A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

GDCh

www.angewandte.org

Accepted Article

Title: Molecular bases for anesthetic agents: Halothane as halogen and hydrogen bond donor

Authors: Giuseppe Resnati, Susanta K. Nayak, Giancarlo Terraneo, Quirino Piacevoli, Federica Bertolotti, Patrick Scilabra, John T. Brown, and Sergiy Rosokha

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201907829
Angew. Chem. 10.1002/ange.201907829

Link to VoR: http://dx.doi.org/10.1002/anie.201907829
http://dx.doi.org/10.1002/ange.201907829

WILEY-VCH

10.1002/anie.201907829

WILEY-VCH

Molecular bases for anesthetic agents: Halothane as halogen and hydrogen bond donor

Susanta K. Nayak,[a,b] Giancarlo Terraneo,[a] Quirino Piacevoli,[c] Federica Bertolotti,[a] Patrick Scilabra,[a] John T. Brown,[d] Sergiy Rosokha,*[d] Giuseppe Resnati*[a]

Dedicated to Dr. Tullio Pilati on the occasion of his 73th birthday

Abstract: *While instrumental for optimizing their pharmacological activity, a molecular understanding of the interactions preferentially involving volatile anesthetics is quite poor. This paper confirms the ability of halothane to work as hydrogen bond (HB) donor and gives the first experimental proof that halothane also works as a halogen bond (HaB) donor in solid and in solution. A halothane/hexamethylphosphortriamide cocrystal is described and its single crystal X-ray structure shows short HaBs between bromine, or chlorine, and phosphoryl oxygen. New UV-Vis absorption bands appear on addition of diazabicyclooctane and tetra-n-butylammonium iodide to halothane solutions indicating that also nitrogen atoms and anions may mediate HaB driven binding processes involving halothane. The ability of halothane to work as bidentate/tridentate tecton by acting as HaB and HB donor, gives an atomic rational for the eudismic ratio shown by this agent.*

Inhalation anesthetics are a major subgroup of the compounds clinically used to induce general anesthesia, a crucial and instrumental conditions in many medical treatments. Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) was one of the first volatile anesthetics introduced into common practice and it is included on the WHO's List of Essential Medicines.[1] General anesthesia is associated with a reversible change of lipid membrane properties, this change being effected by the structural perturbation determined by the weak anesthetic-membranes interactions. It is well established that the potency of volatile anesthetics is correlated with their lipid solubility,[2] and in the last decades converging evidence emerged that inhalation anesthetics bind to proteins, especially membrane proteins. Ion channels (e.g., $GABA_A$ receptors, K^+ channels, and *N*-methyl-D-aspartate receptors) may be primary targets of these agents.[3] Consistent with the time honored correlation between anesthetic potency and solubility in lipid environment,[4] thermodynamic data indicates that lipophilic regions of proteins may serve as targets for volatile anesthetics. But potential target proteins of halothane have multiple binding sites for this agent in the pharmacologically relevant range of concentrations, e.g., at least seven binding sites and far more than that in human serum albumin and the nicotinic acetylcholine receptor, respectively.[5] The specific forces driving the binding of volatile anesthetics to biomolecular targets thus remain largely unclear, and the same holds for the structural aspects of the binding.

Molecular dynamic simulations of halothane,[6] its low boiling and melting points (50 and -118 °C, respectively), and the pattern of short contacts observed in its homocrystal[7] indicate that the compound has a poor tendency to form intermolecular interactions. In order to map the interactions landscape of halothane, we studied the formation of adducts with small and simple halogen bond (HaB) and hydrogen bond (HB) acceptors which can be regarded as models for binding moieties of the agent with biomolecules. Specifically, dimethylsulfoxide (DMSO) and hexamethylphosphortriamide (HMPA) were employed to study interactions in the liquid and in the solids and diazabicyclooctane (DABCO) and tetra-*n*-butylammonium iodide (TBAI) to study interactions in solutions. The reported results show that halothane can concomitantly function as HB and HaB donor both in solid and in solution. The ability of halothane to work as a polydentate tecton affords a molecular rational for its eudismic ratio[8] and the different catabolism of its enantiomers.[9] The obtained crystallographic evidence of HaB and HB between halothane and HMPA oxygen suggests that *both interactions* may mediate an active role of the P=O group of phospholipids, major components of cell membranes, in promoting the well-established high membrane affinity of halothane.

IR spectra indicate halothane acts as HB and/or HaB donor with DMSO and HMPA in the liquid. The $\nu_{(X=O)}$ stretchings (X=S and P) of sulfinyl and phosphoryl groups of the two compounds are typically red shifted on oxygen interaction with electron density acceptors (e.g. on HB or HaB formation and metal coordination).[10] Maximum absorbances are at 1102 and 1210 cm^{-1} in pure gases of the two compounds (where HBs, if any, are minimized), at 1042 and 1202 cm^{-1} in their pure liquids (where weak HBs are present), and at 1026 and 1175 cm^{-1} in respective 1:1 mixtures with halothane.

