ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c5cc04885k

Received 12th June 2015,
Accepted 1st August 2015

DOI: 10.1039/c5cc04885k

www.rsc.org/chemcomm

Adsorption of fluorinated anesthetics within the pores of a molecular crystal†

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Commonly used inhalation anesthetics—enflurane, isoflurane, sevoflurane, halothane, and methoxyflurane—are adsorbed within the pores of a porous fluorinated molecular crystal to the tune of up to 73.4(±0.2)% by weight. Uptake of all studied anesthetics is quite fast, typically reaching saturation in less than three minutes.

Many commonly used inhalational anesthetics are extensively fluorinated molecules. Among these are fluorinated ethers—such as enflurane (**1**, Fig. 1), isoflurane (**2**), sevoflurane (**3**), or methoxyflurane (**4**), and fluorinated hydrocarbons such as halothane (**5**). Capture and release of fluorinated anesthetics is an important problem from at least four viewpoints. First, they are expensive and their recycling is economically beneficial. Second, unnecessary postoperative exposure of medical personnel to anesthetic vapors may be harmful in the long term.[1,2] Third, their adsorption under well-defined conditions is useful in controlled-release devices. Finally, fluorinated anesthetics are potent greenhouse gases. Anesthetics contribute 0.03% to the global warming effect; this percentage is very low because of their miniscule concentrations in the atmosphere—but per unit of mass, fluorinated anesthetics are quite damaging. Their tropospheric lifetimes are significant (from 1.2 years for sevoflurane to 10 years for desflurane), and their 20 year global warming potentials (GWP_{20}) are hundreds of times higher than that of CO_2.[1,3,4] Some fluorinated anesthetics are also damaging to the tropospheric ozone layer.[2,5]

Adsorption of fluorinated anesthetics in porous materials has been studied previously. Adsorption of enflurane (**1**, Fig. 1) and isoflurane (**2**) was studied in soda lime,[6] activated carbons,[7] and zeolites.[8] Differential adsorption of enflurane enantiomers was used to separate them on a cyclodextrin-based gas chromatography column.[9] Sevoflurane (**3**) is adsorbed to the tune of approx. 150 wt% within the pores of a crystalline metal–organic framework (MOF).[10] Halothane (**5**) has been adsorbed on activated charcoal to the tune of 37%,[11] as well as on soda lime and even glass syringes.[12] Zeolites have also been used to adsorb desflurane.[13] Finally, commercially used anesthesia devices, such as AnaConDa® (anesthetic conserving device) reflection filter,[14,15] are also based on adsorption of anesthetics in porous materials. Apart from practical interest, study of anesthetics' adsorption is also fundamentally relevant as a model for their binding to membranes.[16]

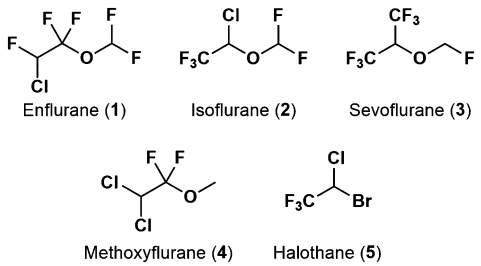

Fig. 1 Chemical structures of the five fluorinated anesthetics studied in this work.

Here, we report that porous molecular crystals of compound **6** (Fig. 2)[17] can bind fluorinated anesthetics **1**–**5** to the tune of up to 73.4(±0.2) percent by weight. Porous molecular crystals

