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可用于表征可电离化合物离子化影响的描述符研究进展

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摘要: 在人为有意生产的化学品或无意识产生的化学品中,可电离有机化合物(IOCs)均占有较大比重。在环境水体、生理或实验 pH 条件下,IOCs 可解离为分子和离子形态。研究表明,IOCs 的分子和离子形态均对其表观物理化学、环境归趋和行为、生态和健康毒性效应参数具有不可忽视的影响,因而在开展 IOCs 相关实验或理论研究时不应忽略离子化的影响。在构建 IOCs 相关预测模型时,核心是如何表征离子化的影响。本文从描述符入手,总结了可用于表征 IOCs 离子化影响的 4 类描述符,即酸碱解离常数(pK_a)及其衍生参数(分子态和离子态的比例分数($\delta_{分子}$ 和 $\delta_{离子}$))、考虑离子化影响的分配系数包括正辛醇-水分布系数($\log D_{OW}$(pH))和进行形态修正的脂质体-水分配系数($\log D_{lip/w}$(pH))、考虑离子参数的多参数线性自由能关系(离子描述符 J^+和 J^-)、基于形态修正的量化参数,并展望了表征 IOCs 离子化影响的未来研究重点。

关键词: 可电离有机化合物;离子化;离子形态;分子形态;分配参数;水生生物毒性;描述符;量化描述符;定量结构-活性/属性关系

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Progress in Descriptors Used to Correct Influence of Ionization for Ionizable Organic Chemicals

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Abstract: Ionogenic organic chemicals (IOCs) are organic compounds with one or more ionizable function groups in their molecular structures. A large fraction of artificial chemicals or unintentional production chemicals are IOCs. Under the environmental, physiological and experimental pH condition, the IOCs may dissociate and exist as a mixture of neutral and ionized forms. It had been well documented that the neutral and ionized species of IOCs indeed had distinct physicochemical properties, environmental fate and behavior, ecological and health toxic effects. The observed parameters, properties, or endpoints influenced by ionization include but not limited to partition coefficients, photolysis rate constant, rate constants of hydroxyl radical, the adsorption capability to zeolite, bioconcentration, aquatic toxicity on fish, *Daphnia magna*, algae, *Tetrahymena pyriformis*, protein binding interaction, and so

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on. In addition, the previous studies also implied that both forms of IOCs may contribute to their observed aforementioned apparent parameters. Thus, ionization should not be ignored in the related experimental and theoretical research of IOCs. Hitherto, how to correct the influence of ionization is one of the critical issues in deriving the predictive models (e.g. (quantitative) structure-activity/property relationship ((Q)SA/PR)) for IOCs. In this work, the available descriptors could be used to describe the effect of ionization for IOCs in the modeling were reviewed and summarized. Those descriptors include acid dissociation constant (pK_a) and derived parameters (the fractions of the neutral (δ_M) and ionized species (δ_I) at a given pH), distribution coefficient (the *n*-octanol/water distribution coefficient ($\log D_{OW}$(pH)) and speciation-corrected liposome-water distribution ratios ($\log D_{lip/w}$(pH))), ionic descriptors in polyparameter linear free energy relationship (pp-LFER) equation (ionic descriptors J^+ and J^-), chemical form adjusted quantum chemical descriptors. Further investigations in correcting the ionization of IOCs were further discussed.

Keywords: ionogenic organic chemicals (IOCs); ionization; ionized form; neutral form; partition coefficients; aquatic toxicity; descriptors; quantum chemical descriptor; (quantitative) structure-activity/property relationship

可电离有机化合物(ionizable organic chemicals, IOCs)是指分子结构中包含解离基团(如羟基(—OH)、羧基(—COOH)、磺酸基(—SO_3H)和氨基(—NH_2)等)的有机酸碱、有机两性离子和有机盐等。在人为有意生产的化学品或无意识产生的化学品中, IOCs 均占有较大比例。据估计,在欧盟《化学品的注册、评估、授权和限制法规》(REACH 法规)中登记注册的 14 多万种化学品中,约半数属于 IOCs[1-3];在目前使用的药物中,约 80% 属于 IOCs[4],而 85%~95% 的原料药也属于 IOCs[5]。在水消毒副产物等无意识产生的化学品中,也存在大量的取代有机羧酸类、取代酚类等 IOCs[6]。由于 IOCs 在生产、生活中的大量使用,以及在水消毒等过程中无意识的产生,导致其会通过多种途径进入各环境介质。人群、环境生物也会通过经皮、经口和呼吸等多种途径暴露于 IOCs,进而引发潜在的健康和/或生态危害效应。因此,有必要从人工化学品或无意识产生的化学品中筛选识别具有潜在健康和/或生态危害效应的 IOCs,并对其采取适当的管控措施,以期保护人群健康和生态安全[7]。

