydrolyase by Chalcones Epoxides[132]

		log 1/C			
no.	substituent	obsd	calcd (eq 133)	σ^+	L
1	H	5.54	5.63	0.00	2.06
2	F	5.89	5.83	−0.07	2.65
3	Br	6.16	6.07	0.15	3.82
4	CH_3	5.72	6.00	−0.31	2.87
5	OCH_3	6.70	6.54	−0.78	3.98
6	NO_2	5.75	5.67	0.79	3.44
7	C_6H_5	6.85	6.92	−0.18	6.28
8	OC_6H_5	6.85	6.56	−0.50	4.51
9	$OCH_2C_6H_5$[a]	6.55	7.69	−0.66	8.20
10	$CH(CH_3)_2$	6.33	6.34	−0.28	4.11
11	$(CH_2)_6CH_3$[a]	6.19	7.75	−0.29	9.03
12	$(CH_2)_3CH_3$	6.82	6.94	−0.29	6.17
13	$NHCOCH_3$	6.66	6.77	−0.60	5.09

[a] Data points not included in deriving equation.



I_{50} of murine epoxidase hydrolyase by chalcones epoxides (Table 124)[132]

$$\log 1/C = -0.46(\pm 0.32)\sigma^+ + 0.29(\pm 0.10)L + 5.04(\pm 0.41) \quad (133)$$

$$n = 11,\ r^2 = 0.904,\ s = 0.177,\ q^2 = 0.845$$

outliers: $OCH_2C_6H_5$; $(CH_2)_6CH_3$

The equation is different than that published by the original authors.[132] Two data points are omitted for lack of *L* values.

The following example from the physical database is pertinent.

Table 125. Nucleophilic Substitution of X−C_6H_4−ethylene oxide by Benzylamine in Ethanol[133]

		log *k*		
no.	substituent	obsd	calcd (eq 134)	σ^+
1	3,4-di-Me	−4.26	−4.32	−0.38
2	4-Me	−4.47	−4.39	−0.31
3	3-Me	−4.62	−4.63	−0.07
4	H	−4.86	−4.69	0.00
5	3-OMe	−4.57	−4.74	0.05
6	4-Br	−4.78	−4.84	0.15
7	3-Cl	−5.18	−5.08	0.40
8	3-CF_3	−5.16	−5.20	0.52

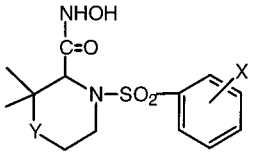
Nucleophilic substitution of X−C_6H_4−ethylene oxide by benzylamine in ethanol (Table 125)[133]

$$\log k = -0.97(\pm 0.35)\sigma^+ - 4.69(\pm 0.10) \quad (134)$$

$$n = 8,\ r^2 = 0.888,\ s = 0.117,\ q^2 = 0.824$$

It seems likely that the inhibitory reaction covered by eq 133 could involve a reaction of the chalcone epoxide with an electron-rich moiety of the enzyme somewhat like that of eq 134. These equations resemble eqs 36 and 37.

XVII. Thiazepines



Y = S or SO_2

XIX

Table 126. I_{50} of Metalloproteinase MMP-7 by XIX[134]

	substituent		log 1/C		
no.	X	Y	obsd	calcd (eq 135)	σ^+
1	S	4-OMe	7.52	7.45	−0.78
2	SO_2	4-OMe	7.39	7.45	−0.78
3	S	4-Br[a]	7.77	5.53	0.15
4	SO_2	4-Br[a]	7.10	5.53	0.15
5	S	2-Me,4-Br	6.45	6.17	−0.16
6	SO_2	4-OC_4H_9	7.57	7.51	−0.81
7	S	4-C_3H_7	6.20	6.44	−0.29
8	S	4-C_5H_{11}	6.48	6.44	−0.29
9	S	4-$O(CH_2)_2OMe$	6.29	6.44	−0.29
10	S	4-OC_6H_5[a]	7.80	6.87	−0.50

[a] Data points not included in deriving equation.

I_{50} of metalloproteinase MMP-7 by XIX (Table 126)[134]

$$\log 1/C = -2.06(\pm 0.68)\sigma^+ + 5.84(\pm 0.37) \quad (135)$$

$$n = 7, r^2 = 0.924,\ s = 0.186,\ q^2 = 0.896$$

Y = S or SO_2

outliers: Y = S, X = 4-Br; Y = SO_2, X = 4-Br; Y = S, X = 4-OC_6H_5

Table 127. I_{50} of Metalloproteinase MMP-3 by XIX[134]

	substituent		log 1/C		
no.	X	Y	obsd	calcd (eq 136)	σ^+
1	S	4-OMe[a]	9.16	8.27	−0.78
2	SO_2	4-OMe	8.16	8.27	−0.78
3	S	4-Br[a]	8.00	6.90	0.15
4	SO_2	4-Br	7.05	6.90	0.15
5	S	2-Me,4-Br	7.06	7.36	−0.16
6	S	4-OC_4H_9	8.18	8.32	−0.81
7	SO_2	4-OC_4H_9	8.57	8.32	−0.81
8	S	4-C_3H_7	7.34	7.55	−0.29
9	S	4-C_5H_{11}	7.60	7.55	−0.29
10	S	4-$O(CH_2)_2OMe$	7.77	7.55	−0.29
11	S	4-OC_6H_5	7.96	7.86	−0.50

[a] Data points not included in deriving equation.

I_{50} of metalloproteinase MMP-3 by XIX (Table 127)[134]

$$\log 1/C = -1.48(\pm 0.53)\sigma^+ + 7.12(\pm 0.28) \quad (136)$$

$$n = 9,\ r^2 = 0.860,\ s = 0.211,\ q^2 = 0.790$$

outliers: Y = S, X = 4-OMe; Y = S, X = 4-Br

Table 128. I_{50} of Metalloproteinase MMP-1 by XIX[134]

	substituent		log 1/C		
no.	X	Y	obsd	calcd (eq 137)	$L_{X,4}$
1	S	4-OMe	9.10	8.98	3.98
2	SO_2	4-OMe	8.72	8.98	3.98
3	S	4-Br	9.16	9.06	3.82
4	SO_2	4-Br	8.92	9.06	3.82
5	S	2-Me,4-Br	9.30	9.06	3.82
6	S	4-OC_4H_9	7.75	7.50	6.86
7	SO_2	4-OC_4H_9	7.72	7.50	6.86
8	S	4-C_3H_7[a]	7.66	8.50	4.92
9	S	4-C_5H_{11}	7.22	7.45	6.97
10	S	4-$O(CH_2)_2OMe$	7.38	7.58	6.71
11	S	4-OC_6H_5	8.64	8.71	4.51
12	S	4-(4-F−C_6H_4)[a]	8.54	7.50	6.87

[a] Data points not included in deriving equation.

I_{50} of metalloproteinase MMP-1 by XIX (Table 128)[134]

$$\log 1/C = -0.51(\pm 0.11)L_{X,4} + 11.02(\pm 0.59) \quad (137)$$

$$n = 10,\ r^2 = 0.934,\ s = 0.216,\ q^2 = 0.906$$

outliers: Y = S, X = 4-C_3H_7; Y = S, X = 4-(4-F−C_6H_4)

In eqs 135 and 136, two data points were omitted because of lack of σ^+ values. In eq 137, one data point was omitted because of the lack of L_4. The above three metalloproteinases are a structurally related class of enzymes that metabolize extra cellular matrix proteins. This family of enzymes (which includes collagenases, stromelysins, and gelatinases) is involved in tissue remodeling processes such as wound healing, angiogenesis, and pregnancy.[134] The crystallographic structure of the complex of XIX when Y = S and X = 4-OMe with stromelysin (MMP-3) was established.[134] Our interest is in the comparative QSAR. In the three examples, we could find no evidence for a hydrophobic interaction. In two of the examples, σ^+ was the only significant parameter, and in the third, no electronic effect could be found for the substituents. In searching our bio database, one example of interest is found.

Table 129. I_{50} of Rat Lens Aldol Reductase by X−$C_6H_4SO_2NHCHC_6H_5$[135]

		log 1/*C*			
no.	substituent	obsd	calcd (eq 138)	σ^+	*I*
1	H(*R*) [b]	3.34	3.52	0.00	0
2	H(*S*)	4.96	5.00	0.00	1
3	4-Me(*R*)	4.05	3.79	−0.31	0
4	4-Me(*S*)	5.05	5.27	−0.31	1
5	4-OMe(*R*)	4.44	4.21	−0.78	0
6	4-OMe(*S*)[a]	4.89	5.69	−0.78	1
7	4-Cl(*R*)	3.47	3.42	0.11	0
8	4-Cl(*S*)	5.15	4.90	0.11	1
9	4-F(*R*)	3.02	3.58	−0.07	0
10	4-F(*S*)	4.60	5.06	−0.07	1
11	4-NO_2(*R*)	3.01	2.82	0.79	0
12	4-NO_2(*S*)[a]	5.07	4.30	0.79	1
13	34-$(CH)_4$(*R*)	3.64	3.64	−0.14	0
14	34-$(CH)_4$(*S*)	5.60	5.12	−0.14	1

[a] Data points not included in deriving equation. [b] (*R*) and (*S*) denote *R*-isomer and *S*-isomer, respectively.

