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Toxicity of organometallic compounds: Correlation analysis via substituent constants

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ABSTRACT

Organometallic compounds have many uses in industry, agriculture and in research laboratories, and their toxicity being an environmental hazard. Nevertheless, the influence of the substituents bound to the central atom M on the toxicity and other biological properties BP is poorly understood. In this work, the literature data on substituent influence on the toxicity (the lethal doses LD_{50} and LDL_0) of mercury, boron, silicon, germanium, tin, lead, phosphorus, arsenic, and platinum compounds (27 series) have been analyzed, using the correlation analysis. Such BP as antitumour, fungicidal, and insecticidal activities as well as mutagenicity (4 series) have been considered for comparison. Generally the BP were first established to depend not only on the inductive, resonance, and steric effects but also on the polarizability of substituents which can be characterized by the σ_α constants. The polarizability effect owes its existence to the appearance of an excess charge on M atom as a result of donor–acceptor interaction organometallic molecule-biological target. The presence or absence of certain effects are governed by the type of series. In most cases the influence of the substituents on BP can be realistically explained only if the polarizability effect is taken into consideration. The knowledge of substituent effects permits a better understanding of factors influencing biological activity of organometallics.

1. Introduction

Organometallic toxicity essentially depends not only on the nature of the central atom M, but also on the substituents bound to the M [1–11]. One of the brightest examples is very toxic phenylsilatrane [2]. Nevertheless, the existing concepts of substituent effects are neither complete nor conclusive. Even a cursory examination shows that in most cases the influence of substituents on the toxicity cannot be adequately explained in the framework of classic inductive, resonance, and steric effects [1–11]. The reason of this is still unclear. Trying to get the solution to this problem, we invoked the correlation analysis. Let us briefly consider our approach.

We will look at the so-called classic and non-classic narrow reaction (indicator) series XBR_c and XR_c in which the reaction centre R_c or fragment BR_c remains fixed whereas the substituents X vary. The distinguishing feature of the charged classic series 4-$XC_6H_4R_c^q$ is an excess charge q on R_c, the large distance of X from R_c (bridge B = C_6H_4 is long) as well as the absence of the through resonance effect which consists in the resonance interaction between X and R_c^q via the π-electron system. In these series the chemical (logarithms of equilibrium and reaction rate constants) and physical properties P are described as follows:

$$P = P_0 + a\sigma_I + b\sigma_R\left(\sigma_R^+, \sigma_R^-\right), \quad (1)$$

where σ_I is a universal inductive constant of X substituents; σ_R, σ_R^+, and σ_R^- are parameters characterizing the resonance effect of X in the presence of a small, large positive and large negative charge q, respectively, e.g. Ref. [12].

In non-classic charged series XBR_c^q and XR_c^q the distance d between X and R_c^q is less than that in classic ones, because the bridge B is shorter than $-C_6H_4-$ fragment or absent at all. The short distance d and the charge q on R_c give rise to the polarizability effect which consists in the ion–dipole interaction between q and dipole moment induced by charge q in the substituent X [13]. The energy of this electrostatic interaction is given by equation

$$E = -q^2\alpha/\left(2d^4\right), \quad (2)$$

where α is substituent polarizability [14]. The polarizability effect depends strongly on the distance d and therefore it has no influence

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Table 1
LD_{50} values (mmol kg^{-1}) for series I–VII.

Series I [1]		Series II [1]	Series III [1]		Series IV [2]		Series V [3]		SeriesVI [1,2]		Series VII [2]	
X_2Hg		X_2Hg	$(XO)_3B$		X_4Si		X_4Si		$X_2Si(OEt)_2$		$X_3Si(CH_2)_3NH_2$	
X_2	LD_{50}, I[a]	LD_{50}, II[b]	X	LD_{50}, III[b]	X_4	LD_{50}, IV[a]	X_4	LD_{50}, V[b]	X_2	LD_{50}, VI[a]	X_3	LD_{50}, VII[b]
Et_2	0.20	0.17	H	55.82	$H(EtO)_2Cl$	40.72	$MePh(MeO)_2$	3.73	Me_2	62.58	$MeEt_2$	0.30
$(CN)_2$	0.10	0.13	Me	12.46	$Et(H_2C{=}CH)Cl_2$	18.25	$(MeO)_4$	4.74	H(EtO)	56.79	Et_3	0.52
MeCl	0.12	0.23	Et	14.38	$EtCl_3$	8.14	$Me_2(Octo)Cl$	8.08	Et(EtO)	71.31	Pr_3	0.35
EtCl	0.15	0.21	Pr	11.06	$C_5H_{11}Cl_3$	11.38	$MePhCl_2$	1.58	$C_5H_{11}(EtO)$	83.58	Et_2Ph	0.63
PhCl	0.19	–	*i*-Pr	13.29	$H_2C{=}CHCl_3$	7.93	Ph_2Cl_2	1.51	$(EtO)_2$	30.09	$EtPh_2$	0.44
Br_2	0.11	0.10	Bu	9.34	$PhCl_3$	11.30	$PhCl_3$	0.81	HCl	40.72	$Et(EtO)_2$	1.05
			Ph	0.69	$PhCH_2Cl_3$	12.54					$(EtO)_3$	1.17
					PhF_3	1.91						

