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Enumeration of the constitutional isomers of environmentally relevant substituted polycyclic aromatic compounds

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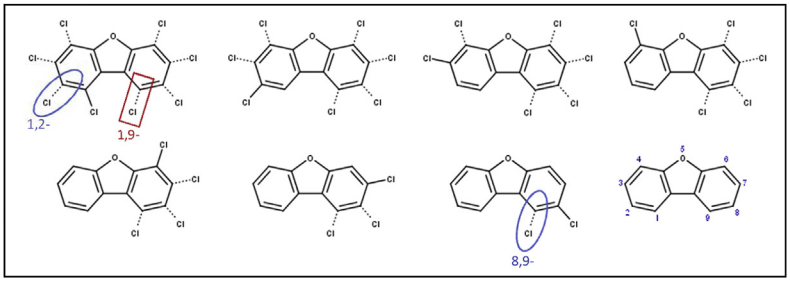
HIGHLIGHTS

- Number of theoretical isomers for polycyclic aromatic compounds were deduced.
- Combinatorics and molecular symmetry were used in this study.
- Approach was ground-truthed on similar compound classes.

GRAPHICAL ABSTRACT



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ABSTRACT

Polycyclic aromatic compounds (PACs) are a diverse group of environmentally relevant compounds which can be persistent, bioaccumulative and toxic. The cyclic backbone of PACs can be substituted with halogens or hydrocarbon chains. The amount and positions of these substituents influence their toxicity. For many classes of PACs, substitution creates mixtures containing large numbers of isomers. For example, 209 theoretical isomers of chlorinated biphenyls are possible. Many other classes of environmentally relevant PACs exist where the number of theoretical isomers are unknown. Here, a mathematical approach using molecular symmetry and the binomial coefficient is presented that determines the number of theoretical isomers of PACs. The approach was validated on PACs with known isomer numbers and then applied to PACs with unknown isomer numbers. When the approach was applied to alkylated polycyclic aromatic hydrocarbons, the possible theoretical isomers ranged from 2 for C_1 naphthalene up to 19 502 for C_6 dibenzo(ah)anthracene. Heterocyclic PACs had similar numbers ranging from 4 isomers for C_1 dibenzothiophene to 13 938 for C_6 dibenzo[a,i]carbazole. The work presented will aide analytical chemists and ecotoxicologists in their efforts to develop methods to measure these compounds, and in attempting to assess the toxicity and environmental fate of individual isomers.

1. Introduction

Concerns regarding the possible adverse effects of toxic environmental contaminants have received considerable global attention during the past half-century. A commonly studied group of

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organic contaminants include polycyclic aromatic compounds (PACs) (Besis and Samara, 2012; Storelli et al., 2011; Abdel-Shafy and Mansour, 2016). Many of the compounds in this diverse group are known to be persistent, bioaccumulative and toxic (PB&T) and have been detected in remote regions of the world (Blumer, 1976; Boffetta et al., 1997; Lauby-Secretan et al., 2013; Allan et al., 2012; Nisbet and LaGoy, 1992; Jacobson and Jacobson, 1996; Robertson and Hansen, 2015; Lans et al., 1993). In fact, since 2000, polycyclic aromatic hydrocarbons (PAHs) have dominated the summed contaminant burdens in lower trophic biota in the Arctic (De Laender et al., 2011).

The PACs that have received the most attention include PAHs, polychlorinated biphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polybrominated diphenyl ethers (PBDEs). With the exception of PAHs, all the aforementioned compounds have been recognised by the Stockholm Convention as persistent organic pollutants (POPs). Many chemicals listed on the Stockholm Convention are classified as industrial chemicals and by-products and are sourced from either anthropogenic or pyrogenic origins (Besis and Samara, 2012; Abdel-Shafy and Mansour, 2016; Cairns and Siegmund, 1981).

It is now widely acknowledged that the number of substituents (defined here as the moiety attached to the cyclo-aromatic backbone) and their position on the aromatic molecule are major drivers of the environmental fate and toxicities of these compounds. For example, while 209 theoretical isomers are possible for PCBs, less than half of these isomers are environmentally significant with resultant adverse health effects (Wolff et al., 1997; Seegal et al., 1990; McFarland and Clarke, 1989). Isomer-based toxicity studies on PCBs suggest the coplanar PCBs, 3,3′,4,4′-tetrachlorobiphenyl (tetraCB), 3,3′,4,4′,5-pentaCB, 3,3′,4,4′,5,5′-hexaCB, and their monoortho analogs are aryl hydrocarbon(Ah)-receptor agonists and contribute significantly to the toxicity of PCB mixtures (Safe, 1990). Another example that highlights how the amount and positioning of substituents impacts toxicity is for PCDDs. The 2,3,7,8- TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) isomer has repeatedly been shown as the most toxic compound of the PCDDs (Safe, 1990; Focant et al., 2002). In fact, the toxicities of all other PCDDs are reported relative to the toxicity of 2,3,7,8-TCDD.