I_{50} of rat lens aldol reductase by X−$C_6H_4SO_2NHCH$-(COOH)C_6H_5 (Table 129)[135]

$$\log 1/C = -0.89(\pm 0.65)\sigma^+ + 1.48(\pm 0.45)\mathrm{I} + 3.52(\pm 0.30) \quad (138)$$

$$n = 12,\ r^2 = 0.880,\ s = 0.343,\ q^2 = 0.777$$

outliers: 4-OMe(S-isomer); 4-NO_2(S-isomer)

For each X, both the *R* and *S* stereoisomers were tested. The indicator variable *I* takes the value of 1 for *S* and 0 for *R*. The importance of through-resonance as brought out by σ^+ is apparent in eqs 135, 136, and 138. High electron density on the sulfonamido moiety is important. We could find nothing similar from mechanistic organic chemistry.

XVIII. Cinnamic Acids

Table 130. ED_{50} for Reducing Accumulation of Malonic Acid Dialdehyde (antioxidant activity biosystem not given) by X−C_6H_4CH=CHCOOH[136]

		log 1/*C*			
no.	substituent	obsd	calcd (eq 139)	σ^+	$B5_3$
1	H	2.94	2.82	0.00	1.00
2	2-Cl	2.87	2.75	0.11	1.00
3	3-Cl	2.87	2.91	0.37	1.80
4	3-NO_2	2.95	2.96	0.71	2.44
5	2-OMe	2.95	3.32	−0.78	1.00
6	3,4-di-OMe[a]	2.96	4.09	−0.66	3.07
7	3-NH_2	3.24	3.32	−0.16	1.97
8	3-OH,4-OMe	3.48	3.62	−0.66	1.93
9	4-NMe_2	3.98	3.90	−1.70	1.00
10	3,4-di-OH	4.08	3.71	−0.80	1.93
11	3-OMe,4-OH	4.14	4.18	−0.80	3.07

[a] Data point not included in deriving equation.

ED_{50} for reducing accumulation of malonic acid dialdehyde (antioxidant activity bio system not given) by X−C_6H_4CH=CHCOOH (Table 130)[136]

$$\log 1/C = -0.64(\pm 0.25)\sigma^+ + 0.41(\pm 0.25)B5_3 + 2.41(\pm 0.48) \quad (139)$$

$$n = 10,\ r^2 = 0.867,\ s = 0.219,\ q^2 = 0.798$$

outlier: 3,4-di-OMe

Note: 3-OCH_2COOH and 4-OCH_2COOH omitted for lack of σ^+ values.

There has been considerable interest in the radical scavenging activity of cinnamic acids and their esters for commercial purposes.[137] Turning to data from physical organic chemistry for further insight, we uncover the following two equations.

Table 131. Oxidation of X−C_6H_4CH=CHCOOH in 30% Aqueous Acetic Acid by Quinolinium Dichromate[138]

		log k_2		
no.	substituent	obsd	calcd (eq 140)	σ^+
1	H	0.91	0.95	0.00
2	4-OMe	1.53	1.47	−0.78
3	4-Me	1.07	1.16	−0.31
4	4-Cl	0.88	0.88	0.11
5	3-Cl	0.75	0.71	0.37
6	3-NO_2	0.59	0.48	0.71
7	4-NO_2	0.33	0.43	0.79

Oxidation of X−C_6H_4CH=CHCOOH in 30% aqueous acetic acid by quinolinium dichromate (Table 131)[138]

$$\log k_2 = -0.66(\pm 0.16)\sigma^+ + 0.95(\pm 0.08) \quad (140)$$

$$n = 7,\ r^2 = 0.959,\ s = 0.084,\ q^2 = 0.897$$

Table 132. Oxidation of X−C_6H_4CH=CHCOOH in 20% Aqueous Acetic Acid by $HBrO_3$[139]

		log *k*		
no.	X	obsd	calcd (eq 141)	σ^+
1	H	−3.68	−3.71	0.00
2	4-NO_2	−4.42	−4.42	0.79
3	3-NO_2	−4.30	−4.34	0.71
4	2-NO_2[b]	−4.40	−4.42	0.79
5	4-Cl	−3.85	−3.81	0.11
6	3-Cl	−4.09	−4.04	0.37
7	2-Cl[b]	−4.14	−3.81	0.11
8	4-Br	−3.90	−3.85	0.15
9	3-Me	−3.60	−3.65	−0.07
10	4-Me[a]	−3.98	−3.44	−0.31
11	2-Me[b]	−4.28	−3.44	−0.31
12	2-OMe[b]	−2.78	−3.02	−0.78

[a] Data point not included in deriving equation. [b] Ortho substituents omitted

Oxidation of X−C_6H_4CH=CHCOOH in 20% aqueous acetic acid by $HBrO_3$ (Table 132)[139]

$$\log k = -0.89(\pm 0.15)\sigma^+ - 3.71(\pm 0.07) \quad (141)$$

$$n = 7,\ r^2 = 0.979,\ s = 0.049,\ q^2 = 0.960$$

outlier: 4-Me

Note: ortho substituents were omitted since they required two more parameters. Including them gave $r^2 = 0.975$ using F and $B1_2$ for 2-NO_2, 2-Cl, 2-Me, 2-OMe.

Equations 139−141 illustrate the advantage of comparative QSAR. The agreement between ρ^+ for the three examples is very close and provides evidence for radical mechanisms.

XIX. Acetyl Phenols

While there has been considerable work done on the nonenzymatic hydrolysis of phenyl acetates, we have only one good example for an enzymatic reaction.

Table 133. Acylation of Chymotrypsin by X−$C_6H_4OCOCH_3$ at pH 7.5[140]

		log k_2/K_s		
no.	substituent	obsd	calcd (eq 142)	σ^-
1	4-NO_2	3.15	3.13	1.27
2	4-CN	2.62	2.59	1.00
3	4-Cl[a]	1.47	0.94	0.19
4	H	0.59	0.56	0.00
5	4-CHO	2.76	2.65	1.03
6	3-NO_2	1.73	2.00	0.71
7	3-CHO	1.60	1.27	0.35
8	3-$COCH_3$	1.06	1.33	0.38

[a] Data point not included in deriving equation.

Acylation of chymotrypsin by X−$C_6H_4OCOCH_3$ at pH 7.5 (Table 133)[140]

$$\log k_2/K_S = 2.03(\pm 0.54)\sigma^- + 0.56(\pm 0.43) \quad (142)$$

$$n = 7,\ r^2 = 0.950,\ s = 0.232,\ q^2 = 0.920$$

outlier: 4-Cl

The reaction appears to involve a nucleophilic substitution of the X−$C_6H_4O^-$ moiety.

Searching our physical database, we find 20 examples of the hydrolysis of acetyl phenols correlated by σ^-. Most of these are simple hydrolyses in various solvents and have low values of ρ ranging from 0.28 to about 1, depending on experimental conditions. Using OH^- yields the lowest ρ values. Four are of interest in that relatively weak nucleophiles have been employed.

Table 134. Reaction of X−$C_6H_4OCOCH_3$ with H_2NNH_2 in Aqueous Solution at 18 °C[141]

		log *k*		
no.	substituent	obsd	calcd (eq 143)	σ^-
1	4-NO_2	2.51	2.67	1.27
2	3-NO_2	1.60	1.30	0.71
3	H	−0.61	−0.43	0.00
4	4-CH_3	−0.89	−0.85	−0.17
5	4-OCH_3	−1.01	−1.09	−0.27

Reaction of X−$C_6H_4OCOCH_3$ with H_2NNH_2 in aqueous solution at 18 °C *(Table 134)*[141]

$$\log k = 2.44(\pm 0.55)\sigma^- - 0.43(\pm 0.36) \quad (143)$$

$$n = 5,\ r^2 = 0.985,\ s = 0.227,\ q^2 = 0.944$$

Table 135. Nucleophilic substitution of X−$C_6H_4OCOCH_3$ with $H_2NCH_2COOC_2H_5$ in aqueous solution at 25 °C[142]

		log k_2		
no.	substituent	obsd	calcd (eq 144)	σ^-
1	H	−1.96	−1.82	0.00
2	4-Cl	−1.33	−1.44	0.19
3	4-COMe	−0.08	−0.11	0.84
4	4-OMe	−2.33	−2.35	−0.26
5	4-NO_2	0.73	0.77	1.27

