Division Control No. 145B

QSAR OF ACUTE TOXICITY OF MONO-SUBSTITUTED BENZENE DERIVATIVES TO PHOTOBACTERIUM PHOSPHOREUM

Kaiser, Klaus L.E., Virginia S. Palabrica and
Juan M. Ribo[1]

NWRI Contribution No. 87-23

Environmental Contaminants Division
National Water Research Institute
Canada Centre for Inland Waters
Burlington, Ontario, Canada L7R 4A6

[1]Toxicology Research Centre
University of Saskatchewan
Saskatoon, Saskatchewan S7N 0W0

. Environment Canada

RQSA DE LA TOXICITÉ AIGUË DES DÉRIVÉS DE BENZÈNE MONOSUBSTITUÉ AU PHOTOBACTERIUM PHOSPHOREUM

KLAUS L.E. KAISER, VIRGINIA S. PALABRICA et JUAN M. RIBO[1]
Division des contaminants de l'environnement
Institut national de recherche sur les eaux
C.P. 5050, Burlington (Ontario) L7R 4A6 CANADA

RÉSUMÉ

Une centaine de dérivés monosubstitués du benzène de formule générale C_6H_5-X, où X = groupe aliphatique ou aromatique, ont été testés pour en connaître la toxicité aiguë pour le Photobacterium phosphoreum. La gamme de toxicités observées est près de cinq ordres de grandeur sur une base molaire. Les corrélations quantitatives structure-toxicité avec le coefficient de partition octanol/eau, l'énergie de la bande d'absorption U.V. des composés, la réfringence molaire des substituants en unités logarithmiques et un indicateur des groupes acides-OH expliquent 61 % de la variation observée. Trois sous-ensembles de ces composés de formule générale C_6H_5-Y-Z, où Z = groupe aliphatique ou aromatique et Y = NH ou CO, C_6H_4 ou N=N-C_6H_4 et 0 ou 0C0, peuvent être décrits avec une plus grande précision par les mêmes paramètres lorsqu'ils sont groupés de façon adéquate. La toxicité d'un autre sous-ensemble avec Y = CH_2 est décrite par la méthode de la réfringence molaire et le paramètre B_3 Sterimol.

---

[1] Adresse actuelle : Toxicology Research Centre, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0.

TEXTNAME: Klaus (R)P: 01

QSAR OF ACUTE TOXICITY OF MONO-SUBSTITUTED BENZENE DERIVATIVES TO PHOTOBACTERIUM PHOSPHOREUM

KLAUS L.E. KAISER, VIRGINIA S. PALABRICA and JUAN M. RIBO[1]

Environmental Contaminants Division, National Water Research Institute, P.O. Box 5050, Burlington, Ontario L7R 4A6 CANADA

ABSTRACT

One hundred mono-substituted benzene derivatives of the general formula C_6H_5-X, where X = aliphatic or aromatic group, were tested for acute toxicity to Photobacterium phosphoreum. The observed toxicity range is close to five orders of magnitude on a molar basis. Quantitative structure-toxicity correlations with the octanol/water partition coefficient, the energy of the ultraviolet absorption band of the compounds, the substituents' molar refractivity in logarithmic

[1] Present address: Toxicology Research Centre, University of Saskatchewan, saskatoon, Saskatchewan S7N 0W0.

units, and an indicator for acidic -OH groups, explains 61% of the variation observed. Three subsets of these compounds of the general formula C_6H_5-Y-Z, where Z = aliphatic or aromatic group and Y = NH or CO, C_6H_4 or N=N-C_6H_4, and O or OCO, can be described with higher accuracy by the same parameters when grouped accordingly. The toxicity of another subset with Y = CH_2 is best described by the molar refractivity and the B_3 Sterimol parameter.

KEYWORDS

Mono-substituted benzene, acute toxicity, Photobacterium phosphoreum, QSAR.

INTRODUCTION

With the recent development of reliable microbiological tests for acute toxicity determination, such as the Microtox™ test* (Bulich et al. 1981) and the resazurin test (Thomson et al. 1986), convenient tools became available for the investigation of larger series of chemicals in relatively short time and independent of local biological species and environments. It has also been demonstrated that these tests are generally quite representative of such chemicals' acute and sublethal effects to a variety of fish and other aquatic species (Ribo and Kaiser 1983) and - to a lesser degree - to terrestrial species (Hodson 1985).

---

* Trademark of Microbics Corp., Carlsbad, California, U.S.A.

TEXTNAME: Klaus (R)P: 03

We have previously used the Microtox™ test to determine the acute toxicities of several series of chlorobenzenes, -phenols, -anilines, -nitrobenzenes, and -pyridines (Kaiser and Ribo 1985; Ribo and Kaiser 1983). For each of these series, a major dependence of the toxicity on the octanol/water partition coefficient (log P) was demonstrated. However, additional parameters, such as the hydrophilic effect parameter (V_H) were required to reduce the variation between the different groups of congeners.

Recently, we have extended our research on the above relationships with a series of 39 para-chloro substituted benzene derivatives of the general formula 1-Cl-C_6H_4-4-X, where X is a substituent, ranging from simple functional groups, such as -OH, -NH_2, and -CN to larger molecule fragments, such as SO_2-C_6H_4Cl, -CO-C_6H_5, and -CH_2-$CH(NH_2)$-COOH (Kaiser et al. 1985). The results of these investigations essentially indicated a general relationship of the observed toxicities with log P. However, only 50% to 70% of the observed variation could be explained by log P, either alone or in combination with other simple independent variables. Consequently, a significant percentage of the predicted values were outside one standard deviation of the estimate, representing an uncertainty factor of approximately 5 to 10 times the predicted toxic concentrations. While such predictions may be useful as rough estimates of the compounds' acute toxicities, more accurate predictions are most

desirable. We have now investigated a larger set of 100 mono-substituted benzene derivatives of the general formula C_6H_5-X and report here the oberved toxicity values and quantitative structure-activity relationships.

METHODS AND MATERIALS

General

The test chemicals were purchased in the best grade available from Aldrich Chemical Co., Inc. or Fluka Chemical Corp. and were used without further purification, except where noted. The acute toxicities to Photobacterium phosphoreum were determined with the Microtox™ toxicity analyzer, following the procedure described previously. In some cases, up to 5% methanol was used to increase substrate solubility (Ribo and Kaiser 1983).

