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## COMMUNICATION

# Potent Affinity Material for Tracing Acetone and related Analytes based on Molecular Recognition by Halogen Bonds

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*Dedicated to Julius Rebek, Jr. on the occasion of his 70<sup>th</sup> birthday*

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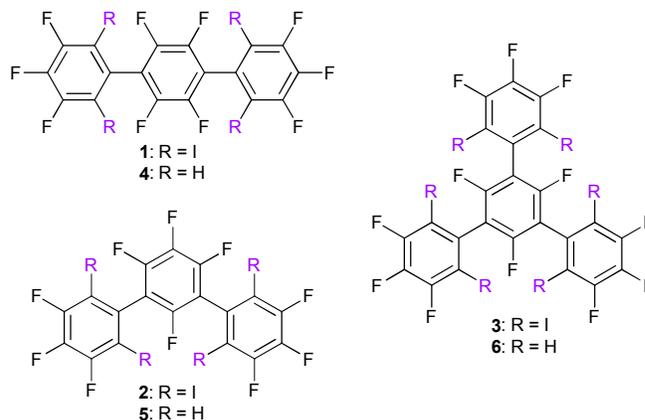
**Affinity materials based on halogen bonds turned out to be a powerful tool for the molecular recognition of acetone or related carbonyl compounds in the presence of ubiquitous protic molecules. The superior selectivity and sensitivity were found by the gravimetric detection of volatile organic compounds by quartz crystal microbalances.**

Halogen bonds (XBs)<sup>1</sup> - non-covalent interactions based on electrophilic halogen substituents - have attracted increased interest within the past two decades.<sup>2</sup> Compared to the related hydrogen bonds, halogen bonds feature an even higher directionality: the R-X...LB angle (R = backbone group, X = halogen substituent, LB = Lewis base) is always close to 180° in reasonably strong interactions.<sup>1,3</sup> Based on this highly predictable bond geometry, halogen bonding has by now been established as a reliable interaction in crystal engineering.<sup>4</sup> As an example, iodinated polyfluorobenzenes like 1,4-diiodo-tetra-fluorobenzene (1,4-DITFB) or 1,3-diiodotetra-fluoro-benzene (1,3-DITFB) form co-crystals with 4,4'-bipyridine as Lewis base, which feature either a linear (1,4-DITFB)<sup>5</sup> or a herringbone-pattern (1,3-DITFB)<sup>6</sup> structural motif in the solid state structure. As halogen bond acceptors, mostly anions and nitrogen-based Lewis bases like amines were employed.<sup>1,4,7</sup> In addition to these applications of halogen bonds in solid-state supramolecular chemistry<sup>8</sup> and material chemistry,<sup>9</sup> halogen bonding is starting to find use in solution-phase processes as well.<sup>10</sup> For instance, there is a growing awareness concerning the occurrence of halogen bonds in biological systems (and drug design).<sup>2e,11</sup> Also, halogen bond donors (halogen-based Lewis acids) based on neutral (polyfluorinated) or cationic backbones have found first applications in anion recognition,<sup>12</sup> organic synthesis<sup>13</sup> and organocatalysis.<sup>14</sup> Finally, pioneering work by Legon *et al.* using rotational spectroscopy has also established the presence of halogen bonding in the gas phase.<sup>1c,15</sup>

Oxygenated Lewis bases, *i.e.* acetone and related aldehydes, are of significant interest for medical and veterinary aspects since they indicate metabolic disorders or the progress of a disease.<sup>16</sup> The direct analysis of breath can indicate the potential presence of lung cancer by tracing such molecular markers as acetone.<sup>17</sup> For all gravimetric analysis methods, the corresponding affinity material is important

for the generation of an exploitable signal for acetone in the presence of ubiquitous water and ethanol.

This work demonstrates the unique power of XBs for tracing volatile organic compounds (VOCs) in the vapor phase.