Nucleophilic substitution of X−$C_6H_4OCOCH_3$ with $H_2NCH_2COOC_2H_5$ in aqueous solution at 25 °C *(Table 135)*[142]

$$\log k_2 = 2.04(\pm 0.27)\sigma^- - 1.82(\pm 0.18) \quad (144)$$

$$n = 5,\ r^2 = 0.995,\ s = 0.105,\ q^2 = 0.989$$

Table 136. Nucleophilic Substitution of X−$C_6H_4OCOCH_3$ with Aziridine[143]

		log *k*		
no.	substituent	obsd	calcd (eq 145)	σ^-
1	4-OMe	0.29	0.20	−0.26
2	4-Me	0.36	0.39	−0.17
3	H	0.48	0.74	0.00
4	4-Cl	1.24	1.13	0.19
5	3-NO_2	2.43	2.21	0.71
6	4-NO_2	3.24	3.36	1.27

Nucleophilic substitution of X−$C_6H_4OCOCH_3$ with aziridine (Table 136)[143]

$$\log k = 2.06(\pm 0.41)\sigma^- + 0.74(\pm 0.25) \quad (145)$$

$$n = 6,\ r^2 = 0.980,\ s = 0.197,\ q^2 = 0.942$$

Table 137. Hydrolysis of X−$C_6H_4OCOCH_3$ Catalyzed by Imidazole[144]

		log k_2		
no.	X	obsd	calcd (eq 146)	σ^-
1	4-NO_2	3.33	3.48	1.27
2	3-NO_2	2.66	2.45	0.71
3	4-Cl	1.66	1.49	0.19
4	H	1.03	1.14	0.00
5	4-Me	0.72	0.83	−0.17

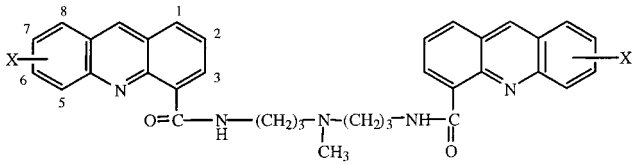
Hydrolysis of X−$C_6H_4OCOCH_3$ catalyzed by imidazole (Table 137)[144]

$$\log k_2 = 1.84(\pm 0.53)\sigma^- + 1.14(\pm 0.35) \quad (146)$$

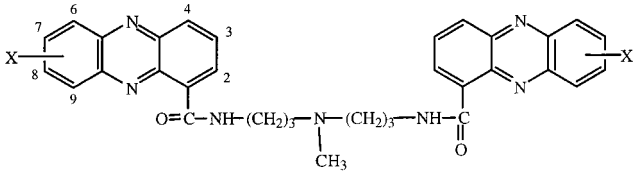
$$n = 5,\ r^2 = 0.976,\ s = 0.197,\ q^2 = 0.884$$

Equations 143−146 have ρ^- values similar to 142 and suggest that the reaction of chymotrypsin with the phenyl acetates involves a nucleophilic substitution with a relatively weak nucleophilic moiety. Weak nucleophiles need more help from the substituents and hence have higher coefficients. Strong nucleophiles (e.g., OH^-) need little substituent help and have smaller coefficients. The mechanism of chymotrypsin's action has been discussed in detail.[145]

XX. Bis-acridines and Bis-phenazines[146,147a,147b]



XX



XXI

The data for eqs 147−152 are from Gamage et al.[147a] Although we have nothing in our physical database with which to compare these interesting potential antitumor agents, they bring out again how relatively small structural changes can profoundly effect QSAR (see eqs 77 and 80). Adding an ortho substituent causes the phenol to bind to the receptor in such a way that the hydrophobic term is no longer valid.

Table 138. I_{50} of Bis-acridines XX for Murine P388 Leukemia Cells[147a]

		log 1/C					
no.	substituent	obsd	calcd (eq 147)	Clog P	$B5_5$	L_6	$B5_7$
1	H	6.89	6.93	6.74	1.00	2.06	1.00
2	1-Me	6.77	6.84	7.34	1.00	2.06	1.00
3	1-Cl	6.40	6.82	7.47	1.00	2.06	1.00
4	2-Me	6.66	6.78	7.74	1.00	2.06	1.00
5	2-Cl	6.95	6.69	8.30	1.00	2.06	1.00
6	3-Me[a]	5.46	6.84	7.34	1.00	2.06	1.00
7	3-Cl[a]	6.82	0.00	1.00	1.00	1.00	0.00
8	5-Me	7.64	7.57	7.74	2.04	2.06	1.00
9	5-C_2H_5[a]	6.77	5.68	8.80	3.17	2.06	1.00
10	5-$CHMe_2$	5.56	5.56	9.59	3.17	2.06	1.00
11	5-C_6H_5	5.91	5.58	10.52	3.11	2.06	1.00
12	5-OMe	6.37	6.17	7.29	3.07	2.06	1.00
13	5-F	7.80	7.40	7.07	1.35	2.06	1.00
14	5-Cl	7.34	7.52	8.21	1.80	2.06	1.00
15	5-Br	7.82	7.48	8.51	1.95	2.06	1.00
16	5-CF_3	6.62	6.90	8.64	2.61	2.06	1.00
17	5-NMe_2	5.67	6.05	7.90	3.08	2.06	1.00
18	6-Me	6.46	6.98	7.74	1.00	2.80	1.00
19	6-OMe	7.12	7.34	7.29	1.00	3.98	1.00
20	6-F	7.62	7.03	7.07	1.00	2.65	1.00
21	6-Cl	7.18	7.08	8.21	1.00	3.52	1.00
22	6-Br	7.31	7.11	8.51	1.00	3.82	1.00
23	6-CF_3[a]	5.02	6.96	8.64	1.00	3.30	1.00
24	6-NMe_2[a]	6.12	7.13	7.90	1.00	3.53	1.00
25	7-Me	6.57	6.54	7.74	1.00	2.06	2.04
26	7-C_2H_5	5.97	6.12	8.80	1.00	2.06	3.17
27	7-$CHMe_2$	5.84	6.00	9.59	1.00	2.06	3.17
28	7-CMe_3	5.75	5.89	10.39	1.00	2.06	3.17
29	7-C_6H_5	6.15	5.88	10.52	1.00	2.06	3.11
30	7-OMe	6.88	6.37	7.29	1.00	2.06	3.07
31	7-F	6.85	6.80	7.07	1.00	2.06	1.35
32	7-Cl	6.77	6.52	8.21	1.00	2.00	1.80
33	7-Br	6.65	6.44	8.51	1.00	2.06	1.95
34	7-NMe_2	6.01	6.28	7.90	1.00	2.06	3.08
35	8-Me	6.75	6.78	7.74	1.00	2.06	1.00
36	8-Cl	6.13	6.71	8.21	1.00	2.06	1.00
37	5,7-di-Me	6.68	7.19	8.74	2.04	2.06	2.04
38	5,8-di-Me	7.62	7.43	8.74	2.04	2.06	1.00
39	1,5-di-Me	7.68	7.49	8.34	2.04	2.06	1.00
40	5-Me,8-Cl	7.39	7.35	9.21	2.04	2.06	1.00
41	1-Cl,5-Me	7.32	7.47	8.47	2.04	2.06	1.00

[a] Data points not included in deriving equation.

I_{50} of bis-acridines XX for murine P388 leukemia cells (Table 138)[147a]

$$\log 1/C = -0.15(\pm 0.14)\text{Clog } P + 4.00(\pm 1.03)B5_5 - 1.06(\pm 0.26)(B5_5)^2 + 0.26(\pm 0.24)L_6 - 0.23(\pm 0.18)B5_7 + 4.69(\pm 1.43) \quad (147)$$

$$n = 36,\ r^2 = 0.800,\ s = 0.313,\ q^2 = 0.706$$

$$\text{optimum } B5_5 = 1.88\ (1.78-1.97)$$

outliers: 3-Cl; 6-CF_3; 3-Me; 5-C_2H_5; 6-NMe_2

Table 139. I_{50} of Bis-acridines XX on Murine Lewis Lung Cells (LL_C)[147a]