Experimental Values

All toxicity values reported here are the negative logarithms to base ten ("p" values) of the millimolar concentrations at which a 50% light reduction (Gamma = 1) was observed on 30 min exposure. Each value is the mean of at least three independent determinations, usually performed with different bacterial suspensions to reduce any systematic errors or biases. The standard deviations of such triplicate analyses were normally in the order of 0.05 (logarithmic)

toxicity units and as high as 0.10 units for a few compounds of either high toxicity, sensitivity to light, oxygen or water, or for those of very low solubility, where extrapolation to Gamma = 1 was necessary from lower Gamma values, due to limiting solubility. The λ[nm] values were single determinations, measured in methanol with a Unicam SP 1700 spectrophotometer, and converted from wavelength units (in nm) to energy units (in eV) using the formula: $\lambda[eV] = 1{,}240/\lambda[nm]$..

Computations

All toxicity value computations from the concentration/light reduction plots were done with the COMPUTOX™ program on an HP 86 computer. The statistical calculations were performed on the same with prerecorded linear and multiple regression analysis programs.

Parameters

Octanol/water partition coefficients (log P) were taken from the compilation by Hansch and Leo (1979). Where no experimental values were recorded, log P was calculated from pi or fragment values and related compounds, if neither was available, log P was estiamted on the basis of similar compounds' or groups' partition coefficients. TABLE 1 gives a complete list of the investigated compounds, including their Chemical Abstracts Service registration numbers (CAS), log P, λ[eV], and the substituents' molar refractivity contributions (ΔMR), the latter also taken from Hansch and Leo (1970) or calculated or estimated, as indicated.

RESULTS

Entire Data Set

TABLE 1 gives the measured toxicity values (pTm) of the entire set of compounds. Based on the (unsubstantiated and not necessarily true) assumption of strictly nonspecific, narcotic type toxicity of each of the investigated compounds, a strong dependence of the observed toxicity values (pTm, TABLE 1) on log P should be expected. This type of toxicity has been described for a variety of benzene derivatives, such as phenols (Lipnick et al. 1986), anilines (Newsome et al. 1987) and for a variety of other polar and nonpolar compounds (Veith et al. 1987).

FIGURE 1 shows a plot of pTm versus log P, indicating a general dependence of this nature. However, significant variations occur for many compounds and the correpsonding linear least square correlation (equation 1) provides for less than 40% explanation of the total variation observed:

$$pTm = 0.22 + 0.48 \log P \qquad (1)$$

$$n = 100; \quad r^2 = 0.37; \quad s = 0.78$$

TEXTNAME: Klaus (R)P: 07

The most prominent divergence of estimated and measured values is observed for the most toxic compound (X = CH_2NCS), which is subsequently removed from all regression analyses. Without this compound, the new linear regression is found to be:

$$pTm = 0.21 + 0.47 \log P \qquad (2)$$

$$n = 99; \quad r^2 = 0.39; \quad s = 0.74$$

which represents a highly significant statistical relationship.

Naturally, it is of interest to explore which other structural parameters or properties may be useful in describing the observed toxicities. Several of the most common parameters were investigated, including the molar refractivity of the substituents (ΔMR) and their logarithmic values, the compounds' electronic status (λ[eV]), and the presence (I = 1) or absence (I = 0) of an acid function, defined as M(O)(OH), where M = C, P, As, or Se. Values of ΔMR and measured λ[eV] are also given in TABLE 1. Details of the results are given

further down. TABLE 2 gives the linear correlation coefficients between the independent parameters of the set of 99 compounds (excluding the CH_2NCS derivative).

FIGURE 2 gives a plot of the observed toxicities versus the molar refractivity (ΔMR) of the substituents. It reveals both a general dependence of pTm on ΔMR and the existence of three clusters, which are centered around the mean values of X for compounds without, with one, and with two phenyl rings in the substituent. In comparison, no such clustering is evident from the corresponding plot of pTm versus log P (FIGURE 1).

As evident from TABLE 2, the correlation coefficients (r) between both the dependent variable (pTm) and the independent variables and between the independent variables themselves are mostly in the 0.4 to 0.6 range. Exceptions are found to be the ΔMR/log ΔMR pair ($r = 0.89$) and the acidic function indicator variable (Ia) with ΔMR ($r = 0.09$) and with log ΔMR ($r = 0.02$). These values indicate an acceptable degree of co-linearity between the independent variables. Of these variables, log P has the single highest correlation coefficient ($r = 0.62$) with pTm (TABLE 2), confirming the significance of the correlation shown in equation 2. The independent parameters ΔMR and log ΔMR have similar correlation coefficients with pTm, but log ΔMR is significantly less co-linear with log P compared to ΔMR and, therefore, the variable of choice here. TABLE 3 gives the statistical coefficients for the

multiple linear regression analyses of the data set with up to four independent parameters, according to the general equation 3:

$$pTm = a + b\ (\log P) + c\ (\lambda[eV]) + d\ (\log \Delta MR) + e\ (Ia) \qquad (3)$$

It is apparent from the data in TABLE 3, that the most significant improvement of the statistics is derived from the addition of λ[eV] (equation 3b) to the linear equation 3a with log P as sole independent parameters. This introduction of λ[eV] increases the quality of fit, essentially by bringing into line the otherwise more toxic than predicted compounds with longer chains of conjugated double bonds, especially the azobenzene and benzophenone derivatives. An attempt to use the compounds' ionization potentials, as measured by UV absorption on charge-transfer complex formation with chloranil (Birks and Slifkin 1961), failed to produce any significant result.

Introduction of the molar refractivity contribution (ΔMR) of the substituents, transformed to the logarithmic values (log ΔMR), results in a further increase of the quality of fit (equation 3d in TABLE 3). As noted by Hansch and Leo (1979), ΔMR is a parameter which reflects both molar volume and the hydrophobic effect of the substituent. We find here that the use of ΔMR instead of log ΔMR provides for a smaller improvement of the regression, compared to log ΔMR. This result is mainly a consequence of the above noted clustering of

compounds with equal number of phenyl rings per substituent (FIGURE 2). If one removes the compounds with two phenyl rings per substituent from the data set (X = NR_2, PR_2, $AsOR_2$, and $C(OH)R_2$, with R = C_6H_5, ΔMR becomes more highly correlated with pTm than log ΔMR.