与不可电离化合物相比,IOCs 的重要特点是在环境水体、生理或实验不同 pH 条件下,会解离,从而以不同比例的分子和离子形态共存。分子和离子形态存在比例取决于其本身的酸碱解离常数(pK_a)和环境/生理/试验 pH 条件(图 1)。式(1)显示了一元酸碱解离程度的计算方程[8]:

$$\delta_{分子}=\frac{[M]}{[M]+[I]}=\frac{1}{1+10^{(pH-pK_a)\cdot I_{ab}}}$$
$$\delta_{离子}=\frac{[I]}{[M]+[I]}=\frac{10^{(pH-pK_a)\cdot I_{ab}}}{1+10^{(pH-pK_a)\cdot I_{ab}}} \quad (1)$$

$\delta_{分子}$和 $\delta_{离子}$分别是分子态和离子态的比例分数; I_{ab} 是酸和碱指示系数,酸和碱的 I_{ab} 分别取 1 和 −1。对 IOCs 而言,存在如下 2 个问题需要回答:一是其共存的分子和离子形态是否具有不同的物理化学、环境归趋和行为、生态和健康毒性效应? 二是哪个形态对化合物的表观属性和效应贡献更大?

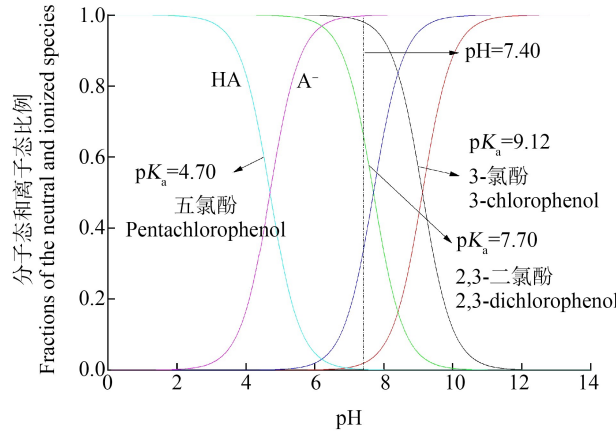

图 1 五氯酚、2,3-二氯酚和 3-氯酚形态分布曲线

注:HA 和 A^-分别代表分子态和离子态;化合物 pK_a 实验数据来源于 EPI Suit 4.1™ 的 PhysProp 数据库[9]。

Fig. 1 Species distribution of pentachlorophenol, 2,3-dichlorophenol and 3-chlorophenol

Note: HA and A^- are the neutral and anionic forms, respectively; the pK_a values of those compounds were obtained from PhysProp Database in EPI Suit 4.1™[9].

过去数十年的研究表明,IOCs 的不同形态确实表现不同的物理化学、环境归趋和行为、生态和健康毒性效应[10-14]。受到离子化影响的参数包括但不仅限于分配参数(包括有机碳-水分配系数[15-16]、牛血

清白蛋白-水分配系数[17-18]、肌肉蛋白-水分配系数[19-20]、脂质体-水分配系数[3,21-23])、光解速率常数[24-25]、羟基自由基速率常数[26]、沸石的吸附能力[27]、生物富集[28]、鱼、大型溞、绿藻和梨形四膜虫等水生生物的急性毒性[29-32]、蛋白相互作用[33-34]等。相关研究已证实,部分 IOCs 的表观属性或毒性效应值,受其分子态对应的属性或毒性效应值控制,如生物富集、水生生物毒性效应等参数[32,35-37];而有的则取决于其离子态对应的属性或毒性效应值。我们前期的研究表明,在 IOCs 与人运甲状腺素蛋白(hTTR)相互作用的过程中,阴离子形态的酚类化合物、全氟/多氟类化合物与 hTTR 的亲和力强于对应的分子态[34,38]。Goss 等[39]的研究也表明,有机酸的生物分配系数主要受阴离子控制。因此,现有的研究结果,一方面表明 IOCs 的表观物理化学、环境归趋和行为、生态和健康毒性效应参数确实受其离子化的影响,这意味着在开展 IOCs 相关的实验或理论研究时,不应忽视离子化的影响[40];二是部分 IOCs 的表观属性或毒性效应参数值虽然取决于分子或离子态的相应参数值,但不可否认的是仅考虑分子态或离子态贡献时,往往会导致低估其属性或毒性效应参数值[41],这说明在进行 IOCs 相关的研究中,应同时考虑其分子态和离子态的贡献[42]。

目前,无论是人为有意生产的化学品,亦或无意识产生的化学品,大部分仍缺乏基本的物理化学、环境归趋和行为、生态和健康毒性效应参数数据[43-45]。而由于实验方法面临成本高、耗时长等问题,很难对所有化学品一一进行实验测试。为了应对和解决该问题,欧美等国家及经济合作与发展组织(OECD)等国际组织都积极倡导使用预测技术来进行化学品优先级设定、填补数据缺失等[46-50],如(定量)结构活性/属性关系((Q)SA/PR)模型。在过去几十年里,科学家构建了许多能够预测化学品物理化学、环境归趋和行为、生态和健康毒性效应参数的定量、定性预测模型/软件/工具或专家系统。但是研究发现,绝大部分预测模型/软件/工具或专家系统并不适用于 IOCs[43,51-53]。一方面的原因是这些预测工具或专家系统的模型应用域不含有 IOCs[54-55];二是现有预测模型选用的描述符未考虑离子化的影响,而仅是基于 IOCs 分子态的描述符而构建的。而且仅采用 IOCs 分子态的描述符,有时很难构建可接受的模型。例如,Endo 课题组在研究 IOCs 与牛血清蛋白之间的分配系数($K_{BSA/W}$)时,就发现常规描述符不能构建具有较好预测能力的 IOCs $K_{BSA/W}$ 模型[18]。因此,为了构建能够涵盖 IOCs 的预测模型,需要从两方面着手,一是在选择建模化学品时,需涵盖 IOCs;二是选用能够表征离子化影响的描述符进行建模。