		log1/*C*				
no.	substituent	obsd	calcd (eq 148)	Clog *P*	$B5_5$	$B5_7$
1	H	7.52	7.72	6.74	1.00	1.00
2	1-Me	7.85	7.57	7.34	1.00	1.00
3	1-Cl	7.38	7.54	7.47	1.00	1.00
4	2-Me	7.17	7.48	7.74	1.00	1.00
5	2-Cl	8.23	7.34	8.30	1.00	1.00
6	3-Me[a]	5.62	7.57	7.34	1.00	1.00
7	3-Cl[a]	5.53	7.54	7.47	1.00	1.00
8	5-Me	8.75	8.45	7.74	2.04	1.00
9	5-C_2H_5[a]	7.57	6.04	8.80	3.17	1.00
10	5-$CHMe_2$	5.98	5.85	9.59	3.17	1.00
11	5-C_6H_5	5.97	5.82	10.52	3.11	1.00
12	5-OMe	6.77	6.74	7.29	3.07	1.00
13	5-F	7.46	8.28	7.07	1.35	1.00
14	5-Cl	8.10	8.36	8.21	1.80	1.00
15	5-Br	8.22	8.29	8.51	1.95	1.00
16	5-CF_3	7.41	7.56	8.64	2.61	1.00
17	5-NMe_2	6.17	6.56	7.90	3.08	1.00
18	6-Me	7.25	7.48	7.74	1.00	1.00
19	6-OMe	7.70	7.59	7.29	1.00	1.00
20	6-F	7.70	7.64	7.07	1.00	1.00
21	6-Cl	7.89	7.36	8.21	1.00	1.00
22	6-Br	7.75	7.29	8.51	1.00	1.00
23	6-CF_3	6.80	7.25	8.64	1.00	1.00
24	6-NMe_2	6.50	7.44	7.90	1.00	1.00
25	7-Me	7.14	7.12	7.74	1.00	2.04
26	7-C_2H_5	6.11	6.47	8.80	1.00	3.17
27	7-$CHMe_2$	5.68	6.28	9.59	1.00	3.17
28	7-CMe_3	5.85	6.08	10.39	1.00	3.17
29	7-C_6H_5	6.22	6.07	10.52	1.00	3.11
30	7-OMe	7.70	6.88	7.29	1.00	3.07
31	7-F	7.50	7.52	7.07	1.00	1.35
32	7-Cl	7.34	7.09	8.21	1.00	1.80
33	7-Br	7.46	6.96	8.51	1.00	1.95
34	7-NMe_2	6.74	6.72	7.90	1.00	3.08
35	8-Me	7.80	7.48	7.74	1.00	1.00
36	8-Cl	6.91	7.36	8.21	1.00	1.00
37	5,7-di-Me	7.70	7.85	8.74	2.04	2.04
38	5,8-di-Me	8.50	8.20	8.74	2.04	1.00
39	1,5-di-Me	8.85	8.30	8.34	2.04	1.00
40	5-Me,8-Cl	8.06	8.09	9.21	2.04	1.00
41	1-Cl,5-Me	8.22	8.27	8.47	2.04	1.00

[a] Data points not included in deriving equation.

I_{50} of bis-acridines XX for murine Lewis lung LL_C cells (Table 139)[147a]

$$\log 1/C = -0.24(\pm 0.18)\text{Clog } P + 4.91(\pm 1.33)B5_5 - 1.31(\pm 0.34)(B5_5)^2 - 0.34(\pm 0.22)B5_7 + 6.11(\pm 1.64) \quad (148)$$

$$n = 38,\ r^2 = 0.764,\ s = 0.426,\ q^2 = 0.690$$

$$\text{optimum } B5_5 = 1.87\ (1.78-1.96)$$

outliers: 3-Me; 3-Cl; 5-C_2H_5

Table 140. I_{50} of Bis-acridines XX for Human Jurkat Leukemia Wild-Type Cells (JL_C)[147a]

		log 1/*C*				
no.	substituent	obsd	calcd (eq 149)	Clog *P*	$B5_5$	$B5_7$
1	H	6.96	7.16	6.74	1.00	1.00
2	1-Me	7.39	7.07	7.34	1.00	1.00
3	1-Cl	6.90	7.05	7.47	1.00	1.00
4	2-Me	6.59	7.01	7.74	1.00	1.00
5	2-Cl	7.34	6.93	8.30	1.00	1.00
6	3-Me[a]	5.89	7.07	7.34	1.00	1.00
7	3-Cl[a]	6.05	7.05	7.47	1.00	1.00
8	5-Me	7.96	7.87	7.74	2.04	1.00
9	5-C_2H_5[a]	6.95	5.94	8.80	3.17	1.00
10	5-$CHMe_2$	5.68	5.82	9.59	3.17	1.00
11	5-C_6H_5	5.60	5.86	10.52	3.11	1.00
12	5-OMe	6.46	6.43	7.29	3.07	1.00
13	5-F	7.31	7.66	7.07	1.35	1.00
14	5-Cl	7.48	7.82	8.21	1.80	1.00
15	5-Br	7.62	7.78	8.51	1.95	1.00
16	5-CF_3	6.94	7.20	8.64	2.61	1.00
17	5-NMe_2	6.75	6.31	7.90	3.08	1.00
18	6-Me	6.75	7.01	7.74	1.00	1.00
19	6-OMe	7.29	7.08	7.29	1.00	1.00
20	6-F	7.28	7.11	7.07	1.00	1.00
21	6-Cl	7.29	6.94	8.21	1.00	1.00
22	6-Br	7.24	6.90	8.51	1.00	1.00
23	6-CF_3	6.45	6.88	8.64	1.00	1.00
24	6-NMe_2	6.65	6.99	7.90	1.00	1.00
25	7-Me	6.56	6.59	7.74	1.00	2.04
26	7-C_2H_5	5.79	5.99	8.80	1.00	3.17
27	7-$CHMe_2$	5.68	5.87	9.59	1.00	3.17
28	7-CMe_3	5.97	5.76	10.39	1.00	3.17
29	7-C_6H_5	5.99	5.76	10.52	1.00	3.11
30	7-OMe[a]	6.83	6.24	7.29	1.00	3.07
31	7-F	7.02	6.97	7.07	1.00	1.35
32	7-Cl	6.87	6.62	8.21	1.00	1.80
33	7-Br	6.65	6.52	8.51	1.00	1.95
34	7-NMe_2	6.12	6.15	7.90	1.00	3.08
35	8-Me	7.15	7.01	7.74	1.00	1.00
36	8-Cl	6.62	6.94	8.21	1.00	1.00
37	5,7-di-Me	6.98	7.31	8.74	2.04	2.04
38	5,8-di-Me	7.96	7.73	8.74	2.04	1.00
39	1,5-di-Me	8.41	7.78	8.34	2.04	1.00
40	5-Me,8-Cl	7.70	7.66	9.21	2.04	1.00
41	1-Cl,5-Me	7.92	7.77	8.47	2.04	1.00

[a] Data points not included in deriving equation.

I_{50} of bis-acridines XX for human jurkat leukemia wild-type cells (JL_c) (Table 140)[147a]

$$\log 1/C = -0.14(\pm 0.13)\text{Clog } P + 4.19(\pm 0.92)B5_5 - 1.11(\pm 0.23)(B5_5)^2 - 0.40(\pm 0.17)B5_7 + 5.44(\pm 1.16) \quad (149)$$

$$n = 37,\ r^2 = 0.842,\ s = 0.293,\ q^2 = 0.789$$

$$\text{optimum } B5_5 = 1.89\ (1.89-1.97)$$

outliers: 3-Cl; 3-Me; 5-C_2H_5; 7-OMe

Two of the above three equations are not very sharp, so that one might look at one standing alone. However, the very good agreement among them for the three different types of cells is impressive. There is no positive hydrophobic effect, only weak negative terms. This is similar to the QSAR for the anilinoacridines. The optimum steric effects of substituents in the 5-position ($B5_5$), the most important factor, are identical. The small negative steric effect of 7-substituents ($B5_7$) are in good agreement. These results can now be compared with the phenazines.

Table 141. I_{50} of Bis-phenazines XXI for Murine P388 Leukemia Cells[147b]

		log 1/C				
no.	substituent	obsd	calcd (eq 150)	Clog P	L_8	Es_9
1	H[a]	6.28	5.30	5.87	2.06	0.00
2	2-Cl	4.92	5.04	5.68	2.06	0.00
3	3-Me	6.33	6.15	6.87	2.06	0.00
4	3-Cl	6.69	6.25	7.34	2.06	0.00
5	4-Me	6.43	6.15	6.87	2.06	0.00
6	6-Me	6.23	6.15	6.87	2.06	0.00
7	6-Cl[a]	5.11	6.25	7.31	2.06	0.00
8	7-Me	6.21	6.15	6.87	2.06	0.00
9	7-Cl	5.53	6.25	7.31	2.06	0.00
10	7-OMe	6.22	6.00	6.60	2.06	0.00
11	8-Me	6.16	6.56	6.87	2.87	0.00
12	8-Cl	7.01	6.99	7.31	3.52	0.00
13	8-OMe	7.13	6.97	6.60	3.98	0.00
14	9-Me	7.82	7.69	6.87	2.06	−1.24
15	9-Cl	7.41	7.36	6.87	2.06	−0.97
16	9-F	6.53	6.33	6.17	2.06	−0.55
17	9-OMe	6.09	6.68	6.60	2.06	−0.55
18	6,9-di-Me	7.59	7.70	7.87	2.06	−1.24
19	6-Cl,9-Me	7.54	7.43	8.31	2.06	−1.24

[a] Data points not included in deriving equation.