Undoubtedly, the possible addition of other potential independent parameters to equation 3e would increase the correlation coefficient and decrease the standard error of the estimate. Specifically, the following variables were also investigated but were found to result only in negligible contributions to the quality of the regressions: modified Swain and Lupton's field $(F)_2$ and resonance (R) parameters (Hansch and Leo 1979), $(\log P)^2$, $(\Delta MR)^2$, the number of conjugated double bonds, ionization potential (in methanol), and several indicator variables for structural fragments, such as N, NH_2, CO, and so forth. However, for several of these parameters only incomplete data sets are available and no significant increase of the correlations over that of equation 3d with up to five independent variables was observed.

DISCUSSION

The multiple linear equations given in TABLE 3 indicate a significant relationship of the observed toxicities with several physico-chemical characteristics of these compounds. However, only some 60% of the total variation is explained by equation 3d and the corresponding

standard error of the estimate, s = 0.60 is quite large. This means that for a number of compounds the predicted toxic concentrations differ by more than one order of magnitude from those observed experimentally. As there is a spread of close to five orders of magnitude between the molar concentrations of the least and most toxic compounds, the predictive capacity of equation 3d is still of value, though somewhat limited in applicability. This fact stimulates the desire for a closer inspection of the data with a view to delineate more precise relationships for smaller, more easily defined subsets of mono-substituted benzene derivatives.

Benzyl Derivatives

Inspection of the data given in TABLE 1 reveals the presence of a total of 16 benzyl derivatives of the general formula $C_6H_5-CH_2-Z$, where, in ascending order of toxicity, Z = COOH, $CH(NH_2)COOH$, OH, H, NH_2, CH_2NH_2, CH_3, CH_2OH, Cl, COCl, C_6H_5, CN, SH, SCN, C_6H_4OH, and NCS. It is interesting to note that this subset includes both the least (Z = COOH) and most toxic ones (Z = NCS) of all 100 compounds investigated. Therefore, it may be appropriate to view this subset as representative of the complete set of compounds.

Analysis of the benzyl derivative subset shows that log P, λ[eV], and Ia are inadequate descriptors of the observed toxicities. Instead, there is a good dependence on ΔMR (of CH_2-Z) in combination with

TEXTNAME: Klaus (R)P: 12

Verloop's (Verloop et al. 1976) Sterimol parameters L, B_2, and B_3 (of the group Z) for 12 compounds where the values are tabulated. The corresponding multiple linear equation is:

$$pTm = 2.55 + 0.23\ \Delta MR - 2.24\ B3 \qquad (4)$$

$$n = 12;\quad r^2 = 0.72;\quad s = 0.72;\quad F = 11.5$$

Equation 4 is statistically significant at the $P < 0.025$ level or better, but suffers from a quite large standard error (s), similar to equations 3a to 3d. It is also interesting to note that there appears to be little or no relationship with both log P and λ[eV] for this subset. This indicates that the hydrophobicity and electronic state of the molecule are of little importance for these compounds' toxicity. The latter is not surprising, as the $-CH_2-$ group does not allow through-conjugation of any double bonds in the group Z with those in the phenyl ring. Consequently, λ[eV] is very similar for all compounds in this subset. It is evident then that other factors control the wide variation in toxicity of these benzyl derivatives. It is also apparent that their toxicity increases with increasing nucleophilicity and/or polarizability of Z. However, quantitative measurements of these properties are difficult to obtain for these groups. Therefore, no further analysis is possible at this time.

TEXTNAME: Klaus (R)P: 13

Aniline Derivatives

TABLE 1 gives data on a total of 13 aniline derivatives of the general formula C_6H_5-NH-Z, where, in ascending order of toxicity, Z = $COCH_3$, H, NH_2, $CONH-NH_2$, CH_3, $NH-CO-NH_2$, CHO, C_6H_5, $CSNH_2$, $CS-NH-NH_2$, $NH-C_6H_5$, $NH-C_6H_4-NO_2$, and $NH-C_6H_4-NH_2$. These compounds comprise a toxicity range of approximately three orders of magnitude, therefore appear to be - in this respect - less representative of the total data set than the benzyl derivatives. This subset can be reasonably well described by a correlation with ΔMR and λ[eV], according to:

$$pTm = 1.12 + 0.064\ \Delta MR - 0.32\ \lambda[eV] \qquad (5)$$

$$n = 13;\quad r^2 = 0.77;\quad s = 0.50;\quad F = 16.3$$

Most of the variation is actually explained by ΔMR alone (71%) with λ[eV] providing only another 6%. However, it should be noted that the three most toxic compounds of this subset have a second phenyl ring in their structure, consequently also a much higher ΔMR than the other compounds. It is possible, therefore, that equation 5 is a chance correlation, given the limited number of data.

TEXTNAME: Klaus (R)P: 14

Benzoyl Derivatives

There is a total of 16 benzoyl derivatives of the general formula C_6H_5-CO-Z given in TABLE 1. In ascending order of toxicity, Z = NH-NH_2, NH_2, CF_3, OH, CH_3, Cl, C_6H_5, H, CH_2CH_3, C_6H_4-OH, OCH_3, C_6H_4-NO_2, CN, C_6H_4-Cl, CO-C_6H_5, and C_6H_4-$N(CH_3)_2$, comprising close to four orders of magnitude in toxicity. Very similar to equation 5 for the aniline derivatives, this subset can be described by:

$$pTm = 1.80 + 0.048\ \Delta MR - 0.37\ \lambda[eV] \qquad (6)$$

$n = 16;\ r^2 = 0.64;\ s = 0.61;\ F = 11.8$

As for equation 5, the independent parameter ΔMR accounts for most of the total variation, namely 74%, while λ[eV] adds only another 3%. No significant improvement is obtained with any of the Sterimol parameters (Verloop et al. 1976).

It is apparent that equations 5 and 6 are quite similar. Combination of the aniline and benzoyl subsets leads to the correlation:

$$pTm = 1.66 + 0.052\ \Delta MR - 0.38\ \lambda[eV] \qquad (7)$$

$n = 29;\ r^2 = 0.69;\ s = 0.55;\ F = 28.3$

with ΔMR as the most significant independent variable.