考虑到描述符是预测模型构建的核心要素之一[43,50],选用合适的描述符来表征离子化的影响,对于构建能预测 IOCs 物理化学、环境归趋和行为、生态和健康毒性效应参数的模型具有重要意义。基于此,本文总结了可用于表征可电离化合物离子化影响的描述符,即酸碱解离常数及其衍生参数、考虑离子化影响的分配系数、考虑离子参数的多参数线性自由能关系、基于形态修正的量化参数,对其主要特点进行了分析,并提出了研究展望。

1　酸碱解离常数及其衍生参数(Acid dissociation constant and derived parameters)

根据 Henderson-Hasselbalch 方程(式 2),给定化合物的 pK_a 值取决于其在平衡条件下分子态和离子态的浓度[56-57]。在某一特定 pH 条件下,具有较小 pK_a 值的化合物,在平衡溶液中存在更大比例的离子态浓度(式 3)。

$$pK_a=-\log K_a=-\log\frac{[A^-][H^+]}{[HA]}=-\log\frac{[A^-]}{[HA]}-\log[H^+]=-\log\frac{[A^-]}{[HA]}+pH \quad (2)$$

$$\frac{[A^-]}{[HA]}=10^{pH-pK_a} \quad (3)$$

式中:[HA]、[A^-]和[H^+]分别是酸性物质平衡条件下对应的分子态、阴离子和氢离子浓度。

从物理意义来看,pK_a 值可用于表征给定化合物在特定 pH 条件下的离子化状态[58]。因此,在建模中可采用 pK_a 来表征化合物离子化影响[59-60]。自 20 世纪 60 年代 Fujita[61]开始使用 pK_a 以来,pK_a 就常被作为预测变量来表征离子化的影响[29,62-67]。例如,Schultz 等[67]在构建酚类化合物对梨形四膜虫急性毒性预测模型时,当采用 pK_a 作为第 2 个预测变量时(式(4)和(5)),模型的决定系数($R^2_{训练集}$)从 0.783 提高到 0.843。

$$-\log IGC_{50}=-0.772+0.627\log K_{OW} \quad (4)$$

$$n_{训练集}=54,\ R^2_{训练集}=0.783,\ s=0.366$$

$$-\log IGC_{50}=-0.120+0.614\log K_{OW}-0.077pK_a \quad (5)$$

$$n_{训练集}=54,\ R^2_{训练集}=0.843,\ s=0.315$$

$-\log IGC_{50}$ 是梨形四膜虫急性毒性效应值;$\log K_{OW}$

是正辛醇-水分配系数；$n_{训练集}$是训练集化合物数量；s是标准误差。

使用该方法表征离子化影响时，前提是能获取准确的 pK_a 值。然而，部分化合物却很难准确测定其 pK_a 值。例如，全氟辛酸的实验 pK_a 值介于 1.0～3.8[68]，其他全氟/多氟化合物的 pK_a 值也存在类似问题[69]。对于无法获取准确 pK_a 值的 IOCs，该如何处理呢？在这种情况下，可采用分子态($\delta_{分子}$)和离子态($\delta_{离子}$)的比例分数作为预测变量，而替代 pK_a 值。根据式(1)，化合物 $\delta_{分子}$和 $\delta_{离子}$的值取决于环境/生理/实验 pH 值和其 pK_a。在一定程度上，使用 $\delta_{分子}$和 $\delta_{离子}$可减少因 pK_a 变化带来的偏差。比如，在生理 pH=7.40 的条件下，pK_a 值介于 1.0～3.8 的全氟辛酸 $\delta_{离子}$值取值均为 1。目前，已有很多模型采用 $\delta_{分子}$和 $\delta_{离子}$作为预测变量。例如，梨形四膜虫、发光菌、大型溞和鲤鱼急性毒性[32,70−72]、土壤-水分配系数[73]、溶解有机质-水分配系数[74]等参数预测模型。例如，Qin 等[70]采用 $\delta_{分子}$作用预测变量构建了能预测中性分子、IOCs 对发光菌(*V. fischeri*) (式 6)、大型溞(*D. magna*)(式 7)和鲤鱼(式 8)急性毒性的预测模型：

$$-\log EC_{50}(发光菌)=1.04+0.701\log K_{OW}+1.11S+1.12I_{NO_2}-0.157\log\delta_{分子} \quad (6)$$