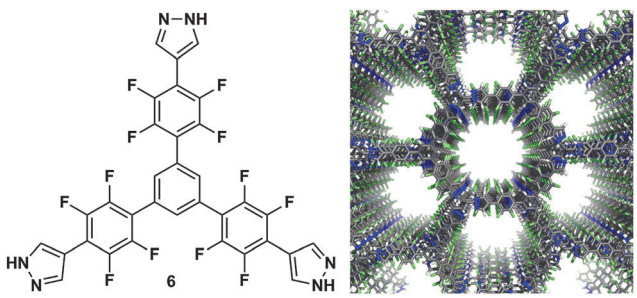

Fig. 2 Compound **6** (left) self-assembles into a porous structure with infinite channels protruding through a three-dimensional crystal (right). Approximate diameter of these channels is 1.6 nm.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5cc04885k

are generally rare,[18,19] and have not been previously explored as adsorbents in medicine—albeit they have been utilized as adsorbents and sensors in a more general sense.[20] They could offer some important advantages over other adsorbents (*e.g.* zeolites or activated carbons): they are lightweight, do not contain potentially toxic metals, can be easily recycled, and their pore sizes can be engineered. However, many of the recently reported porous molecular structures are also hydrolytically sensitive, making them unsuitable for use in hospitals and other environments where contact with moisture is more than likely. In contrast, compound **6** is both porous (with a surface area of 1159 $m^2 g^{-1}$) and very robust. It is stable up to 250 °C and is unaffected by exposure to moisture, dilute acids and bases. Furthermore, our recent work has shown that adsorption of analytes within the pores of **6** results in measurable changes in its UV/Vis absorption properties, suggesting possible uses as a sensor.[21]

Trispyrazole compound **6** was previously shown to act as a competent adsorbent for other fluorinated species, including fluorocarbons and chlorofluorocarbons (CFCs), as well as for hydrocarbons, nitrogen, oxygen, and carbon dioxide. Quantification of adsorption was performed using thermogravimetric analysis (TGA) setup previously reported by us[17] and others.[22] Briefly, crystals of compound **6** were placed into the thermogravimetric balance and first heated to 120 °C (temperature program depicted in Fig. 3). They were kept at that temperature for 1 h, with the intention of removing residual solvent and/or volatile guests from the pores of **6**. The heating was then discontinued and the material was allowed to cool. After the balance reached 25 °C (approx. 1 h), the flow of carrier gas was switched from pure nitrogen to nitrogen that was allowed to pass over a bubbler reservoir containing the liquid anesthetic of interest. Using this methodology, we determined uptake capacities for five fluorinated anesthetics (Table 1).

All five of the examined fluorinated anesthetics were adsorbed within the pores of **6** (Fig. 4 and Table 1). In the first attempt, the adsorbed weight of anesthetics varied from the 56.7% for methoxyflurane (relative to the weight of **6**) to 73.4% for halothane. In the second attempt at adsorption on the same material, differences of ±0.3% or less were observed. For all of the examined samples, molar ratios suggested that between two and three molecules of an anesthetic are being captured per molecule of **6**.

Except in the case of methoxyflurane, uptake of all studied anesthetics appears quite fast. Once the flow of carrier gas is switched from pure nitrogen (black curves in Fig. 4) to anesthetic-enriched nitrogen (red curves in Fig. 4), adsorbed amount within the porous crystals of **6** increases from <1% to 90% of saturation values in: 130 s for enflurane, 72 s for isoflurane, 75 s for sevoflurane, and 130 s for halothane. With methoxyflurane, more than 7 minutes (461 s) were needed to reach 90% saturation.

Full desorption of the examined anesthetics was achieved either if mild vacuum was applied to the adsorbent's crystals, or if they were heated at atmospheric pressure. Previous work on the absorption of other guests within the pores of **6** has shown that adsorption/desorption cycles can be repeated 20 times

Table 1 Adsorption parameters for binding of **1–5** within the pores of **6**

Anesthetic	M_w [g mol^{-1}]	Boiling point [°C]	Adsorption in **6** Weight[a] [%]	In moles, per mole of **6**[b]	Desorption temperature [°C]
1	184.5	56.5	59.3 (59.0)	2.31	57
2	184.5	48.5	59.7 (59.8)	2.33	60
3	200.1	58.6	59.6 (59.4)	2.14	63
4	165.0	104.8	56.7 (56.4)	2.47	83
5	197.4	50.2	73.4 (73.6)	2.67	55

[a] Values in parenthesis indicate weight adsorption capacities observed in the second attempt. [b] Molar values were calculated using weight adsorption data from the first attempt.