TEXTNAME: Klaus (R)P: 15

Ethers and Esters

There are 13 aliphatic and aromatic ethers and esters in TABLE 1 of the general formulat C_6H_5-O-Z, where, in ascending order of toxicity, Z = $(CH_2)_3$-COOH, $OPO(OH)OC_6H_5$, CH_2-COOH, CH_2CH_2OH, H, CH_3, $COCH_3$, COCl, C_6H_4-OH, C_6H_5, CO-C_6H_5, C_6H_4-NO_2, and C_6H_4-NH_2. In contrast to the aforementioned subsets, this group, which comprises 4.5 orders of magnitude in toxicity, is more dependent on log P than on ΔMR. With the additional variables λ[eV] and Ia, the best regression equation is:

$$pTm = 2.71 + 0.33 \log P - 0.52\ \lambda[eV] - 0.93\ Ia \qquad (8)$$

$n = 13;\ r^2 = 0.92;\ s = 0.32;\ F = 32.4$

As this group contains also several acids, phenols and esters, it is to be expected that ΔMR is not a good descriptor of the compounds' lipophilicity and/or steric bulk of the "real" functional groups which may be different from groups "Z". For example, the diphenylphosphate (Z = $OPO(OH)$-OC_6H_5) has the highest ΔMR (39.73) within the subset, but a much lower log P (1.3) than the p-nitrodiphenyl ether (Z = O-C_6H_4-NO_2) with a log P of 3.97.

TEXTNAME: Klaus (R)P: 16

Biphenyls and Azobenzenes

The compounds investigated include five azobenzenes $C_6H_5-N=N-C_6H_4-Z$, ($Z = NH_2$, H, OH, OCH_3, and $N(CH_3)_2$) and six biphenyls $C_6H_5-C_6H_4-Z$, where $Z = NH_2$, CH_2OH, OH, CH_3, H, and CN. Their combined toxicity range is approxiamtely 2.5 orders of magnitude and is close to the upper end of the total range of observed values. These compounds differ from the previous subsets as they all have two phenyl rings which are conjugated either directly or through the azo group. Consequently, they are comparatively rigid molecules with a high potential for electron dislocation within the molecules. This is also apparent from the much lower λ[eV] values for the azobenzenes, while those of the biphenyls are only slightly lower than the λ[eV] values for most other compounds. Due to the limited number of compounds, no significant correlations could be obtained with more than one independent variable for each of these groups. Nevertheless, it is of interest to determine whether log P or ΔMR are highly correlated with pTm. Furthermore, as the λ[eV] values are nearly the same for five of the six biphenyls, no significant correlation can be derived for this set at all. In contrast, the toxicities of the five azobenzenes are highly correlated with both log P ($r^2 = 0.73$) and ΔMR ($r^2 = 0.80$). No significant improvement over these correlations is obtained from either variable with λ[eV]. For both groups combined, the best two-parameter equation is:

$$pTm = -3.48 + 0.146\ \Delta MR + 0.31\ \lambda[eV] \qquad (9)$$

$n = 11;\ r^2 = 0.69;\ s = 0.49;\ F = 8.75$

which is significant at $P < 0.01$.

Other Compounds

There are a number of compounds in TABLE 1, which do not belong to any of the aforementioned groups. These compounds include a variety of halogenated benzenes and toluenes, three sulfonyl compounds, and several arsenic, selenium, phosphorus, mercury, sulphur and nitrogen containing groups. With the possible exception of the halobenzenes of the general formula C_6H_5-Z, where, in ascending toxicity, Z = F, Cl, Br, I, these compounds will have to be viewed on an individual basis as their composition and structure varies widely. Due to the limited number of group representatives, no attempt has been made to model their toxicities, other than with the general equations 3a to 3d (TABLE 2).

Conclusions

Given the dependencies of the analyzed subsets on the various independent variables, as shown in equations 5 to 9, it is apparent that the following groupings can be made.

Group 1. Compounds whose toxicity can be modeled by ΔMR, λ[eV] and Ia. This group includes the substituted biphenyls and azobenzenes. The best correlation is given by equation 9.

Group 2. Esters and ethers. Their toxicity is best described by log P, λ[eV], and Ia, as shown in equation 8.

Group 3. N-substituted anilines and benzoyl derivaties. They are modeled by equation 7.

Group 4. The benzyl derivatives. These compounds are the most difficult to model. Of these investigated, ΔMR, and the Sterimol parameter B3 appear to be the best variables, as shown in equation 4.

Group 5. This group contains all other compounds not belonging to any of the above. They include primarily, halogen, nitrogen, sulphur, selenium, phosphorus, arsenic, and mercury containing derivatives. The toxicities of these compounds can be estimated with a lower degree of confidence from equation 3d. More refined models which accurately describe their toxicity will have to await the determination of additional toxicity data as well as physico-chemical properties for such types of compounds.

ACKNOWLEDGEMENT

We thank Mr. Brian M. Zaruk for the determination of some of the toxicity values reported here.

REFERENCES

Birks, J.B. and Slifkin, M.A. 1961. π-Electronic excitation and ionization energies of condensed ring aromatic hydrocarbons. **Nature 191**: 761-764.

Bulich, A.A., Greene, M.W. and Isenberg, D.L. 1981. Reliability of the bacterial liminescence assay for determination of the toxicity of pure compounds and complex effluents. In **Aquatic Toxicology and Hazard of Assessment: Fourth Conference**, Branson, D.R. and Dickson, K.L. (Eds.), ASTM STP 737, American Society for Testing and Materials, Philadelphia, pp. 338-347.

Curtis, C., Lima, A., Lozano, S.J. and Veith, G.D. 1982. Evaluation of a bacterial bioluminescence bioassay as a method for predicting acute toxicity of organic chemicals to fish. In **Aquatic Toxicology and Hazard Assessment: Fifth Conference**, Pearson, J.G., Foster, R.B. and Bishop, W.E. (Eds.), ASTM STP 766, American Society for Testing and Materials, Philadelphia, pp. 170-178.

Hansch, C. and Leo, A.J. 1979. **Substituent Constants for Correlation Analysis in Chemistry and Biology.** John Wiley & Sons, Inc., New York, NY, 339 p.

Hodson, P.V. 1985. A comparison of the acute toxicity of chemicals to fish, rats and mice. **J. Appl. Toxicol. 4:** 220-226.

Kaiser, K.L.E. and Ribo, J.M. 1985. QSAR of toxicity of chlorinated aromatic compounds. In **QSAR in Toxicology and Xenobiochemistry**, Tichy, M. (Ed.), Elsevier, Amsterdam, pp. 27-38.