$$n_{训练集}=102,\ R^2_{训练集}=0.790,s=0.400$$

$$-\log EC_{50}(大型溞)=1.73+0.628\log K_{OW}+0.772S+0.899I_{NO_2}+0.542\log\delta_{分子} \quad (7)$$

$$n_{训练集}=102,\ R^2_{训练集}=0.790,s=0.400$$

$$-\log EC_{50}(鲤鱼)=1.52+0.581\log K_{OW}+0.767S+1.33I_{NO_2}+0.461\log\delta_{分子} \quad (8)$$

$$n_{训练集}=102,\ R^2_{训练集}=0.790,s=0.400$$

$-\log EC_{50}$(发光菌)、$-\log EC_{50}$(大型溞)和$-\log EC_{50}$(鲤鱼)分别是发光菌、大型溞和鲤鱼急性毒性效应值；S是化合物极化性参数；I_{NO_2}是分子中硝基个数。在构建全氟和多氟化合物的 hTTR 干扰效应预测模型时，我们选取了 $\delta_{离子}$值作为预测变量(式 9)[38]：

$$\log RP=-5.91+2.27HATS6m+0.898\delta_{离子}-1.94qO^-_{adj} \quad (9)$$

$$n_{训练集}=20,\ R^2_{训练集}=0.934,\ Q^2_{CUM}=0.903,\ RMSE_{训练集}=0.258,\ P<10^{-4}$$

$$n_{验证集}=9,\ Q^2_{验证集}=0.654,\ RMSE_{验证集}=0.874$$

logRP 是化合物与 hTTR 的相互作用势(logRP)；HATS6m 是分子质量加权的杠杆自相关指数；qO^-_{adj}是形态修正的分子中最负氧原子电荷；$n_{验证集}$是验证集化合物数量；Q^2_{CUM}是模型所提取的所有 PLS 主成分所能解释的因变量总方差的比例；$Q^2_{验证集}$是验证集外部可解释方差；$RMSE_{训练集}$和 $RMSE_{验证集}$代表训练集和验证集均方根误差；P为显著性水平。

pK_a 实验值可从文献或数据库查询，如 eChemPortal (https://www.echemportal.org/echemportal/)，Drugbank (https://www.drugbank.ca/)，ChemIDplus (https://chem.nlm.nih.gov/chemidplus/)，Physprop (http://esc.syrres.com/fatepointer/search.asp)，OECD QSAR toolbox (https://qsartoolbox.org/)等。若无实验 pK_a 值，可采用 ChemAxon (http://www.chemaxon.com)，Virtual Computational Chemistry Laboratory (http://www.vcclab.org/lab)，SPARC (http://www.archemcalc.com/sparc.html)，SciFinder (https://scifinder.cas.org)等软件预测。

2 考虑离子态贡献的分配系数(Distribution coefficient with ionization correction)

$\log K_{OW}$ 可表征不可电离化合物或 IOCs 的分子态从水相分配到有机相的能力，因而从 20 世纪 60 年代开始[75]，$\log K_{OW}$ 就被用来预测各种涉及分配的环境归趋和行为、生态和健康毒性效应参数[76]。例如，EPI Suit 4.1™ 的 ECOSAR™ 模块主要通过 $\log K_{OW}$ 来预测化合物鱼、大型溞和绿藻急慢性毒性效应数据。但是，在涉及 IOCs 的场合，$\log K_{OW}$ 的预测能力可能变差。例如，图 2(a)显示了在 pH=6.0、7.8 和 9.0 条件下，$\log K_{OW}$ 与 IOCs 对大型溞 24 h 急性毒性数据($-\log EC_{50}$)之间的关系。由该图可知，$\log K_{OW}$ 与$-\log EC_{50}$之间不存在显著线性相关性(pH=7.8 和 9.0)或仅存在较弱的相关性(pH=6.0)。如何提高二者之间的相关性呢？一般认为，考虑离子态贡献的正辛醇-水分布系数($\log D_{OW}$(pH))比 $\log K_{OW}$ 更适合 IOCs[77−78]。如图 2(b)所示，在 pH=6.0、7.8 和 9.0 条件下，$\log D_{OW}$(pH)与$-\log EC_{50}$ 的 Pearson 线性相关系数分别从与 $\log K_{OW}$ 的 0.350 (P<0.01)、0.250 (P>0.05)和 0.174 (P>0.05)提高到 0.678 (P<0.0001)、0.798 (P<0.0001)和 0.845 (P<0.0001)。这进一步说明了考虑离子化的重要性。

$\log D_{OW}$(pH)可以通过式(10)或(11)计算：

$$\log D_{OW}(pH)=\log K_{OW}-\log(1+10^{pH-pK_a}) \quad (10)$$

$$\log D_{OW}(pH)=\frac{\sum_{i=1}^{n}[species]_{i,octanol}}{\sum_{i=1}^{n}[species]_{i,water}} \quad (11)$$