I_{50} of bis-phenazines XXI for murine P388 leukemia cells (Table 141)[147b]

$$\log 1/C = 6.26(\pm 5.11)\text{Clog } P - 0.42(\pm 0.37)(\text{Clog } P)^2 + 0.51(\pm 0.38)L_8 - 1.25(\pm 0.47)Es_9 - 17.90(\pm 17.7) \quad (150)$$

$$n = 17,\ r^2 = 0.838,\ s = 0.356,\ q^2 = 0.762$$

$$\text{optimum log } P = 7.37\ (6.94-10.25)$$

outliers: H; 6-Cl

Table 142. I_{50} of Bis-phenazines XXI for Murine Lewis Lung Cells (LL_C)[147b]

		log 1/C			
no.	substituent	obsd	calcd (eq 151)	Clog P	Es_9
1	H[a]	6.97	5.76	5.87	0.00
2	2-Cl	5.08	5.28	5.68	0.00
3	3-Me	7.32	7.27	6.87	0.00
4	3-Cl	7.92	7.43	7.34	0.00
5	4-Me	7.59	7.27	6.87	0.00
6	6-Me	7.34	7.27	6.87	0.00
7	6-Cl	6.82	7.43	7.31	0.00
8	7-Me	7.14	7.27	6.87	0.00
9	7-Cl	7.08	7.43	7.31	0.00
10	7-OMe	7.19	7.01	6.60	0.00
11	8-Me	6.97	7.27	6.87	0.00
12	8-Cl	7.36	7.43	7.31	0.00
13	8-OMe	7.62	7.01	6.60	0.00
14	9-Me	8.80	8.61	6.87	−1.24
15	9-Cl	8.06	8.31	6.87	−0.97
16	9-F	6.92	6.97	6.17	−0.55
17	9-OMe[a]	6.80	7.60	6.60	−0.55
18	6,9-di-Me	8.28	8.53	7.87	−1.24
19	6-Cl,9-Me	8.28	7.99	8.31	−1.24

[a] Data points not included in deriving equation.

I_{50} of bis-phenazines XXI for murine Lewis lung cells (LL_C) (Table 142)[147b]

$$\log 1/C = 11.62(\pm 5.10)\text{Clog } P - 0.79(\pm 0.37)(\text{Clog } P)^2 - 1.08(\pm 0.45)Es_9 - 35.12(\pm 17.71) \quad (151)$$

$$n = 17,\ r^2 = 0.845,\ s = 0.357,\ q^2 = 0.617$$

$$\text{optimum log } P = 7.32\ (7.09-7.77)$$

outliers: H; 9-OMe

Table 143. I_{50} of Bis-phenazines XXI for Human Jurkat Leukemia Wild-Type Cells (JL_C)[147b]

		log 1/C				
no.	substituent	obsd	calcd (eq 152)	Clog P	L_8	Es_9
1	H[a]	6.76	5.90	5.87	2.06	0.00
2	2-Cl	5.63	5.66	5.68	2.06	0.00
3	3-Me	6.68	6.70	6.87	2.06	0.00
4	3-Cl	7.13	6.81	7.34	2.06	0.00
5	4-Me	6.99	6.70	6.87	2.06	0.00
6	6-Me	6.76	6.70	6.87	2.06	0.00
7	6-Cl	6.68	6.80	7.31	2.06	0.00
8	7-Me	6.55	6.70	6.87	2.06	0.00
9	7-Cl	6.60	6.81	7.31	2.06	0.00
10	7-OMe	6.71	6.56	6.60	2.06	0.00
11	8-Me	6.83	7.05	6.87	2.87	0.00
12	8-Cl	7.38	7.43	7.31	3.52	0.00
13	8-OMe	7.52	7.39	6.60	3.98	0.00
14	9-Me	8.24	8.04	6.87	2.06	−1.24
15	9-Cl	7.85	7.75	6.87	2.06	−0.97
16	9-F	6.75	6.82	6.17	2.06	−0.55
17	9-OMe	6.91	7.15	6.60	2.06	−0.55
18	6,9-di-Me	7.68	8.05	7.87	2.06	−1.24
19	6-Cl,9-Me	8.01	7.80	8.31	2.06	−1.24

[a] Data point not included in deriving equation.

I_{50} of bis-phenazines XXI for human jurkat leukemia wild-type cells (JL_C) (Table 143)[147b]

$$\log 1/C = 5.86(\pm 3.21)\text{Clog } P - 0.40(\pm 0.23)(\text{Clog } P)^2 + 0.43(\pm 0.22)L_8 - 1.08(\pm 0.29)Es_9 - 15.69(\pm 11.16) \quad (152)$$

$$n = 18,\ r^2 = 0.903,\ s = 0.226,\ q^2 = 0.837$$

$$\text{optimum log } P = 7.38\ (7.09-8.11)$$

outlier: H

Again, although the three equations are not very sharp and one would like more data points, the good agreement is reassuring. The optimum log *P* values are identical. The Es terms are also close. These six equations remind us of the results from eqs 77 and 80, where we see what appears to be a small molecular change that can result in a grossly different SAR. Introducing the second nitrogen into acridines to yield phenazines does greatly lower the basicity of the acridine nitrogen. This must be an important factor in determining the orientation of the phenazines in their receptor interaction so that one set has no dependence on hydrophobicity and the other is highly dependent on it.

XXI. Benzylamines

Table 144. Monoamine Oxidase (bovine kidney cortex) Oxidation at pH 7.6 of X−$C_6H_4CH_2NH_2$[147c]

		log V_{max}		
no.	substituent	obsd	calcd (eq 153)	σ^+
1	3-Cl	0.49	0.53	0.40
2	4-Cl	0.42	0.39	0.11
3	4-F	0.40	0.30	−0.07
4	H	0.28	0.34	0.00
5	3-Me	0.29	0.30	−0.07
6	4-Me[a]	−0.28	0.19	−0.31
7	4-OMe	−0.05	−0.03	−0.78

[a] Data point not included in deriving equation.

Monoamine oxidase (bovine kidney cortex) oxidation at pH 7.6 of X−$C_6H_4CH_2NH_2$ (Table 144)[147c]

$$\log V_{max} = 0.47(\pm 0.20)\sigma^+ + 0.34(\pm 0.07) \quad (153)$$

$$n = 6,\ r^2 = 0.917,\ s = 0.062,\ q^2 = 0.787$$

outlier: 4-Me

Table 145. Oxidation of X−$C_6H_4CH_2NH_2$ by Methylamine Dehydrogenase from *Paracoccus denitrificans*[148]

		log k_3/K_s		
no.	substituent	obsd	calcd (eq 154)	σ^+
1	4-OMe	−1.76	−1.83	−0.78
2	4-Me	−1.19	−1.17	−0.31
3	H	−0.77	−0.73	0.00
4	4-Br	−0.61	−0.52	0.15
5	4-NO_2	0.46	0.38	0.79

Oxidation of X−$C_6H_4CH_2NH_2$ by methylamine dehydrogenase from Paracoccus denitrificans (Table 145)[148]

$$\log k_3/K_S = 1.40(\pm 0.23)\sigma^+ - 0.73(\pm 0.12) \quad (154)$$

$$n = 5,\ r^2 = 0.992,\ s = 0.084,\ q^2 = 0.955$$

k_3 is equivalent to k_{cat} and K_S to K_m

Table 146. Oxidation of X−$C_6H_4CH_2NH_2$ by *N*-Chlorosuccinimide[149]

		log k_2			
no.	substituent	obsd	calcd (eq 155)	σ^+	$B1_2$
1	H	−2.55	−2.57	0.00	1.00
2	4-Me	−1.92	−1.94	−0.31	1.00
3	4-OMe	−0.93	−0.97	−0.70	1.00
4	4-F	−2.38	−2.43	−0.07	1.00
5	4-Cl	−2.82	−2.80	0.11	1.00
6	4-Br	−2.75	−2.88	0.15	1.00
7	4-NO_2	−4.17	−4.19	0.79	1.00
8	4-CF_3	−3.63	−3.82	0.61	1.00
9	4-COOMe	−3.37	−3.58	0.49	1.00
10	4-NHCOMe	−1.18	−1.34	−0.60	1.00
11	3-Me	−2.30	−2.43	−0.07	1.00
12	3-OMe	−2.56	−2.82	0.12	1.00
13	3-F	−3.40	−3.27	0.34	1.00
14	3-Cl	−3.35	−3.33	0.37	1.00
15	3-I	−3.30	−3.29	0.35	1.00
16	3-NO_2	−4.40	−4.03	0.71	1.00
17	3-CF_3	−3.78	−3.45	0.43	1.00
18	3-COOMe	−3.53	−3.31	0.36	1.00
19	3-NH_2	−2.33	−2.24	−0.16	1.00
20	2-Me	−1.19	−1.38	−0.31	1.52
21	2-OMe	−1.00	−0.60	−0.78	1.35
22	2-F	−2.41	−2.05	−0.07	1.35
23	2-Cl	−2.30	−1.94	0.11	1.80
24	2-Br	−2.15	−1.86	0.15	1.95
25	2-NO_2[a]	−2.48	−3.44	0.79	1.70
26	2-CF_3	−2.43	−2.75	0.61	1.99
27	2-COOMe	−2.43	−2.89	0.49	1.64
28	2-NHCOMe	−0.57	−0.97	−0.60	1.35

[a] Data point not included in deriving equation.