TEXTNAME: Klaus (R)P: 21

Kaiser, K.L.E., Ribo, J.M. and Zaruk, B.M. 1985. Toxicity of para-chloro substituted benzene derivatives in the Microtox text. **Water Poll. Res. J. Can. 20**: 36-43.

Lipnick, R.L., Bickings, C.K., Johnson, D.E. and Eastmond, D.A. 1986. Comparison of QSAR predictions with fish toxicity screening data for 110 phenols. In **Aquatic Toxicology and Hazard Assessment: Eighth Symposium**, Bahner, R.C. and Hansen, D.J. (Eds.), ASTM STP 891, American Society for Testing and Materials, Philadelphia, pp. 153-176.

Newsome, L.D., Johnson, D.E., Cannon, D.J. and Lipnick, R.L. 1987. Comparison of QSAR predicted toxicities based on data from alkyl- and chloroanilines with fish toxicity screening data for 48 aniline derivatives. In **QSAR in Environmental Toxicology - II**, Kaiser, K.L.E. (Ed.), D. Reidel Publ. Co., Dordrecht, Holland, pp. 000-000.

Qureshi, A.A., Flood, K.W., Thompson, S.R., Janhurst, S.M., Inniss, C.S. and Rokosh, D.A. 1982. Comparison of a luminescent bacterial test with other bioassays for determining toxicity of pure compounds and complex effluents. In **Aquatic Toxicology and Hazard Assessment: Fifth Conference**, Pearson, J.G., Foster, R.B. and Bishop, W.E. (Eds.), ASTM STP 766, American Society for Testing and Materials, Philadelphia, pp. 179-195.

Ribo, J.M. and Kaiser, K.L.E. 1983. Effects of selected chemicals to photoluminescent bacteria and their correlations with acute and sublethal effects on other organisms. **Chemosphere 12:** 1421-1442.

Thomson, K., Liu, D. and Kaiser, K.L.E. 1986. A direct resazurin test for measuring chemical toxicity. **Toxicity Assessment 1:** 407-418.

Veith, G.D. and Broderius, S.J. 1987. Structure-toxicity model for type (II) narcotic chemistry. In **QSAR in Environmental Toxicology - II,** Kaiser, K.L.E. (Ed.), D. Reidel Publ, Co., Dordrecht, Holland, pp. 000-000.

Verloop, A., Hoogenstraaten, W. and Tipker, J. 1976. Development and application of new steric substituent parameters in drug design. In **Drug Design,** Vol. 7, Ariens, E. (Ed.), Academic Press, pp. 165-207.

Weast, R.C. (Ed.) 1978. **CRC Handbook of Chemistry and Physics.** CRC Press, Inc., West Palm Beach, Florida, 58th ed.

TEXTNAME: Klaus-Tabs (R)P: 01

TABLE 1: List of compounds of the general formula C_6H_5-X, their 30-min EC50 values (pTm values, see text) for Photobacterium phosphoreum, their CAS numbers, octanol/water partition coefficients (log P) and λ[eV] values, and the substituents' (X) molar refractivity contribution (ΔMR); log P and ΔMR values from Hansch and Leo (1979), except where noted[a]; λ[eV] values measured in methanol.

pTm	X	CAS	log P	ΔMR	λ[eV]
-0.60	$-CH_2-COOH$	103-82-2	1.41	11.88	4.73
-0.48	$-O-(CH_2)_3-COOH$	6303-58-8	1.87	23.4	4.66
-0.46	$-AsO(OH)_2$	98-05-5	0.06	17.**	4.70
-0.39	$-CH_2-CHNH_2-COOH$	150-30-1	-1.35	19.56	4.66
-0.32	$-NH-CO-CH_3$	103-84-4	1.16	14.93	4.66
-0.28	$-F$	462-06-6	2.27	0.92	4.59
-0.23	$-O-PO(OH)-OC_6H_5$	838-85-7	1.3*	39.73	4.68
-0.19	$-SO_2-NH_2$	98-10-2	0.31	12.28	4.77
-0.12	$-H$	71-43-2	2.13	1.03	4.70
0.15	$-NH_2$	62-53-3	0.90	5.42	3.15
0.18	$-CH_2-OH$	100-51-6	1.10	7.19	4.66
0.21	$-NH-NH_2$	100-63-0	1.25	8.44	4.34
0.25	$-CO-NH-NH_2$	613-94-5	0.19	12.83	4.31
0.31	$-CO-NH_2$	55-21-0	0.64	9.81	4.59
0.31	$-O-CH_2-COOH$	122-59-8	1.26	13.99	4.59
0.31	$-CO-CF_3$	434-45-7	2.15	11.17	3.44
0.36	$-CH=CH-COOH$	140-10-3	2.13	17.91	4.73
0.37	$-AsO(C_6H_5)_2$	1153-05-5	3.0**	66.98	4.84
0.42	$-NH-CO-NH-NH_2$	537-47-3	0.8*	18.11	4.31
0.52	$-CHOH-C_6H_5$	91-01-0	2.03	31.52	4.66
0.55	$-NO_2$	98-95-3	1.85	7.36	3.02
0.60	$-CH_3$	108-88-3	2.69	5.65	4.70
0.63[b]	$-O-CH_2-CH_2-OH$	122-99-6	0.86	14.1*	4.66**
0.65	$-OH$	108-95-2	1.48	2.85	4.70
0.65	$-CS-NH_2$	2227-79-4	1.49	18.28	3.15
0.66	$-CF_3$	98-08-8	3.01	5.02	4.70
0.76	$-O-CH_3$	100-66-3	2.11	7.87	4.66
0.77	$-NCO$	103-71-9	3.1*	8.82	4.28
0.80	$-CH_2-NH_2$	100-46-9	1.09	9.09	4.59
0.86	$-COOH$	65-85-0	1.87	6.96	4.59
0.89	$-CO-CH_3$	98-86-2	1.68	11.18	3.54
0.89	$-NH-CH_3$	100-61-8	1.66*	10.33	3.67
0.92	$-N(CH_3)_2$	121-69-7	2.31	15.55	3.65
0.95	$-CN$	100-47-0	1.56	6.33	4.31
0.99	$-CH_2-CH_2-NH_2$	64-04-0	1.41	13.74	4.16
1.00	$-Cl$	108-90-7	2.85	6.03	4.66
1.04	$-CH_2-CH_3$	100-41-4	3.15	10.30	4.88