式中:i 指分子或离子态;$[\text{species}]_{i,\text{octanol}}$ 和 $[\text{species}]_{i,\text{water}}$ 分别指第 i 种形态在正辛醇和水中的浓度。目前,$\log D_{OW}$(pH)已被广泛用于预测可电离环境污染物的相关属性或毒性效应[32,79−82]或可电离药物分子相关参数[12,78,83]。例如,Ou 等[80]基于 $\log D_{OW}$(pH)构建了预测 IOCs 鱼类肌肉蛋白-水分配系数($\log K_{MP/w}$)的预测模型(式 12):

$$\log K_{MP/w} = -0.715 + 0.743 \log D_{OW}(\text{pH} = 7.0) + 0.0604 n_{Car} \quad (12)$$

$n_{\text{训练集}} = 34$, $R^2_{\text{训练集}} = 0.929$, $Q^2_{LOO} = 0.906$, $\text{RMSE}_{\text{训练集}} = 0.262$, $P<0.0001$

$n_{\text{验证集}} = 11$, $Q^2_{\text{验证集}} = 0.915$, $\text{RMSE}_{\text{验证集}} = 0.244$

n_{Car} 是分子结构中 sp2 杂化的芳香碳原子个数;Q^2_{LOO} 是去一法交叉验证系数。

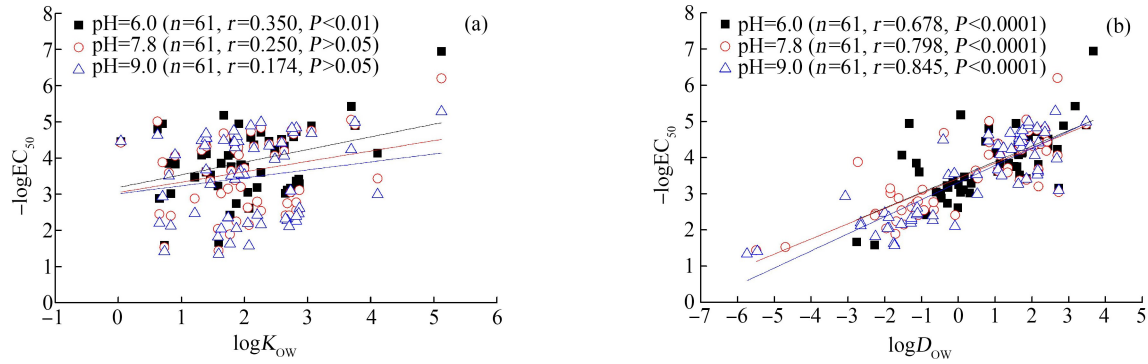

图 2　$\log K_{OW}$, $\log D_{OW}$(pH)与 $-\log EC_{50}$ 的关系

注:$\log K_{OW}$ 表示正辛醇-水分配系数,$\log D_{OW}$(pH)表示正辛醇-水分布系数;可电离有机化合物(IOCs)的大型溞急性毒性数据($-\log EC_{50}$, 24 h)和相应的 $\log K_{OW}$ 数据来源于 Li 等[84];$\log D_{OW}$(pH)数据采用 MarvinSketch 15.6.29.0, 2015(ChemAxo, http://www.chemaxon.com)软件预测。

Fig. 2　Correlation between $\log K_{OW}$, $\log D_{OW}$(pH) and $-\log EC_{50}$

Note: $\log K_{OW}$ is *n*-octanol/water partition coefficient, and $\log D_{OW}$ is *n*-octanol/water distribution coefficient; the acute toxicity data ($-\log EC_{50}$, 24 h) of ionizable organic chemicals (IOCs) to *Daphnia magna*, corresponding $\log K_{OW}$ values were obtained from Li et al[84], and $\log D_{OW}$(pH) values of those IOCs were predicted employing MarvinSketch 15.6.29.0, 2015 (ChemAxon, http://www.chemaxon.com).

从结构上看,测定 $\log K_{OW}$ 和 $\log D_{OW}$(pH)使用的辛醇是均相体系,而真实的生物膜含有磷脂双分子层,属于非均相体系。这意味着化合物在辛醇相的分配行为与其在真实生物膜中的分配或跨膜行为具有较大的差异。因此,相比于 $\log K_{OW}$ 或 $\log D_{OW}$(pH),使用膜-水分配系数($\log K_{m/w}$)来表征化合物的膜通透性或膜累积能力具有更大的优势。然而,由于真实的生物膜很难获取及开展实际的测试,一般采用脂质体-水分配系数($\log K_{lip/w}$)来近似替代 $\log K_{m/w}$[85]。对于不可电离化合物,可以采用分子态的 $\log K_{lip/w-\text{分子}}$作为预测变量。但是对于 IOCs,需要使用在特定 pH 条件下进行形态修正的脂质体-水分配系数(($\log D_{lip/w}$(pH))来表征。其定义如下[86]:

$$\log D_{lip/w}(\text{pH}) = \log K_{lip/w\text{-分子}} \cdot \delta_{\text{分子}} + \sum_{i=1}^{n} \log K_{lip/w\text{-离子-}i} \cdot \delta_{\text{离子-}i} \quad (13)$$