**Figure 1.** Halogen bond donors **1-3** and model compounds **4-6**.<sup>14b</sup>

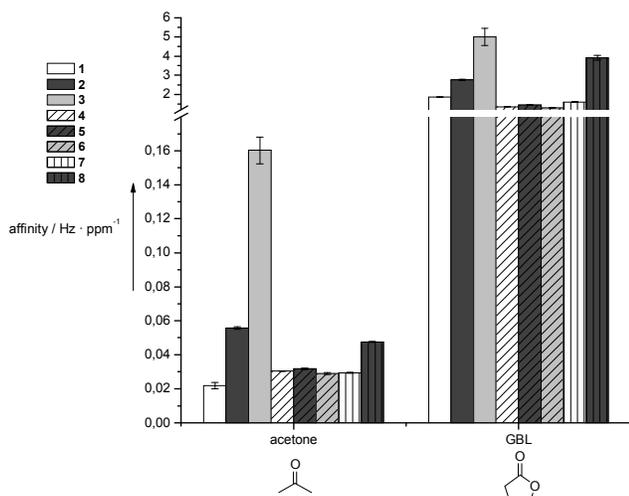
Our gravimetric technology platform is based on 195 MHz high fundamental frequency quartz crystal microbalances (HFF-QCMs). The advantage of HFF-QCMs are a highly improved lower detection limit and a faster response time.<sup>18</sup> Those were modified with the XB donors **1-3**<sup>14b</sup> and their non-iodinated analogues **4-6** via a well-known electrospray protocol.<sup>19</sup> This procedure allows the deposition of a well-defined amount of material in a subnanogram range onto the electrode of the QCM. Recently, we have shown that the properties of the deposited material is not affected by this method, *i.e.* microporosity of organic cages has been preserved in the course of the deposition.<sup>20</sup> More details about the coating process, experimental setup and determination of the affinities are given in the Supporting Information.<sup>†</sup>

For the detection of VOCs the affinity material on the QCM has to fulfil certain requirements. Favourably, there is some sort of cavity cooperating with the access of molecular interaction like hydrogen bonds, C-H- $\pi$ -interaction, or  $\pi$ -stacking. For the detection of  $\gamma$ -butyrolactone (GBL) for instance we have shown that the design of functional groups highly affects the detection signal of the drug.<sup>21</sup>

The other major feature which distinguishes different analytes is the cavity size, or in microporous compounds, the cage size. Predominantly, it is a synergy of both characteristics of the affinity material to develop a specific affinity towards the desired analyte. Compared to most inorganic sensor materials the affinity material covered QCMs operate at room temperature and are superior in their selectivity towards other ubiquitous vapours.<sup>22</sup>

The material chosen to be deposited on the electrode determines both, the selectivity and sensitivity of the detection. Based on the interaction of affinity material and airborne analyte, the system allows a detection on a pg scale within seconds. Usually, this signal is interfered by an unspecific signal of physisorption. Our approach is to use the special nature of the halogen bond to minimize the undesired physisorption. Compared to the typically hydrophilic hydrogen bonding, halogen bonding - especially based on polyfluorinated XB donors - may be considered rather hydrophobic.<sup>23</sup> This feature may help to reduce the interaction with ubiquitous hydrophilic analytes like water and alcohols.<sup>24</sup> Orientating DFT calculations with an intrinsic solvation model indicated that water may have little influence on XB adducts.<sup>25</sup> In combination with a sandwich-coated QCM, wherein the electrode is modified with 1H,1H,2H,2H-perfluorooctylphosphonic acid (FP-8) and then with the affinity materials 1-3, we expect further advances in discrimination of specific analyte signals. The pre-coating with FP-8 may interact with the affinity material due to fluororous interactions and could be useful for a slight preorganization of the deposited material.<sup>26</sup>

The resulting affinities of our measurements are depicted below (see Figure 2). The correlation between the number of electrophilic halogen substituents and the affinity is clearly evident.