These can be compared with the following examples from physical organic chemistry.

Oxidation of X−$C_6H_4CH_2NH_2$ by N-chlorosuccinimide (Table 146)[149]

$$\log k_2 = -2.05(\pm 0.23)\sigma^+ + 1.08(\pm 0.32)B1_2 - 3.65(\pm 0.39) \quad (155)$$

$$n = 27,\ r^2 = 0.940,\ s = 0.253,\ q^2 = 0.916$$

outlier: 2-NO_2

It is surprising that ortho substituents produce a positive steric effect.

Table 147. Oxidation of X−$C_6H_4CH_2NH_2$ by *N*-Bromoacetamide[150]

		log k_2			
no.	substituent	obsd	calcd (eq 156)	σ^+	$B1_2$
1	H	−2.38	−2.34	0.00	1.00
2	4-Me	−1.86	−1.87	−0.31	1.00
3	4-OMe	−0.96	−1.15	−0.78	1.00
4	4-F	−2.15	−2.23	−0.07	1.00
5	4-Cl	−2.44	−2.51	0.11	1.00
6	4-Br	−2.51	−2.57	0.15	1.00
7	4-NO_2	−3.48	−3.55	0.79	1.00
8	4-CF_3	−3.11	−3.27	0.61	1.00
9	4-COOMe	−3.02	−3.09	0.49	1.00
10	4-NHCOMe	−1.18	−1.42	−0.60	1.00
11	3-Me	−2.20	−2.23	−0.07	1.00
12	3-OMe	−2.41	−2.52	0.12	1.00
13	3-F	−2.98	−2.86	0.34	1.00
14	3-Cl	−2.96	−2.91	0.37	1.00
15	3-I	−2.86	−2.88	0.35	1.00
16	3-NO_2	−3.67	−3.43	0.71	1.00
17	3-CF_3	−3.22	−3.00	0.43	1.00
18	3-COOMe	−3.10	−2.89	0.36	1.00
19	3-NH_2	−2.17	−2.10	−0.16	1.00
20	3-NHCOMe	−2.53	−2.66	0.21	1.00
21	2-Me	−1.52	−1.59	−0.31	1.52
22	2-OMe	−1.31	−0.96	−0.78	1.35
23	2-F	−2.34	−2.05	−0.07	1.35
24	2-Cl	−2.26	−2.09	0.11	1.80
25	2-Br	−2.18	−2.07	0.15	1.95
26	2-I	−2.00	−1.95	0.14	2.15
27	2-NO_2[a]	−2.24	−3.18	0.79	1.70
28	2-CF_3	−2.31	−2.75	0.61	1.99
29	2-COOMe[a]	−1.54	−2.75	0.49	1.64
30	2-NHCOMe	−1.13	−1.24	−0.60	1.35

[a] Data points not included in deriving equation.

Oxidation of X−$C_6H_4CH_2NH_2$ by N-bromoacetamide (Table 147)[150]

$$\log k_2 = -1.53(\pm 0.17)\sigma^+ + 0.53(\pm 0.20)B1_2 - 2.87(\pm 0.25) \quad (156)$$

$$n = 28,\ r^2 = 0.940,\ s = 0.180,\ q^2 = 0.912$$

outliers: 2-NO_2; 2-COOMe

Table 148. Oxidation of X−$C_6H_4CH_2NH_2$ by Permanganate[151]

		log *k*		
no.	substituent	obsd	calcd (eq 157)	σ^+
1	H	1.54	1.56	0.00
2	4-Me	1.61	1.63	−0.31
3	4-Et	1.62	1.63	−0.30
4	4-OMe	1.76	1.74	−0.78
5	4-Cl	1.51	1.54	0.11
6	4-NO_2[a]	1.60	1.38	0.79
7	3-Me	1.67	1.58	−0.07
8	3-OMe	1.52	1.55	0.05
9	3-Cl	1.44	1.47	0.40
10	3-NO_2	1.45	1.41	0.67

[a] Data point not included in deriving equation.

Oxidation of X−$C_6H_4CH_2NH_2$ by permanganate (Table 148)[151]

$$\log k = -0.23(\pm 0.09)\sigma^+ + 1.56(\pm 0.04) \quad (157)$$

$$n = 9,\ r^2 = 0.839,\ s = 0.045,\ q^2 = 0.739$$

outlier: 4-NO_2

Both the biochemical and the simple chemical oxidations depend heavily on σ^+, but the signs with σ^+ are opposite indicating different mechanisms of reaction. There is considerable evidence that haloamides are effective means for radical oxidations.[9] The first step for eqs 155−157 would seem to be •H abstractions from the CH_2 moiety. Permanganate is so potent that only a small but highly significant coefficient is evident in eq 157. The weaker oxidants need more help from the substituent, and hence, one finds the larger coefficients in eq 155 and 156. For eqs 153 and 154, the initial step might be abstraction of H^+ aided by delocalization of a positive charge.

XXII. Multiple Drug Resistance

A very interesting phenomenon that first became exceedingly important in cancer research was the ability of cells to expel a variety of drugs. This was termed 'multiple drug resistance'. It is now recognized as a general problem in the treatment of cancer patients (or cancer cells) with a single drug, as the cells are found to become quite resistant to a large variety of other drugs. This led to the use of a cocktail of drugs in treating cancer as well as other diseases that became resistant. The pioneering work of Beidler and Riehm[152] showed that the exposure of Chinese hamster cells to increasing concentrations of actinomycin D resulted in the development of resistance to a broad range of various structurally unrelated drugs.[152] Juliano and Ling[153] then identified the so-called P-glycoprotein that appears to extrude from resistant cells many unrelated molecules. While Beidler and Reihm observed that the extrusion of various chemicals appeared to be associated with molecular weight, they did not attempt to derive a QSAR. Other authors thought that it was associated with lipophilicity but also made no attempt at a QSAR study. Our laboratory undertook an examination of their data.[154]

Table 149. Cross Resistance (CR) Induced in Chinese Hamster Ovary Cells by Actinomycin D[154]

		log CR		
no.	substituent	obsd	calcd (eq 158)	log MW
1	Mithramycin	2.83	2.65	3.04
2	Vincristine	2.28	2.40	2.97
3	Puromytine	1.92	1.33	2.67
4	Daunomycine	1.46	1.51	2.72
5	Demecolsine	1.26	0.97	2.57
6	Mitomycin-C	0.49	0.79	2.52
7	Proflavine	0.46	0.69	2.49
8	Novobiocin	0.28	−0.06	2.28
9	Bromodeoxuridine	0.08	0.69	2.49
10	4-Nitroquinoline-*N*-oxide	0.04	−0.06	2.28
11	Amethopterine[a]	0.04	1.29	2.66
12	6-Mercaptopurine	−0.03	−0.24	2.23
13	Hydrocortisone[a]	−0.40	1.40	2.69
14	Nitrogen-mustard	−0.40	−0.06	2.28
15	Actinmycin-D	2.58	2.87	3.10
16	Vinblastine	2.58	2.37	2.96

[a] Data points not included in deriving equation.

Cross resistance (CR) induced in Chinese hamster ovary cells by actinomycin D (Table 149)[154]

$$\log \mathrm{CR} = 3.57(\pm 0.68) \log \mathrm{MW} - 8.20(\pm 1.79) \quad (158)$$

$$n = 14,\ r^2 = 0.916,\ s = 0.342,\ q^2 = 0.891$$

outliers: Amethopterine, Hydrocortisone

CR is the degree of cross resistance induced by actinomycin D compared to that in normal CHO cells (i.e., ED_{50} resistant cells/ED_{50} sensitive cells).

Adding two terms in log P' (P' = distribution coefficient measured at pH 7.4) makes a slight but dubious improvement.

$$\log \mathrm{CR} = 3.43(\pm 0.86) \log \mathrm{MW} + 0.15(\pm 0.21) \log P' - 0.04(\pm 0.08)(\log P')^2 + 7.86(\pm 0.21) \quad (159)$$

$$n = 14,\ r^2 = 0.933,\ s = 0.335,\ q^2 = 0.855$$

Note that the 95% confidence limits on the log P' terms are larger than the coefficients. The ratio of data points to variables is not good. If there is a role for hydrophobicity, it is very small.