TABLE 1 (cont'd):

pTm	X	CAS	log P	ΔMR	λ[eV]
1.04	$-CCl_3$	98-07-7	2.92	20.12	4.43
1.04	-SeOOH	6996-92-5	0.7**	12.8*	4.43
1.06	-CO-Cl	98-88-4	2.2**	10.44	3.41
1.09	$-O-CO-CH_3$	122-79-2	1.49	12.47	3.83
1.14	$-SO_2-C_6H_5$	127-63-9	2.40	33.20	4.66
1.15	$-NH-NH-CO-NH_2$	103-03-7	0.8*	16.8*	4.31
1.22	-Br	108-86-1	2.99	8.88	3.80
1.28[c]	$-CH=CH_2$	100-42-5	2.95	10.99	4.88[d]
1.31	$-CO-C_6H_5$	119-61-9	3.18	30.33	3.32
1.34	-CO-H	100-52-7	1.48	6.88	3.46
1.36	$-CH_2-CH_2-OH$	60-12-8	1.36	11.84	4.59
1.37	$-CO-CH_2-CH_3$	93-55-0	2.19	15.83	3.50
1.40	$-C_6H_4-NH_2$	92-67-1	2.72	29.75	3.65
1.40	$-CO-C_6H_4-OH$	1137-42-4	3.07	32.15	3.43
1.41	-NH-CHO	103-70-8	1.15	10.31	4.37
1.43	$-SO_2-C_6H_4-Cl$	80-00-2	3.11*	38.20	4.77
1.44	-O-CO-Cl	1885-14-9	2.14*	12.26	4.31
1.44	$-CHNH_2-COOH$	2835-06-5	-0.13*	14.96	4.77
1.44	$-CHCl_2$	98-87-3	3.23*	15.30	4.31
1.47	$-CO-OCH_3$	93-58-3	2.12	12.87	4.31
1.48	$-O-C_6H_4-OH$	831-82-3	3.51	29.50	4.31
1.51	$-CO-C_6H_4-NO_2$	1144-74-7	2.90*	36.66	3.15
1.55	$-NH-C_6H_5$	122-39-4	3.34	30.04	4.13
1.60	-CO-CN	613-90-1	1.04**	11.82	3.52
1.63	$-CH_2-Cl$	100-44-7	2.30	10.49	4.56
1.64	$-NH-CS-NH_2$	103-85-5	0.73	22.19	3.46
1.66	$-CH_2-CO-Cl$	103-80-0	0.9**	15.06	4.73
1.67	$-O-C_6H_5$	101-84-8	4.21	27.68	4.66
1.68	$-CH_2-C_6H_5$	101-81-5	4.14	30.01	4.70
1.71	$-NH-CS-NH-NH_2$	5351-69-9	0.7*	26.58	4.25
1.76	$-COH(C_6H_5)_2$	76-84-6	4.57*	56.16	4.92
1.80	-I	591-50-4	3.25	13.94	3.65
1.81	-NCS	103-72-0	3.28	17.24	3.60
1.84	$-C_5H_4N$	939-23-1	2.58*	23.03	4.31
1.85	$-C_6H_4-CH_2OH$	3597-91-9	3.42*	31.52	4.13
1.86	$-C_6H_4-OH$	92-69-3	1.86	27.18	4.31
1.87	$-N=N-C_6H_4-NH_2$	60-09-3	2.58*	35.70	2.62
1.88	$-C_6H_4-CH_3$	644-08-6	4.51*	29.98	4.31
1.91	$-C_6H_5$	92-52-4	4.03	25.36	4.31
1.94	$-CH_2-CN$	140-29-4	1.56	10.11	4.70
2.01	$-CH_2-SH$	100-53-8	2.46*	13.87	3.78
2.05	$-N(C_6H_5)_2$	603-34-9	5.74	54.96	3.63
2.10	-SH	108-98-5	2.52	9.22	4.22

TEXTNAME: Klaus-Tabs (R)P: 03

TABLE 1 (cont'd):

pTm	X	CAS	Log P	ΔMK	λ[eV]
2.11	$-P(C_6H_5)_2$	603-35-0	4.5**	60.55	4.34
2.12	-SeCl	5707-04-0	3.3**	14.52*	2.68
2.14	$-O-CO-C_6H_5$	93-99-2	3.59	32.32	4.33
2.15	$-N=N-C_6H_5$	103-33-3	3.82	31.31	2.62
2.19	$-CO-C_6H_4-Cl$	134-85-0	3.89*	35.33	3.37
2.27	$-NH-NH-C_6H_5$	122-66-7	2.94	33.1	3.41
2.29	$-O-C_6H_4-N)_2$	620-88-2	3.97*	34.53	3.08
2.33	$-N=N-C_6H_4-OH$	1689-82-3	3.17*	33.13	2.57
2.47	$-NH-C_6H_4-NO_2$	836-30-6	3.22*	36.37	2.30
2.52	$-O-C_6H_4-NH_2$	139-59-3	2.98*	32.07	2.38
2.52	$-CO-CO-C_6H_5$	134-81-6	3.38	35.30	2.91
2.57	$-CH_2-SCN$	3012-37-1	1.99	18.05	4.31
2.75	$-NH-C_6H_4-NH_2$	101-54-2	2.11*	34.43	2.18
2.87	$-CH_2-C_6H_4-OH$	101-53-1	3.47*	31.83	4.37
2.99	$-C_6H_4-CN$	2920-38-9	3.52*	30.66	4.35
3.28	$-N=N-C_6H_4-OCH_3$	2396-60-3	3.80	38.15	2.64
3.42	$-Hg-C_6H_5$	587-85-9	4.0**	37.3**	4.66
3.52	$-CO-C_6H_4-N(CH_3)_2$	530-44-9	3.36*	45.85	2.98
4.07	$-N=N-C_6H_4-N(CH_3)_2$	60-11-7	4.58	45.83	2.50
4.16	$-CH_2-NCS$	622-78-6	2.83	21.84	4.22

a) * Value derived from similar compound and increment for one group.
** Estimated value.

b) From Curtis et al. (1982); 5-min value.

c) From Qureshi et al. (1982); 5-min value.

d) From Weast (1975).

TEXTNAME: Klaus-Tabs (R)P: 04

TABLE 2: Matrix of correlation coefficients (r) between the dependent variable (pTm) and the independent variables log P, λ[eV], ΔMR, log ΔMR, and Ia for n = 99 compounds (exclusive of X = CH_2NCS).