式中:$\log K_{lip/w-\text{分子}}$ 和 $\log K_{lip/w-\text{离子-}i}$ 分别是 IOCs 分子态和第 i 种离子态的脂质体-水分配系数;$\delta_{\text{离子-}i}$ 是第 i 种离子态的比例分数。目前,已有较多模型采用 $\log D_{lip/w}$(pH)作为预测变量预测 IOCs 的相关属性或毒性。如,细菌毒性[87−88]、藻毒性[22]、斑马鱼胚胎毒性[10,89]、发光菌生物发光抑制毒性[90]、生物累积性[91−92]和吸附属性[93]等。例如,Klüver 等[89]采用 $\log D_{lip/w}$(pH)来预测 IOCs 的斑马鱼胚胎急性毒性参数($-\log LC_{50}$)(式 14):

$$-\log LC_{50} = -2.22 + 0.99 \log D_{lip/w}(\text{pH}) \quad (14)$$

化合物的 $\log K_{OW}$ 和 $\log D_{OW}$ 值可以从文献、数据库查询得到,也可通过软件预测。如 EPI Suit 4.1™、VEGA (https://www.vegahub.eu/)、OECD QSAR toolbox (https://qsartoolbox.org/)、ChemAxon (http://www.chemaxon.com)等。$\log K_{lip/w}$ 和 $\log D_{lip/w}$(pH)数据可通过查阅文献获取或根据文献报道的模型进行预测。例如,在前期的研究中,我们查询了 290 种化合物的分子态脂质体-水分配系数($\log K_{lip/w-\text{分子}}$)、106 种化合物的离子态脂质体-水分配系数($\log K_{lip/w-\text{离子}}$)和 306 种化合物进行形态修正的脂质体-水分配系数(($\log D_{lip/w}$(pH))数据,同时构建了能预测 $\log K_{lip/w-\text{分子}}$、

$\log K_{\text{lip/w-离子}}$和 $\log D_{\text{lip/w}}$(pH)数据的模型[85]。

3 考虑离子参数的多参数线性自由能关系(Ionic descriptors in polyparameter linear free energy relationship (pp-LFER) equation)

传统的多参数线性自由能关系(pp-LFER)模型可用于预测中性化合物从水相/气相到各种有机相的分配参数[94]。pp-LFER 模型一般采用如下 3 个方程来表征[95-97]:

$$\text{SP}=c+eE+sS+aA+bB+vV \quad (15)$$

$$\text{SP}=c+eE+sS+aA+bB+lL \quad (16)$$

$$\text{SP}=c+sS+aA+bB+lL+vV \quad (17)$$

式中:SP 一般指分配系数;E 是化合物过量摩尔折射率;S 是化合物极化性参数;A 和 B 是分子整体氢键酸度和碱度;V 是 McGowan 分子体积;L 是 298 K 条件下,正十六烷-空气分配系数的对数值;c 是常数项;e、s、a、b 和 v 是系数。目前,该方程在预测不可电离化合物的相关分配系数方面得到了较多的应用,例如在 Web of Science 数据库,通过“polyparameter linear free energy relationship”作为关键词,可以检索到数十篇相关论文,在这里我们就不详细列出相关应用。为了适用于 IOCs,Abraham 和 Zhao[98]在传统 pp-LFER 方程基础上通过引入了 2 个新的离子描述符,即 J^+和 J^-,提出了考虑离子参数的 pp-LFER 方程:

$$\text{SP}=c+eE+sS+aA+bB+vV+j^+J^++j^-J^- \quad (18)$$

通过采用考虑离子参数的 pp-LFER 方程,前人构建了可预测 IOCs 的多种参数,包括有机溶剂-水分配系数[99-101]、脂质体-水分配系数[3]、血清白蛋白-水分配系数[18]、肌肉蛋白水分配系数[20]、活性炭-水分配系数[102]和针铁矿-溶剂分配系数[103]等。例如,Henneberger 等构建了能够预测 IOCs 鸡类肌肉蛋白-水分配系数($\log K_{\text{MP/w}}$)的预测模型[20]:

$$\log K_{\text{MP/w}}=-0.24+0.68E-0.76S-0.20A-2.29B+2.51V-0.68J^++2.89J^- \quad (19)$$

$n_{\text{训练集}}=86$, $R^2_{\text{训练集}}=0.89$, $\text{RMSE}_{\text{训练集}}=0.29$

pp-LFER 建模所需参数 E、S、A、B、V 和 L 可通过查询 UFZ-LSER 数据库(https://www.ufz.de/ index.php? en = 31698&contentonly = 1&m = 0&lserd _ data[mvc]=Public/start)或大连理工大学陈景文教授团队开发的在线程序预测所需参数(http://www.pplfer.online/)。离子描述符 J^+和 J^-可通过查阅文献获取。

4 基于形态修正的量化参数(Chemical form adjusted quantum chemical descriptors)

化合物的量子化学描述符一般具有明确的物理化学意义,有利于进行模型机理解释[59,104]。为了预测 IOCs 的相关属性或毒性效应,可对量化描述符进行形态修正[34,105]:

$$X_{\text{修正}}=X_{\text{分子}}\cdot\delta_{\text{分子}}+\sum_{i=1}^{n}X_{\text{离子-}i}\cdot\delta_{\text{离子-}i} \quad (20)$$