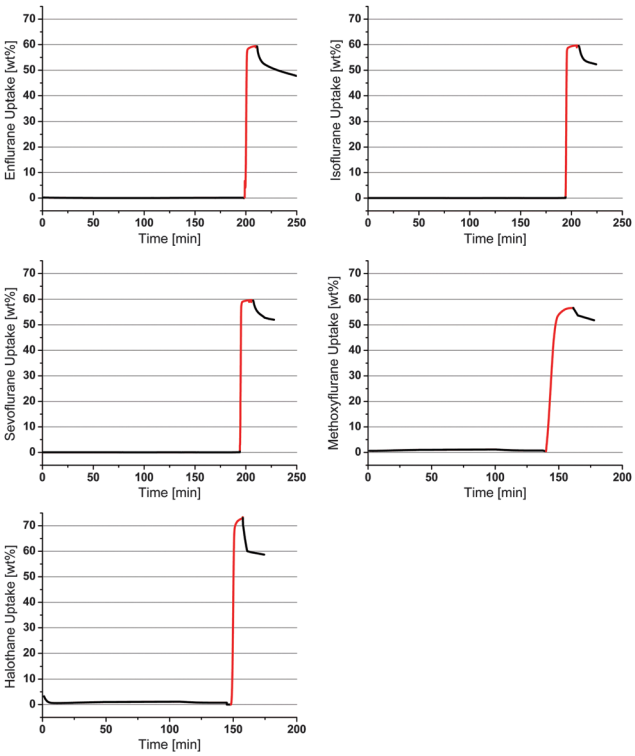

Fig. 4 Thermogravimetric analysis (TGA) traces showing adsorption of enflurane (top left), isoflurane (top right), sevoflurane (center left), methoxyflurane (center right), and halothane (bottom left) within the pores of **6**. Black traces indicate flow of pure nitrogen carrier gas over the crystals of compound **6**, while red traces refer to the flow of nitrogen enriched with the anesthetic vapor of interest.

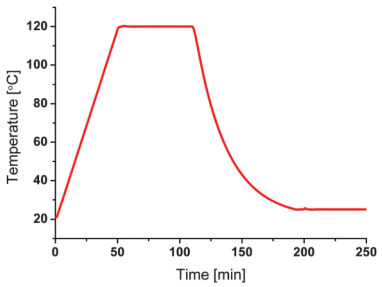

Fig. 3 Temperature program used during thermogravimetric analysis (TGA)-based measurements of adsorption of **1–5** within the pores of **6**.

without any loss of capacity.[17] Interestingly, with the exception of methoxyflurane, full release of all other fluorinated anesthetics from the pores of **6** required heating the crystals above the boiling point of the anesthetic in question—possibly suggesting high affinity of this framework for other fluorinated species.

Our future work will explore four avenues: (a) study of high-pressure adsorption of fluorinated anesthetics within the pores of **6**; (b) ''breakthrough'' experiments in which a mixture of gases is passed through the crystalline material and selectivity of binding is studied; (c) crystallization of adducts of **6** with fluorinated anesthetics and structural studies of specific interactions between the framework and the absorbed anesthetics, and (d) preparation of structural analogs of compound **6** which would have larger internal pores and presumably higher capacities for adsorption of **1–5**. Results of these studies will be reported in due course.

We acknowledge the financial support from the University of Houston (to O. Š. M.), the National Science Foundation (award DMR-1507664 to O. Š. M.), and the Welch Foundation (awards E-0024 to A. J. J. and E-1768 to O. Š. M.). O. Š. M. is a Cottrell Scholar of the Research Corporation for Science Advancement. We gratefully acknowledge Prof. Jorge Tiburcio Báez (CINVESTAV, Mexico) for insightful discussion. Parts of this manuscript were written at New York University Abu Dhabi (NYUAD), where O. Š. M. was on a sabbatical stay.

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