[a] Toxicity for rats.
[b] Toxicity for mice.

on the *P* properties of the classic series. For the non-classic series Eq. (1) transforms to the following:

$$P = P_0 + a\sigma_I + b\sigma_R\left(\sigma_R^+, \sigma_R^-\right) + c\sigma_\alpha, \quad (3)$$

The universal σ_α constants of the X substituents serve as a measure of the polarizability effect. It is more preferable to use σ_α constants (they are tabulated for most of the substituents [15] and normalized to the σ_I, σ_R, σ_R^+, and σ_R^- constants [13]) rather than to carry out laborious calculations, using Formula (2).

The series $4\text{-}XC_6H_4R_c^q$, in which the through resonance effects exist, also belong to the category of non-classic ones. The resonance interaction between the donor substituent X and R_c^q (i.e. the charge transfer from X to R_c^q) to produce conjugated system can be conceived of as an approaching of X to R_c^q (i.e. the decrease of the separation between X and R_c^q), resulting in the polarizability effect.

In the non-classic series XR_c^q and certain ones of XBR_c^q the X and R_c^q fragments are closely spaced, sometimes resulting in the steric effect. In these cases Eq. (3) transforms to

$$P = P_0 + a\sigma_I + b\sigma_R\left(\sigma_R^+, \sigma_R^-\right) + c\sigma_\alpha + dE_s', \quad (4)$$

where E_s' is a steric constant of substituents X [16,17].

As already noted, the polarizability effect arises from an excess charge *q* on R_c. This charge appears in the chemical reaction, electromagnetic impact or complexation. Therefore the polarizability effect influences the spectroscopic and thermodynamical characteristics of different complexes, e.g. Refs. [18–22]. This is of importance to the study of the biological activity.

According to Hansch [23,24], in narrow series the biological properties BP, including toxicity, depend of the electronic (inductive and resonance), steric, and so-called hydrophobic effects of substituents; in doing so in the correlation analysis one must draw on the quantity log 1/BP instead of BP one. The hydrophobic parameter characterizes the free energy change due to moving a molecule from one phase to another, i.e. from the solution outside the cell to the biological target in the cell [23]. The hydrophobic effect will be omitted in the present discussion. It is important here merely to note that organometallics (e.g. mercury [25], tin, lead [26], phosphorus [27] compounds) form donor–acceptor complexes with biological targets. As a consequence an excess charge *q* arises on the central atom M. We speculated that the charge *q* was a cause of the polarizability effect which combined with the inductive, resonance, and steric ones influenced the properties *P*. To our knowledge no consideration has been given to the role of the polarizability effect in studies of BP. The aim of this paper was to prove the above assumption.

2. Result and discussion

The correlation analysis of the narrow series allows our problem to be solved. The BP values for 27 series taken from the literature [1–5,9–11] are given in Tables 1–5. The original values of LD_{50} for each compound were converted as mmol kg^{-1}.

We have considered not only the toxicity (the lethal doses LD_{50} and LDL_0) but also for comparison 4 series of other BP (ID_{50}, IC_{50}, I_{50}, and C, see Table 5). As noted above, the toxicity depends on both: central atom M (Hg, B, Si, etc.) and substituents X bonded to the M. In each of narrow series I–XXIII (as well as XXIV–XXVII) the atom M is fixed and hence the toxicity and other BP vary solely with the substituent effects. The correlation analysis gives no way of investigation of the influence of the atom M on the BP (as far as we know

Table 2
LD_{50} values (mmol kg^{-1}) for series VIII–XII.

Series VIII [2]		Series IX [4]	Series X [4]		Series XI [4]		Series XII [2]
$XMe_2SiCH_2OCONH_2$		$XSi(OCH_2CH_2)_3N$	$4\text{-}XC_6H_4Si(OCH_2CH_2)_3N$		$XOSi(OCH_2CH_2)_3N$		$XSCH_2Si(OCH_2CH_2)_3N$
X	LD_{50}, VIII[a]	LD_{50}, IX[a]	X	LD_{50}, X[a]	X	LD_{50}, XI[a]	LD_{50}, XII[a]
H	–	0.57	H	0.001	H	–	0.24
Me	2.72	15.85	Me	0.0006	Me	10.23	–
Et	3.72	–	Et_2N	0.031	Et	13.67	0.06
Pr	2.28	–	MeO	0.060	Pr	12.85	–
Bu	2.96	–	Cl	0.006	*i*-Pr	12.85	–
Ph	1.91	0.001			*t*-Bu	0.93	–
$PhCH_2$	4.48	4.32			Ph	0.75	–
Cl_2CH	–	2.32			$PhCH_2$	8.00	0.30
$BrCH_2$	–	3.41			MeOC	–	3.38
					CN	–	0.43

[a] Toxicity for mice.