式中:$X_{\text{修正}}$、$X_{\text{分子}}$和 $X_{\text{离子-}i}$ 分别是 IOCs 形态修正、分子态和第 i 种离子态的量化描述符。通过采用形态修正的量化描述符,可显著提高模型的预测质量。例如,在构建 IOCs 牛血清白蛋白-水分配系数[106]和大型溞急性毒性效应参数($-\log\text{EC}_{50}$)[8]时,我们比较了仅采用分子态描述符和基于形态修正的描述符构建的模型质量,发现采用后者构建的模型其 $R^2_{\text{训练集}}$和 $Q^2_{\text{验证集}}$ 分别从 0.508 和 0.220 提高到 0.707 和 0.581(牛血清白蛋白-水分配系数)、从 0.705 和 0.651 到 0.875 和 0.851(大型溞急性毒性效应)。构建的大型溞急性毒性效应预测模型如下(式(21)和(22))[8]:

$$-\log\text{EC}_{50}(\text{pH}=7.8)=15.7-9.59qH^+_{\text{-分子}}-9.12\tau_{\text{-分子}}+474V_{\text{s-分子}}+25.6E_{\text{HOMO-分子}} \quad (21)$$

$n_{\text{训练集}}=48$, $R^2_{\text{训练集}}=0.705$, $Q^2_{\text{LOO}}=0.622$, $\text{RMSE}_{\text{训练集}}=0.569$, $P<0.0001$

$n_{\text{验证集}}=15$, $Q^2_{\text{验证集}}=0.651$, $\text{RMSE}_{\text{验证集}}=0.497$

$$-\log\text{EC}_{50}(\text{pH}=7.8)=-0.906+0.426\log D_{\text{OW}}-4.87qD^-_{\text{-修正}}+0.014\text{polar}_{\text{-修正}}-32.9\Pi_{\text{-修正}} \quad (22)$$

$n_{\text{训练集}}=48$, $R^2_{\text{训练集}}=0.875$, $Q^2_{\text{LOO}}=0.840$, $\text{RMSE}_{\text{训练集}}=0.370$, $P<0.0001$

$n_{\text{验证集}}=15$, $Q^2_{\text{验证集}}=0.851$, $\text{RMSE}_{\text{验证集}}=0.336$

式中:$qH^+_{\text{-分子}}$是分子态中氢原子的最正净电荷;$\tau_{\text{-分子}}$是分子态静电势的平衡参数;$V_{\text{s-分子}}$是分子态分子表面上静电势平均值;$E_{\text{HOMO-分子}}$是分子态分子最高占据轨道能;$qD^-_{\text{-修正}}$是形态修正的分子中电子供体原子电荷;$\text{polar}_{\text{-修正}}$是形态修正的分子极化率;$\Pi_{\text{-修正}}$是形态修正的分子表面静电势的分散度。

在表 1 中列出了 18 种形态修正的量化描述符。基于这些参数,我们已成功构建了 IOCs 与人运甲状腺素蛋白(hTTR)亲和力[34,38,107-110]、牛血清白蛋白-水分配系数[106]、脂质体-水分配系数[85]和大型溞急性毒性[8]等参数预测模型。从定义可知,基于形态修正的量化参数具有 2 个方面的特点:(1)可以直接根据 IOCs 的分子态和离子态结构计算得到;(2)可以同时考虑分子态和共存的多种离子态的贡献。

表 1　基于形态修正的(Q)SA/PR 模型量化参数

Table 1　Proposed chemical form adjusted quantum chemical descriptors used in the (Q)SA/PR modeling