Parameter	log P	ΔMR	log ΔMR	λ[eV]	Ia
log P	1.0	0.58	0.45	-0.28	-0.30
ΔMR		1.00	0.89	-0.27	-0.09
log ΔMR			1.00	-0.30	-0.02
λ[eV]				1.00	0.26
Ia					1.00
pTm	0.62	0.52	0.54	-0.50	-0.41

TEXTNAME: Klaus-Tabs (R)P: 05

TABLE 3: Summary of number of compounds (n), correlation coefficient squares (r^2), standard error of estimate (s), and constants a, b, c, d, and e for multiple linear correlation analyses of data set according to general equation 3.

Equation Number	n	r^2	s	F	Constants for Equation 3				
					a	b	c	d	e
3a (2)	99	0.39	0.74	60.8	0.21	0.47	-	-	-
3b	99	0.51	0.67	49.0	2.29	0.40	-0.47	-	-
3c	99	0.56	0.64	39.7	1.31	0.32	-0.41	0.74	-
3d	99	0.60	0.61	35.5	1.07	0.26	-0.33	0.87	-0.72

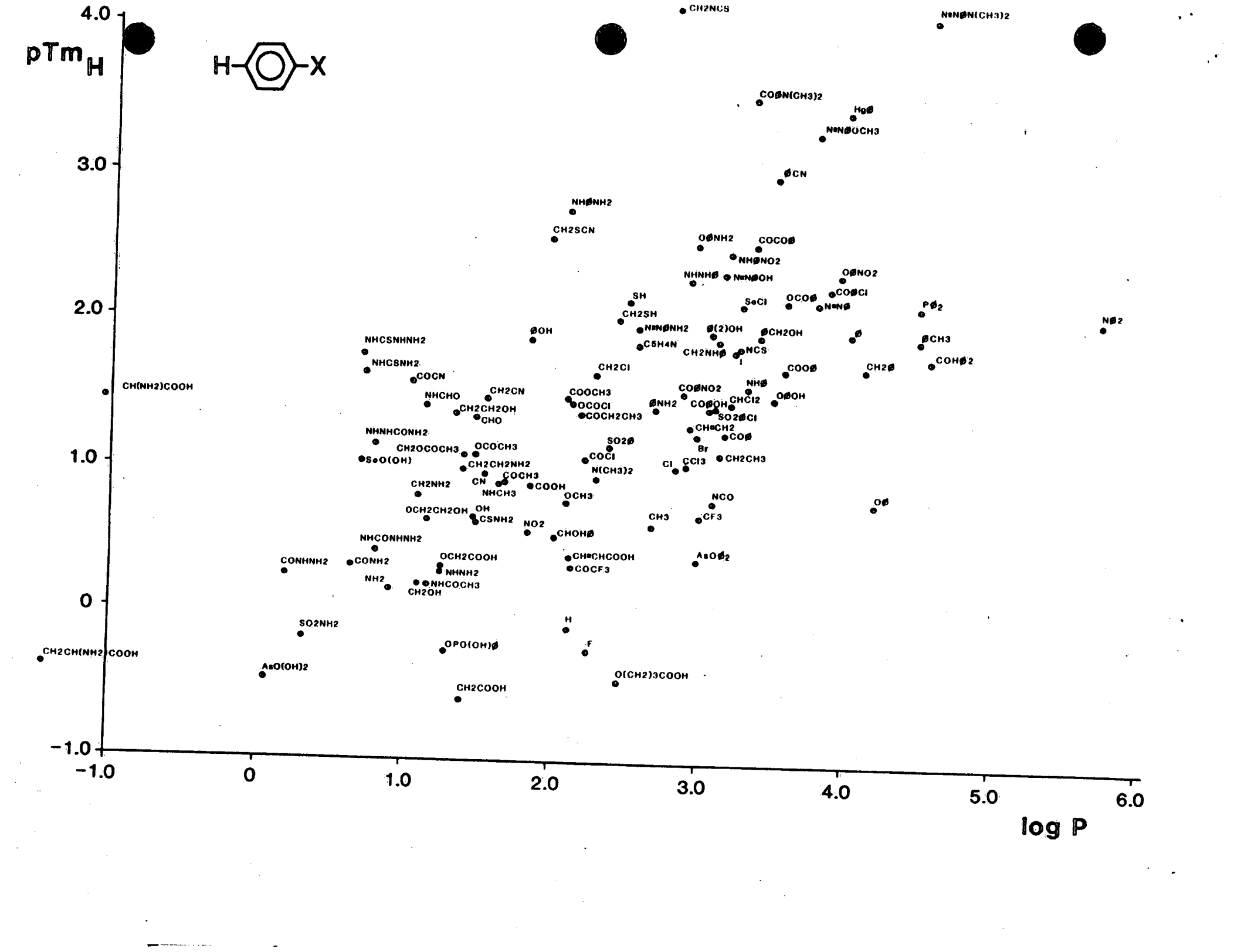
TEXTNAME: Klaus-Fig (R)P: (Klaus-1) 01

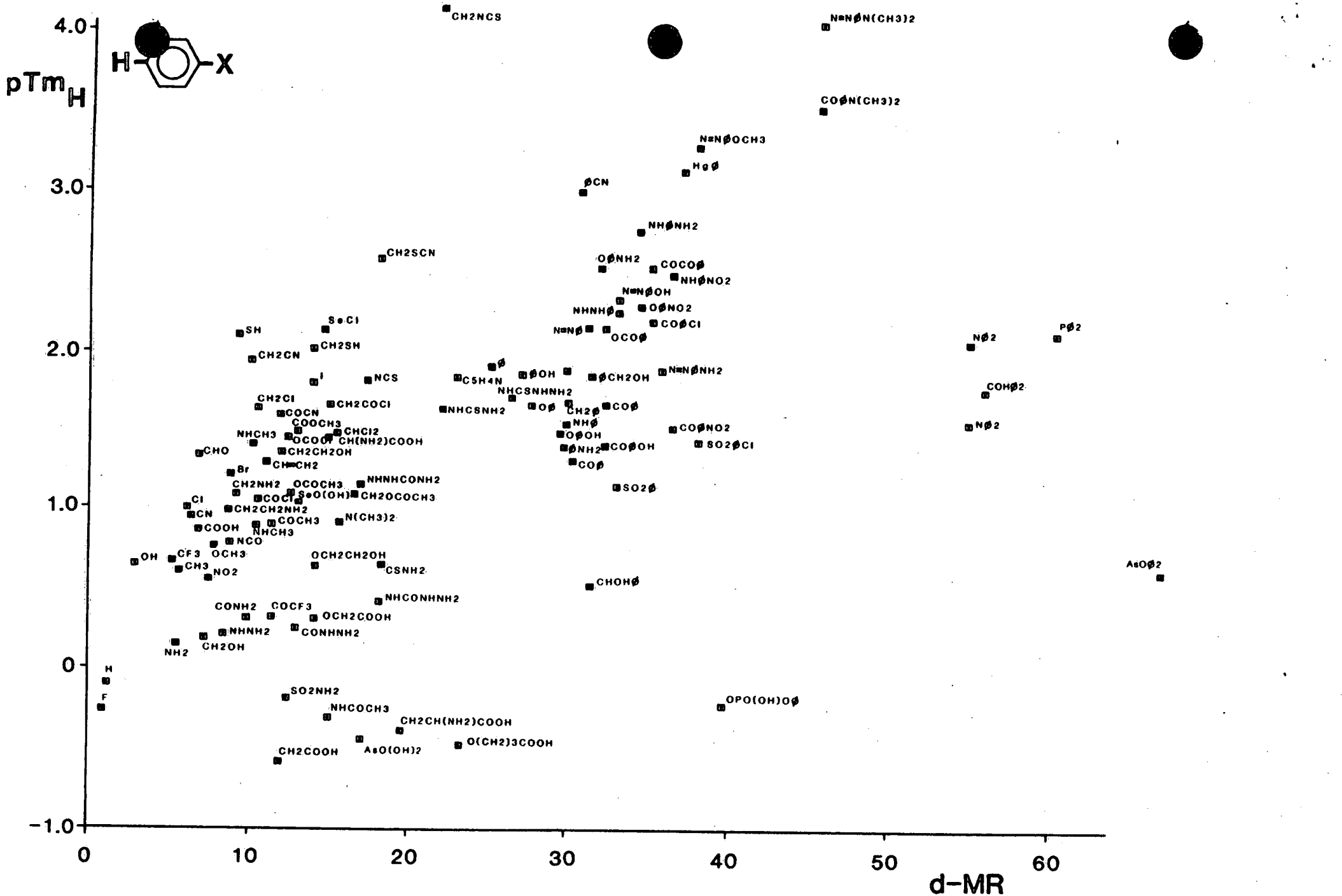
FIGURE 1: Plot of the observed toxicities (pTm) of mono-substituted benzene derivatives of the general formula C_6H_5-X versus their octanol/water partition coefficients (log P).

Full page - horizontal

FIGURE 1: Plot of the observed toxicities (pTm) of mono-substituted benzene derivatives of the general formula C_6H_5-X versus the molar refractivity contribution (ΔMR) of the substitutents X.

Full page - horizontal


pTm H
H X
4.0
3.0
2.0
1.0
0
−1.0
−1.0
0
1.0
2.0
3.0
4.0
5.0