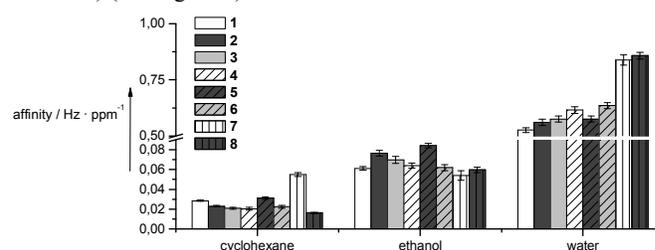
**Figure 2.** Affinities of 1-6 towards halogen bond acceptors acetone and GBL. Materials 7 and 8 are reference compounds from literature studies.<sup>28</sup>

The hatched bars in Figure 2 display the non-iodinated terphenylene derivatives, which are not able to take part in halogen bonding. These show a consistently similar behaviour in affinity which does not indicate a directed favourable type of bonding but is rather a result of unspecific physisorption. The fully coloured bars show the XB donor derivatives. Both terphenyl derivatives 1 and 2 offer the possibility of bidentate coordination, while variant 3 features three electrophilic axes on each side of the molecule. Whereas para-substituted halogen bond donor 1 does not show any improvement compared to the parent compound 4, stronger affinity is observed for the *meta*-substituted halogen bond donor 2, and especially the tridentate variant 3.

This is a first indication that multidentate halogen bond may play an important role in the observed binding. It has been demonstrated before that carbonyl compound may bind in a bidentate fashion to halogen bond donors.<sup>27</sup> The absolute value for the affinity towards acetone is with 0.16 Hz/ppm significantly higher than any other material previously tested (see Supporting Information). The high affinity results from a very good adsorption of acetone vapour at low concentrations. This usually indicates a high selectivity.<sup>28a</sup> To emphasize the potential of XB donor affinity materials, the affinities are compared with other materials already known for their high affinity towards different analyte systems ( $\gamma$ -cyclodextrin (7) and a microporous cage (8)).<sup>20,23</sup> The cage 8 exhibits decent affinities towards acetone and GBL but lacks in the discrimination of water.  $\gamma$ -Cyclodextrin also shows a good affinity towards acetone but as well for water and cyclohexane (see Figure 3). For detailed information about affinity values, structure of 7 and 8 as well as primary experimental data see ESI.<sup>†</sup>

The possibilities of interaction of the affinity material with the supposedly weak halogen bond acceptor acetone are clearly visible. These results implicate further investigations regarding other analytes of interest. The trend is being confirmed by the measurement of the affinity towards GBL. The difference in affinity is not that distinctive as with acetone. While the elucidation of this observation will require further experimental and theoretical studies, it is conceivable that the different affinity towards acetone or GBL is either due to unselective binding of the second oxygen atom of GBL or to steric effects. We note that the relative trend in binding strength (*i.e.*, the tridentate derivative 3 being superior to the bidentate analogues 2 and 1) is in line with the organocatalytic activity of halogen bond donors 1, 2, and 3 in a benchmark reaction involving the binding of chloride.<sup>14b</sup>

To see whether the hydrophobic nature of the halogen bond donors would lead to a selective interaction with certain XB acceptors, we also tested some highly hydrophilic Lewis bases like ethanol and water (as well as cyclohexane as a non-Lewis basic reference substrate) (see Figure 3).

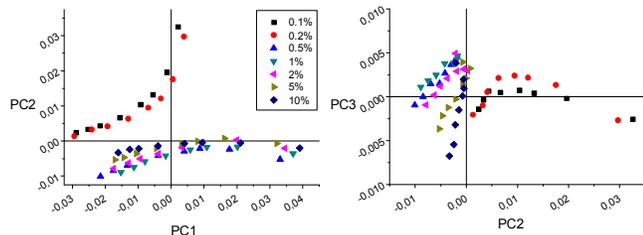


**Figure 3.** Unspecific affinities of ubiquitous airborne molecules.

It is evident that the signals are unspecific due to physisorption or undirected chemisorption. This supports the assumption that the higher hydrophobicity of 1-3 compared to the hydrogen-bond based affinity materials 7 and 8 also markedly influences their binding behaviour, reducing, *e.g.* the affinity towards water. Most remarkably, halogen bond donor 3 shows high affinity for acetone but no specific binding to water. Recently, a study with a host system exhibiting a similar backbone reveals the same effect. In contrast to other uptake of organic vapours, H<sub>2</sub>O was not incorporated. This was attributed to the hydrophobicity of such systems.<sup>24</sup>