There is also compelling evidence showing that the position and extent of alkylation on PAHs can affect overall chemical toxicities. For example, benz(a)anthracene is a potent genotoxic compound which has been classified as a human carcinogen (IARC Air Pollution, 2010; WHO, 1998). However, the 7,12-dimethyl benz(a) anthracene derivative has been reported to be the most potent mutagenic and carcinogenic PAHs (Higginbotham et al., 1993). It has also been shown that the position of a single methyl group on the benz(a)anthracene backbone can strongly affect metabolic activation, mutagenicity, tumor-initiating ability and carcinogenicity (Stevenson, von Haam; Dunning and Curtis, 1960; Glatt et al., 1981; Stevenson, von Haam; Utesch et al., 1987; Wislocki et al., 1982). Similarly, 5-methylchrysene has also been shown to be more carcinogenic than its parent and even more toxic than any other methyl substituted isomer (Hoffmann et al., 1974; Hecht et al., 1974).

Clearly, knowledge of the substitution pattern and degree of substitution of PACs is paramount to assessing their PB&T potential. In fact, substitution patterns and degree of substitution are the basis of toxicity and physico-chemical quantitative structure activity relationship (QSAR) predictive models. Perhaps equally important to knowing the position of substituents and degree of substitution on a cyclo-aromatic molecule is knowledge of the number of theoretical isomers (i.e. isomers) of any PAC class.

Efforts to enumerate the isomers for a particular PAC have largely relied on manually drawing and counting. For PCDDs and PCDFs this task is not overly daunting considering that the number of constitutional isomers are 75 and 135 respectively. For PCBs (and PBDEs) deciphering the number of isomeric structures becomes more tedious. There are some PACs whereby manually enumerating the possible constitutional isomers becomes impossible. This is especially true for alkyl-substituted PAHs. Alkylated PAHs (aPAHs) are substituted PAHs possessing vast structural diversity. They consist of two or more aromatic rings with an alkyl-substituent(s) attached at different positions. The alkyl-substituted polycyclic aromatic compounds which include the C_1 to C_4 homologues of the 16 USEPA priority parent PAHs (including dibenzothiophene; DBT) have significantly greater effects on the toxicity of mixtures than their parent PAHs, especially in crude oils where they are present at greater concentrations relative to their parent group (Turcotte et al., 2011; Renegar et al., 2017; Environmental Contaminants Encyclopedia PAHs Entry, 1997). Alkyl PAHs comprise up to 98% of the total PAH fraction in crude oil, constituting as much as 70% of the total PAH fraction of the sediment in aquatic environments in the event of a spill (Wang et al., 2004; Hawthorne et al., 2006; Malmquist et al., 2015). There are other groups of scarcely studied substituted heterocyclic aromatic PAH-like compounds i.e., where a carbon atom is replaced by nitrogen (aza-arenes) and sulphur atoms (thia-arenes) that can also contain alkyl substituents. More reports exist on the fate and effect of the unsubstituted parent compounds (Hellou and Warren, 1997; Srogi, 2007; Nahrgang et al., 2009) with few focusing on aPAHs despite their known abundance.

This paper uses combinatorics and molecular symmetry to enumerate the theoretical constitutional isomers of PACs. The equations were validated with PCBs, PCDDs, PCDFs and PBDEs where the number of constitutional isomers have already been determined. With a clearer understanding of the number of possible isomers for PACs, especially aPAHs, more isomer-specific analytical separations and detections could be undertaken, resulting in increased environmental relevance for various ecotoxicological studies.

1.1. Mathematical approach

In order to develop mathematical relationships to determine the number of unique constitutional isomers for PAC an understanding of the binomial coefficient and some basic symmetry of these molecules is first necessary.

Consider a set of the form:

$$A = \{a_1,\ a_2,\ a_3 \ldots a_n\}$$

The number of unique subsets of size k that can be made from A is give by the binomial coefficient formula:

$$\binom{n}{k} = \frac{n!}{(n-k)!k!}$$

This relation is valid providing that all elements of the set A are unique. The binomial coefficient was used to count the arrangements of substituents on a parent molecule backbone. The binomial coefficient is not specific to chemistry and when applied to molecular systems, molecular symmetry needs to be considered separately.

Since most PACs exist in planar form, they should have a mirror plane cutting through the plane of the molecule. This is the least amount of symmetry and if no other elements of symmetry are present the point group is C_s. Different point groups can be made by adding symmetry elements, though the majority of the molecules discussed in this paper belong to the C_{2h}, C_{2v} or D_{2h} point groups. These point groups each contain a principle axis that can be rotated