6.0
log P
CH2NCS
N=NØN(CH3)2
CØN(CH3)2
HgØ
N=NØOCH3
ØCN
NHØNH2
CH2SCN
OØNH2
COCOØ
NHØNO2
NHNHØ
N=NØOH
OØNO2
SH
SeCl
OCOØ
COØCl
N=NØ
PØ2
CH2SH
N=NØNH2
Ø(2)OH
ØCH2OH
NØ2
ØOH
NHCSNHNH2
C5H4N
CH2NHØ
NCS
ØCH3
NHCSNH2
COHØ2
CH2Cl
COOØ
CH2Ø
COCN
CH(NH2)COOH
NHCHO
CH2CN
COOCH3
NHØ
COØNO2
CHCl2
OØOH
OCOCl
ØNH2
COØOH
CH2CH2OH
COCH2CH3
SO2ØCl
CHO
CH=CH2
NHNHCONH2
SO2Ø
COØ
CH2OCOCH3
OCOCH3
Br
SeO(OH)
COCl
CH2CH2NH2
Cl
CCl3
CH2CH3
N(CH3)2
COCH3
CN
CH2NH2
COOH
NHCH3
OCH3
NCO
OØ
OCH2CH2OH
OH
CSNH2
CH3
CF3
NO2
CHOHØ
NHCONHNH2
CH=CHCOOH
AsOØ2
CONHNH2
CONH2
OCH2COOH
COCF3
NHNH2
NH2
NHCOCH3
CH2OH
SO2NH2
H
OPO(OH)Ø
F
CH2CH(NH2)COOH
AsO(OH)2
O(CH2)3COOH
CH2COOH


pTm_H
H
X
d-MR
4.0
3.0
2.0
1.0
0
-1.0
0
10
20
30
40
50
60
CH2NCS
N=NØN(CH3)2
COØN(CH3)2
N=NØOCH3
HgØ
ØCN
NHØNH2
CH2SCN
OØNH2
COCOØ
NHØNO2
N=NØOH
NHNHØ
OØNO2
SeCl
SH
N=NØ
COØCl
OCOØ
CH2SH
CH2CN
Ø
I
NCS
C5H4N
ØOH
ØCH2OH
N=NØNH2
NHCSNHNH2
CH2Cl
CH2COCl
COCN
NHCSNH2
OØ
CH2Ø
COØ
COOCH3
NHØ
NHCH3
CHCl2
OCOOH
CH(NH2)COOH
OØOH
CO2ØCl
CHO
CH2CH2OH
ØNH2
COØOH
CH=CH2
COØ
Br
CH2NH2
OCOCH3
NHNHCONH2
SO2Ø
SeO(OH)
CH2OCOCH3
Cl
COCl
CN
CH2CH2NH2
COCH3
N(CH3)2
COOH
NHCH3
NCO
OH
CF3
OCH3
OCH2CH2OH
CH3
CSNH2
NO2
CHOHØ
NHCONHNH2
CONH2
COCF3
OCH2COOH
NHNH2
CONHNH2
NH2
CH2OH
H
F
SO2NH2
NHCOCH3
OPO(OH)Ø
CH2CH(NH2)COOH
O(CH2)3COOH
CH2COOH
AsO(OH)2
NØ2
PØ2
COHØ2
NØ2
AsØ2