序号 No.	描述符 Descriptors	描述 Description
1	$qO^-_{修正}$　qO^-_{Adj}	形态修正的分子中最负氧原子电荷 The chemical form adjusted most negative net atomic charge on an oxygen atom
2	$qX^-_{修正}$　qX^-_{Adj}	形态修正的分子中最负卤素原子电荷 The chemical form adjusted most negative net atomic charge on a halogen atom
3	$qD^-_{修正}$　qD^-_{Adj}	形态修正的分子中电子供体原子电荷 The chemical form adjusted most negative net atomic charge on an electron donor atom
4	$V_{s,\,max\,修正}$　$V_{s,\,max\text{-}Adj}$	形态修正的分子表面最正静电势 The chemical form adjusted most positive values of the molecular surface potential
5	$V_{s,\,min\,修正}$　$V_{s,\,min\text{-}Adj}$	形态修正的分子表面最负静电势 The chemical form adjusted most negative values of the molecular surface potential
6	$V^+_{s\,修正}$　$V^+_{s\,Adj}$	形态修正的分子表面正静电势的平均值 The chemical form adjusted averages of the positive potentials on the molecular surface
7	$V^-_{s\,修正}$　$V^-_{s\,Adj}$	形态修正的分子表面负静电势的平均值 The chemical form adjusted averages of the negative potentials on the molecular surface
8	$V_{s,aver\,修正}$　$V_{s,aver\text{-}Adj}$	形态修正的分子表面静电势平均值 The chemical form adjusted average potentials on the molecular surface
9	$\Pi_{修正}$　Π_{Adj}	形态修正的分子表面静电势的分散度 The chemical form adjusted average deviation of surface potential
10	$\tau_{修正}$　τ_{Adj}	形态修正的静电势平衡参数 The chemical form adjusted balance parameter of the surface potential
11	$dipole_{修正}$　$dipole_{Adj}$	形态修正的分子偶极矩 The chemical form adjusted molecular dipolemoment and its descriptor
12	$polar_{修正}$　$polar_{Adj}$	形态修正的分子极化率 The chemical form adjusted molecular polarizability
13	$E_{HOMO\,修正}$　$E_{HOMO\text{-}Adj}$	形态修正的分子最高占据轨道能 The chemical form adjusted highest occupied molecular orbital energy and its descriptor
14	$E_{LUMO\,修正}$　$E_{LUMO\text{-}Adj}$	形态修正的分子最低未占据轨道能 The chemical form adjusted lowest unoccupied molecular orbital energy and its chemical form adjusted descriptor
15	$\omega_{修正}$　ω_{Adj}	形态修正的电负性指数 The chemical form adjusted electrophilicity index
16	$\mu_{修正}$　μ_{Adj}	形态修正的化学势 The chemical form adjusted chemical potential
17	$\eta_{修正}$　η_{Adj}	形态修正的化学硬度 The chemical form adjusted chemical hardness
18	$V_{修正}$　V_{Adj}	形态修正的分子体积 The chemical form adjusted molecular volume

注:(Q)SA/PR 表示(定量)结构活性/属性关系。

Note: (Q)SA/PR is (quantitative) structure-activity/property relationship.

5　总结与展望(Conclusion and prospect)

IOCs 的分子态和离子态对其物理化学、环境归趋和行为、生态和健康毒性效应参数均具有不同贡献。在开展 IOCs 相关实验和理论研究时,不应忽视 IOCs 离子化的影响。截止目前,研究人员针对在建模中如何考虑 IOCs 离子化影响的问题,提出

了 4 种可用于表征 IOCs 离子化影响的描述符,即酸碱解离常数及其衍生参数、考虑离子化影响的分配系数、考虑离子参数的多参数线性自由能关系、基于形态修正的量化参数,并成功将其应用于 IOCs 各种分配系数、水生毒性和蛋白结合效应等参数的(Q)SA/PR 模型构建。

针对现有研究进展,对今后 IOCs 建模研究提出了以下建议。(1) 预测指标方面:需要进一步识别还有哪些参数受离子化的影响;(2) 描述符方面:需要研究如何更准确获取所需描述符。如前所述,在建模中要考虑离子化的影响,核心是获取 pK_a、$\log D_{OW}(pH)$、$\log D_{lip/w}(pH)$、J^+和 J^-、量化参数等相关描述符。但是,在现有 IOCs 中,仅部分具有可靠的 pK_a、$\log D_{OW}(pH)$和 $\log D_{lip/w}(pH)$等参数的实验数据。例如,仅几百种 IOCs 拥有 $\log D_{lip/w}(pH)$实验数据[85],几千种 IOCs 有 pK_a 实验数据[58]。因此,需要进一步测定 IOCs 的 pK_a、$\log D_{OW}(pH)$和 $\log D_{lip/w}(pH)$等参数的实验数据;同时也可以构建更多能够准确预测这些参数的模型工具。对量化参数而言,已引入了 18 种参数用于建模。根据 Mamy 等[111]的研究结果,目前文献中已报道的量化参数已达 248 种。需要进一步研究是否还存在其他量化参数适合用于进行形态修正并用于建模。(3) (Q)SA/PR 模型构建方面:针对受离子化影响的参数,构建更多预测模型,同时考虑将其集成到现有软件工具中或开发新的软件工具。(4) 非(Q)SA/PR 方法的开发与应用:需积极探索其他适合用于表征离子化影响的非(Q)SA/PR 方法。IOCs 的一些属性或毒性效应参数涉及小分子与生物大分子(如生物膜、蛋白等)的相互作用。而分子对接、分子动力学和耦合量子力学/分子力学(QM/MM)等分子模拟方法常用于研究小分子与生物大分子的相互作用。是否可以采用分子模拟方法来表征 IOCs 离子化的影响呢? 在这方面,已有部分研究进行探讨,例如,Bittermann 等[3,112]采用 COSMOmic 方法成功预测了 IOCs 生物膜-水分配系数。我们采用 QM/MM 方法研究了酚类化合物与 hTTR 的相互作用,发现实验测定的酚类化合物与 hTTR 亲和力数据(logRP)与基于酚类化合物分子态计算的结合能($E_{结合能-分子态}$)之间无显著性线性相关性。但是,当采用形态修正的结合能($E_{结合能-形态修正}$)后,其与 logRP 则存在显著性线性相关性[34]。因此,需要进一步探索采用分子模拟等非(Q)SA/PR 方法来预测 IOCs 相关属性或毒性参数的可行性。

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