Table 150. Cross Resistance (CR) Induced by Methotrexate in L1210/R71 Cells[154]

		log CR			
no.	substituent	obsd	calcd (eq 160)	log P'	log MW
1	H(R)[b,c]	2.18	1.87	−3.00	2.40
2	3-CONH$_2$(R)[b]	1.85	2.16	−4.49	2.47
3	3-COMe(R)[b]	2.20	2.05	−3.55	2.47
4	3-OH(R)[b]	1.86	2.00	−3.67	2.43
5	3-Br[b]	2.06	1.96	−2.14	2.52
6	3-$C_{12}H_{25}$[a,b]	0.52	−73.81	3.41	2.62
7	3-$CH_2OC_6H_4$-3′-C_6H_5[b]	1.22	1.72	0.69	2.64
8	Hydroxyurea	0.30	−0.09	−1.27	1.88
9	Guanazole	0.08	0.45	−1.61	2.00
10	5-fluorouracil[a]	−0.04	−61.03	−0.89	2.11
11	6-mercaptopurine	0.60	1.10	0.01	2.23
12	Azacytidine	1.54	1.76	−2.17	2.39
13	Cytosine-arabinoside	1.61	1.85	−2.13	2.44
14	Metoprine	1.70	1.32	2.56	2.43
15	Etoprine	1.69	1.32	2.93	2.45
16	Mitomycin-C	1.89	1.77	−0.38	2.52
17	Damp	1.63	1.49	2.64	2.57
18	Piritrexim	1.89	1.60	1.77	2.64
19	Methotrexate	2.55	2.06	−2.52	2.66
20	Puromycin	1.82	1.69	0.86	2.67
21	Trimetrexate	1.75	1.68	0.84	2.70
22	Bakers-antifol-I	2.18	1.94	−1.84	2.73
23	Bakers-antifol-II	1.12	1.39	2.42	2.79
24	Tamoxifen	0.59	1.28	4.03	2.75
25	Maytansine	1.23	1.33	1.99	2.84
26	Mithramycin	0.66	0.78	−0.25	3.04
27	Valinomycin	0.59	0.34	3.24	3.05
28	Actinomycin-D	0.12	0.05	3.21	3.10
29	Bleomycin	0.24	0.31	−2.38	3.15
30	Liblomycin[a]	0.29	−89.98	−1.11	3.31

[a] Data points not included in deriving equation. [b] Substituents at 3-position of phenyl ring in 2,4-diamino-6-di-methyl-5-(3-X-phenyl) triazines. [c] (R) denotes R-isomer

Cross resistance induced by methotrexate in L1210/R71 cells (Table 150)[154]

$$\log CR = 5.58(\pm 1.36)MW - 29.7(\pm 6.75)\log(\beta \times 10^{\log MW} + 1) - 0.11(\pm 0.06)\log P' + 10.19(\pm 2.91) \quad (160)$$

$$n = 27,\ r^2 = 0.817,\ s = 0.337,\ q^2 = 0.720$$

$$\text{optimum log MW} = 2.6(\pm 0.13)$$

outliers: 5-F-uracil; liblomycin; 3-$C_{12}H_{25}$-phenyl-triazines

We see no positive log P' term. In this instance, a sharp fall in log CR comes at 2.6. There has been some thought that the molecular weight of the drug inducing cross resistance may play a role in setting the optimum log CR. Actinomycin D has a molecular weight of 1255, vincristine 825, methotrexate 455, and colchicine 399. Hence, our results support this qualitative thinking.

Table 151. Cross Resistance (CR) Induced by Colchicine in CHO Cells[154]

		log CR			
no.	substituent	obsd	calcd (eq 161)	log MW	log P'
1	Colchicine[a]	2.26	1.23	2.60	1.30
2	Puromycin	2.02	1.44	2.67	0.86
3	Daunomycin	1.88	1.57	2.72	0.66
4	Emetine	1.46	1.29	2.74	3.24
5	Ethidium-Bromide	1.04	1.25	2.60	1.15
6	Acriflavin	0.84	0.66	2.41	1.60
7	Cytochalasin-B	1.04	1.15	2.68	3.37
8	Erythromycin[a]	0.70	1.89	2.98	1.26
9	Colcemid	1.20	1.14	2.57	1.37
10	Cinblastine	1.46	1.51	2.91	3.69
11	Gramicidin-D	2.16	2.20	3.27	0.05
12	Adriamycin	1.40	1.70	2.75	0.10
13	Proflavine	0.60	0.43	2.32	1.10
14	Melphalan	1.18	1.27	2.50	−0.52
15	Mechlorethamine	0.48	0.31	2.28	0.91
16	Chlorambucil	0.30	0.89	2.48	1.47
17	Ara-C[a]	0.00	1.22	2.44	−2.13
18	Bleomycin[a]	0.00	2.47	3.15	−2.38
19	5-Flurouracil	0.00	−0.12	2.11	−0.89
20	Thiotepa	0.00	0.36	2.28	0.53

[a] Data points not included in deriving equation.

Cross resistance induced in by colchicine in CHO cells (Table 151)[154]

$$\log CR = 11.76(\pm 9.61)\log MW - 1.80(\pm 1.78)(\log MW)^2 - 0.12(\pm 0.16)\log P' - 17.06(\pm 12.76) \quad (161)$$

$$n = 16,\ r^2 = 0.821,\ s = 0.316,\ q^2 = 0.714$$

$$\text{optimum log MW} = 3.28(2.96-89.47)$$

outliers: colchicine; erythromycin; Ara-C; bleomycin

Table 152. Cross Resistance (CR) Induced by Vincristine in CCRF−CEM Cells[154]

		log CR			
no.	substituent	obsd	calcd (eq 162)	log MW	log P
1	Vindesine	3.00	2.82	2.93	0.67
2	Maytansine[a]	2.85	1.53	2.84	1.99
3	Vincristine	2.76	2.29	2.97	2.57
4	Teniposide	1.56	1.72	2.82	1.22
5	Etoposide	1.51	1.61	2.77	0.60
6	Doxorubicin	1.46	1.68	2.75	0.10
7	Vinblastine	1.28	1.71	2.96	3.69
8	Daunorobucin	1.20	1.20	2.72	0.66
9	Colchicine[a]	1.08	0.10	2.60	1.03
10	Podophyllotoxin	0.07	−0.19	2.62	2.01

[a] Data points not included in deriving equation.

Cross resistance induced by vincristine in CCRF−CEM cells (Table 152)[154]

$$\log CR = 7.77(\pm 2.98)\log MW - 0.45(\pm 0.31)\log P - 19.65(\pm 8.21) \quad (162)$$

$$n = 8,\ r^2 = 0.901,\ s = 0.343,\ q^2 = 0.50$$

outliers: Maytansine; Colchicine

One would like to see sharper QSAR than the above examples; however, it would be extremely difficult using chemically based parameters because

of the unrelated structures involved. In cases such as this, lateral validation is extremely important. We find no evidence for a positive hydrophobic effect. In fact, the results seem astonishing to us considering the extreme variation in structure. One wonders how cells 'decide' to extrude certain xenobiotics and not eliminate chemicals necessary for their existence! We have no idea how often this process may be significant in the long-term treatment of patients. It certainly warrants much more careful study using QSAR and better selected sets of chemicals.

XXIII. General Discussion

The results in this report (and others[2−10]) make clear that we can begin to construct a science of chemical−biological interactions. Using descriptors with a clearly defined chemical meaning is of course a necessity. The current C-QSAR program that contain 15600 data sets and corresponding QSAR and chemical structures is a modest start. Our current goal is to add about 1000 new QSAR/year. The greatest problem is that chemists give very little thought to building data sets with parametrizable structure variation in hydrophobic, steric, and electronic properties. Here we have undertaken a rather limited problem—that of looking for QSAR without hydrophobic terms where, in general, we could tie the results to simple studies from mechanistic organic chemistry. Our constant concern is to find means for validation of QSAR. The problem of rationalization of the mechanism of action of a set of 'congeners' on even simple cells, to say nothing of whole organisms, is so complex that it is easy to understand the reluctance of many to consider it seriously.