In combination with the hydrophobicity of the halogen bond donors (see above), the affinity to the ubiquitous water should also be further reduced, which is favorable for a sensor application. In order to obtain exploitable signals for acetone in the presence of high water vapor pressure, a sensor array of five quartzes was composed. As affinity materials 2, 3, 6, as well as two molecular hosts used in

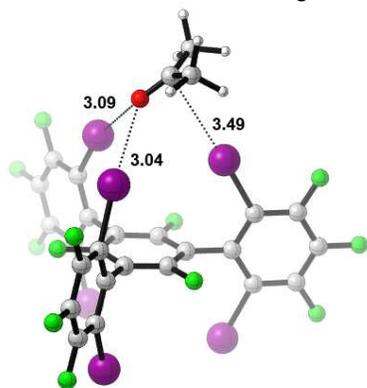
our group were chosen (for details, see SI). Identification of acetone was achieved by principal component analysis (PCA), which transforms a number of correlated variables into a smaller number of uncorrelated variables called principal components. Figure 4 displays the coefficients of the three strongest principal components. Both, different concentrations of acetone in water and mixing of corresponding gas flows were investigated and provided consistent results. The PCA results clearly indicate an identification of acetone (see Figure 4).



**Figure 4.** PCA of an acetone sensor array based on affinity materials **2**, **3** and **6**. The mentioned concentrations are vol% acetone in aqueous solution (from up to down: ■ :0.1vol%, ● :0.2vol%, ▲ :0.5vol%, ▼ :1vol%, ◀ :2vol%, ▶ :5vol%, ◆ :10vol%).

All samples which contain acetone down to a concentration in between 0.2 and 0.5 vol% in aqueous solution can be discriminated in an unequivocal manner. The sharp transition is most likely due to a rapid depletion of acetone at low concentrations in the analyte preparation so that the signal is almost equivalent to a sample lacking acetone. Using an array without the halogen bond donors **2** and **3**, as well as **6**, which works as a non-specific reference material in the setup, a separation of the data in PCA is not achievable.<sup>26,29</sup>

In order to get a first impression on the mode of binding of tridentate halogen-bond donor **3** to acetone,<sup>30</sup> DFT calculations were performed with the M06-2X density functional,<sup>31</sup> the triple-zeta def2-TZVPP basis set,<sup>32</sup> and dispersion corrections by Grimme.<sup>33</sup> The minimum structure, shown in Figure 5, features two halogen bonds between iodine substituents of **3** and the carbonyl oxygen of acetone with I-O distances of 3.09 Å and 3.04 Å, far below the sum of the van-der-Waals radii (3.50 Å; C-I-O angles: 163° and 165°).<sup>34</sup> The acetone molecule is tilted towards the third iodine substituent of **3** in a way that seems to indicate a weak halogen bond between the carbonyl  $\pi$ -system and the halogen substituent.<sup>35</sup> The presence of halogen bonding in this case is supported by the I-C distance of 3.49 Å, which is somewhat shorter than the sum of the van-der-Waals radii (3.68 Å), and the almost linear C-I--C angle of 172°.<sup>36,37</sup>



**Figure 5.** Binding of acetone to halogen-bond donor **3** according to DFT calculations (M06-2X-D3 TZVPP with pseudopotential for iodine).

In conclusion, we have shown that halogen bonds represent a superb tool for designing not only supramolecular structures but also affinity materials for sensor applications. The observed preference for carbonyl based air borne analytes can be attributed to the interaction of the iodine substituents and are therefore product of the XB.<sup>35</sup> Moreover, a novel type of a tridentate molecular recognition pattern for carbonyl moieties could be identified by computational means which provides a fully consistent picture with the experimental findings. The mode of action by the halogen bonds is essential for discrimination of different analytes which are usually challenging for common affinity materials. To our best knowledge, this is the first example of halogen bond directed interaction in affinity materials for continuous gasphase detection of VOCs. These findings might be also of interest for other gravimetric sensing techniques.<sup>38</sup> A combination of XB with other principles for creating selectivity, e.g. cage compounds should provide access to a complete generation of affinity materials in near future.

## Notes and references

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†Electronic Supplementary Information (ESI) available: [experimental data, calculations, PCA details and setup]. See DOI: 10.1039/c000000x/

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