Of course, in the present study, based on the absence of a positive hydrophobic effect, it is highly important to have a good spread in log P or π in the data set. With small sets this cannot easily be accomplished. Still, the small sets provide starting points for more carefully designed studies. Fundamental to the present study is a good program for the calculation of log P. At present, our database contains over 3600 QSAR having a log P term (the vast majority are calculated values) and we have about 800 based on one or more π terms. Thus, we see that about 70% of our equations contain a hydrophobic term. An interesting study that must be done is to consider those that contain only negative hydrophobic terms. The quality of the current version (4) of Leo's calculated Clog P program is illustrated by eq 163.

$$\text{Mlog } P = 0.956(\pm 0.003)\text{Clog } P + 0.0984(\pm 0.009) \quad (163)$$

$$n = 10\ 000,\ r^2 = 0.970,\ s = 0.278,\ q^2 = 0.970$$

The 10 000 measured values (Mlog P) have been carefully selected and evaluated over the past 30 years by Leo. This is not an easy task. Sometimes there are a number of measured values for a given chemical so that one can look for agreement in selecting the proper value. Often one has to take what is available. The experimental values come from many hundreds of laboratories having various levels of experience. How much this affects s (standard deviation) is not known, but it is definitely significant. For instance, we (and others) have observed a number of times that we could obtain slightly better QSAR using Clog P in place of Mlog P! In using Clog P, the parent compound may be somewhat off the mark but the relative values of the derivatives can be reliable so that a good correlation can be obtained. However, this does affect optimum log P and the intercept of the QSAR. Shortcomings in the Hammett parameters must also be noted. The collinearity problem is most serious comparing σ_P and σ_m, and we find the following result.

$$\sigma_P = 1.21(\pm 0.02)\sigma_m - 0.09(\pm 0.01) \quad (164)$$

$$n = 1111,\ r^2 = 0.899,\ s = 0.098,\ q^2 = 0.899$$

This means that unless a careful selection of substituents is made, one does not get as good a picture of electronic effects as possible. The same holds true for σ_P, σ_P^+, and σ_P^-.

$$\sigma_P = 0.58(\pm 0.03)\sigma_P^- + 0.17(\pm 0.02) \quad (165)$$

$$n = 199,\ r^2 = 0.878,\ s = 0.168,\ q^2 = 0.875$$

However, by taking care, one can select a set of values that are not highly collinear.[9] This is very important in order to understand the electronic role of the substituents as, for instance, in radical reactions.[9] Even with their shortcomings, the σ parameters have definite advantages over molecular orbital calculations. The σ parameters for a set of compounds can be auto loaded in the C-QSAR program instantly. More important is the ability to sort out two types of through-resonance revealed by σ^- and σ^+. Also, we have a growing database of over 8300 QSAR from all areas of mechanistic organic chemistry for comparison.

A point that we had not expected is that most of the QSAR are based on σ^+ or σ^-. This means that for these equations, through-resonance is important, i.e., direct resonance interaction between the reaction center (functional group). The σ^+ parameter indicates delocalization of a positive charge or a lone electron, while σ^- implies delocalization of a negative charge in the transition state. It is of the utmost importance, early on, in research on chemical−biological interactions to know which type of sigma parameters (σ, σ^-, σ^+, σ_I, etc.) are important to assist in project development but also to relate a current study to what has been done.

There are important implications from sigma that have a bearing on chemical and biological reaction mechanisms. There is an increasing tendency to use quantum chemical calculations to gain perspective on mechanism. We as well as others have found such an approach to be useful.[10c,33,34,36,71,76,80,127,155−157] What is not yet clear is can one get the same clues out of MO calculations as one can get from σ^+ and σ^-? In any case, where it is possible, we believe that one should start work with the Hammett parameters until it is clear electronically what is going on. Then

one might want to shift to the much more time-consuming use of MO parameters. We found this to be the right approach in the study of phenol toxicity to leukemia cells (eqs 77 and 79).

What information can be deduced from our present study? We have been somewhat aware that when DNA seems to be the target receptor, positive hydrophobic terms are often lacking. Equations 1−20, 25−27, and 147−149 illustrate the point. In general, DNA would seem to be a hydrophilic substance, but some have assumed that intercalculation of ligands between base pairs might be correlated with a positive hydrophobic effect. The only example we have with a known DNA interaction showing a positive hydrophobic effect is the following.

Table 153. Denaturation of DNA from T4-Phage by a Set of Aliphatic Alcohols, Amides, and Phenols[158]

		log 1/*C*			
no.	substituent	obsd	calcd (eq 166)	log *P*	*I*
1	methanol	−0.54	−0.32	−0.66	0
2	ethanol	−0.08	−0.05	−0.16	0
3	2-propanol	0.05	0.12	0.14	0
4	propanol	0.27	0.23	0.34	0
5	allyl alcohol	0.30	0.14	0.17	0
6	2-butanol	0.21	0.38	0.61	0
7	*tert*-butyl alcohol	0.22	0.25	0.37	0
8	cyclohexanol	0.66	0.72	1.23	0
9	benzyl alcohol[a]	1.05	0.65	1.10	0
10	phenol	1.10	0.85	1.46	0
11	4-methoxyphenol	1.05	0.78	1.34	0
12	acetonitrile	−0.08	−0.15	−0.34	0
13	*tert*-amyl alcohol	0.41	0.53	0.89	0
14	butanol	0.48	0.53	0.88	0
15	isobutanol	0.35	0.40	0.65	0
16	hexanamide	0.77	0.97	0.79	1
17	butyramide	0.34	0.42	−0.21	1
18	propanamide	0.21	0.15	−0.71	1
19	acetamide	−0.04	−0.13	−1.21	1
20	formamide	−0.28	−0.41	−1.71	1

[a] Data point not included in deriving equation.

Denaturation of DNA from T4-phage by a set of aliphatic alcohols, amides, and phenols (Table 153)[158]

$$\log 1/C = 0.55(\pm 0.10) \log P + 0.50(\pm 0.20)I + 0.04(\pm 0.10) \quad (166)$$

$$n = 19,\ r^2 = 0.888,\ s = 0.148,\ q^2 = 0.817$$

outlier: benzyl alcohol

The indicator variable *I* is assigned the value of 1 for five aliphatic amides. Considering the amides alone we find (Table 154).

Table 154. Denaturation of DNA from T4-Phage by Amides[158]

		log 1/*C*		
no.	substituent	obsd	calcd (eq 167)	log *P*
1	formamide	−0.28	−0.25	−1.71
2	acetamide	−0.04	−0.05	−1.21
3	propanamide	0.21	0.16	−0.71
4	butyramide	0.34	0.37	−0.21
5	hexanamide	0.77	0.78	0.79

$$\log 1/C = 0.41(\pm 0.06) \log P + 0.45(\pm 0.06) \quad (167)$$

$$n = 5,\ r^2 = 0.994,\ s = 0.037,\ q^2 = 0.986$$

The amides are about three times as potent as the alcohols. We do not know the exact mechanism, but the results suggest that very hydrophobic amides could be quite toxic.

Reactions that appear to involve radical reactions often lack hydrophobic terms.[9] These are generally correlated by QSAR with $-\rho^+$ terms. The studies are mostly on small data sets, and more work is urgently needed.

Normally we have assumed that for chemicals to cross a hydrophobic cell membrane, a positive log *P* would be helpful. Of course, if the receptor where the substance is interacting were hydrophilic, binding to it could offset the hydrophobic contribution to cell entry.

A problem that needs more consideration, of which at present we have no good data, is that of active transport. The QSAR on multiple drug resistance suggests that this could be accomplished without hydrophobic assistance.

It is instructive to review the development of eq 79, from small unusual clues on the action of phenols on rat embryos and CHO cancer cells related to σ^+. From these correlations, we suspected a possible radical reaction. A review of the literature[9] found many examples of phenol radicals in mechanistic organic chemistry and a small number in biochemistry correlated by σ^+. This background stimulated serious work on fast growing cells that at first provided an opaque model (eq 75) with good statistics, but as Mark Twain said "There are lies, damn lies and statistics". What seems to be a strange result of this evolution is that we have a good model for estrogenicity and carcinogenicity of phenols that *disconnects* estrogenicity from the binding of ligands to the estrogen receptor.[10b] Could this model have been developed using some of the hot new approaches to QSAR such as CoMFA, neural networks, genetic algorithms, or electrotopographical surfaces? We believe not, since the parameters used in these methods are not related to the results of 75 years of study of mechanistic physical organic chemistry. In fact, these approaches have paid little or no attention to comparative QSAR. A high correlation coefficient is so often the end point. Comparative molecular field analysis (CoMFA) provides fascinating 3-D pictures, but we know of no successful comparison of pictures on several different data sets.

Another illustration of the use of the C-QSAR program[159] is that of uncovering the phenomenon of ring flipping.[160,161] A number of examples have been uncovered where phenyl rings with substituents in the meta positions can flip to place a meta substituent on a hydrophobic surface or in the aqueous solvent phase. Hence, hydrophobic meta substituents receive a normal π value while hydrophilic substituents are given a π value of 0.

QSAR is such a confusing business. There is the problem of organic synthesis that is confounded by synthetic difficulties. Naturally chemists want to prepare the easiest compounds possible. There is the extremely difficult problem of which biological test system to employ out of an unending number of possibilities. Equation 79 shows that one can get

surprising information out of a very simple system if one can make use of known chemical and biological information. We tend to downplay statistics because of a tendency to rely too much on it. However, it is essential for starting and especially for minimizing the collinearity problem. Finally, one has the choice of a surprising number of model building programs both for the mathematical QSAR and the fitting of chemicals to receptors. Any one of these areas can become a lifetime study. However, we have to do the best that we can to integrate this astonishingly complex business into an increasingly useful system of chemical-bioinformatics. The only way to do this is via QSAR using parameters that are mechanistically understandable and that have received a large amount of testing.

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XXV. References

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