Mixtures of halothane and DMSO or HMPA remain liquid at room temperature in examined molar ratios (from 0.5:2.0 to 2.0:0.5). Differential scanning calorimetry (DSC) analyses revealed sharp peaks different from crystallization/melting of starting compounds only when HMPA was used, consistent with its greater ability to work as a HaB and HB acceptor.[10] When a halothane/HMPA 1:1 mixture was cooled down to -160 °C, then

[a] Dr. S. K. Nayak, Prof. Dr. G. Terraneo, Dr. F. Bertolotti, P. Scilabra, Prof. Dr. G. Resnati
Department of Chemistry, Materials, and Chemical Engineering "Giulio Natta", Politecnico di Milano,
via L. Mancinelli 7, 20131 Milano (Italy)
E-mail: giuseppe.resnati@polimi.it

[b] Dr. S. K. Nayak
Department of Chemistry, Visvesvaraya National Institute of Technology (VNIT), Nagpur, Maharashtra-440010 (India)

[c] Prof. Dr. Q. Piacevoli
San Filippo Neri Hospital, Department of Anesthesia and Intensive Care, Rome (Italy)

[d] J. T. Brown, Prof. Dr. S. V. Rosokha
Chemistry Department, Ball State University, Muncie, IN 47306 (USA)
E-mail: svrosokha@bsu.edu)

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

slowly heated, an exothermic peak was observed at -67 °C (crystallization of the initially formed glass) followed by an endothermic peak at -23 °C (melting of the cocrystal). No signals of starting components were present, suggesting that a 1:1 halothane/HMPA mixture forms a well-defined species.

A single crystal was grown from a 1:1 halothane/HMPA mixture by using the *in situ* cryocrystallization technique (ESI). X-ray analyses (Table S1) of this single crystal revealed that a cyclic tetramer containing two halothane and two HMPA units bound via HaBs and HBs is a well-defined repeating motif in the packing (Fig. 1). Halothane adopts the staggered conformation, which is the preferred arrangement in the gas phase[11] and in the pure crystal.[7] Molecules present some positional disorder as bromine and chlorine atoms reside in the same atomic sites with occupancy factors of 84:16. A similar disorder occurs also in pure halothane with occupancy factors of 50:50. This partial ordering is consistent with the presence, in the cocrystal, of specific interaction(s) pinning the heavier halogens preferentially in a given position. Each halothane molecule is bonded to a nearby HMPA molecule through a HB where the C–H···O separation is 213.8 pm and the ∠C–H···O angles is 172.6°. These values correspond to a quite short and directional interaction (the normalized contact[12] Nc is 0.80). This is consistent with the non-minor Brønsted[13] and Lewis[14] acidity of halothane hydrogen. Halothane has been reported to form similar HBs with a variety of electron density donors, including alkenes, alkynes, and aromatics,[15] water, alcohols, and ethers,[16] ketones, esters, and other carbonyl derivatives,[17] ammonia, amines as well as sulfur and phosphorus sites.[18] Experimental complexation enthalpies of halothane with ammonia[18c] and acetone[17c] are ~20 and ~9 kJ mol-1, respectively. These values are quite close to calculated enthalpies for respective C–H···N/O interactions, suggesting that HB gives a major contribution to the interactional landscape of halothane. This role is also suggested by our calculations of HB energies when HMPA, DABCO, or I¯is the nucleophile (ESI, Table S2).

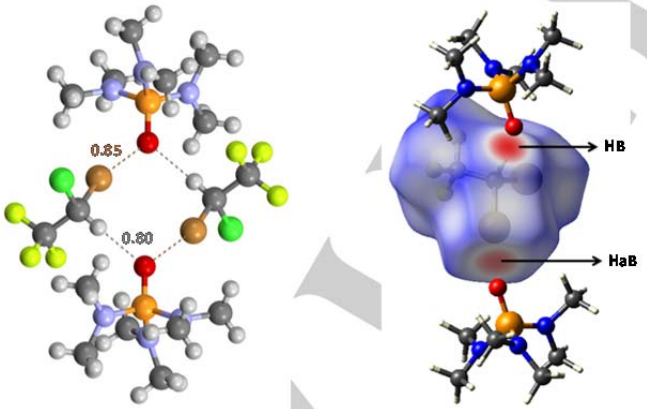


Figure 1. Left: Ball and stick representation of the tetrameric motif formed by halothane and HMPA in the solid under control of HaBs and HBs (ocher and grey dashed lines). While the halogen bonded site is occupied by both bromine and chlorine (the occupancy factor is 84:16) bromine only is represented at the site. NCs values are also reported. Right: Hirshfeld surface of halothane picturing HaBs and HBs with HMPA: Contacts below/above van der Waals radii are in red/blue colors.

Hydrogen bonded dimers pair into cyclic tetramers via two HaBs. At the HaB acceptor and donor sites there are the oxygen of HMPA and bromine, or chlorine, atoms of halothane (with occupancy factors of 84 and 16, respectively). These HaBs account for the decreased positional disorder of halothane in the cocrystal with respect to the homo-crystal. Bromine being a better HaB donor atom than chlorine, the halogen bonded site is preferentially occupied by the former halogen. The ∠C–Cl/Br···O angle is 165.7° and the Cl/Br···O distance is 291.2 pm. This separation is well below the sum of van der Waals radii of involved atoms, but it is averaged over the Br···O and Cl···O separations that are different. We were wondering if both chlorine and bromine were actually at a distance from oxygen shorter than the sum of van der Waals radii. Bromine and chlorine atoms at the halogen bonded site were too close to each other for their respective positions to be refined separately. We determined the geometric features in a cocrystal with no positional disorder by assuming, as restrains, that C–Cl and C–Br bond lengths are the mean values of structurally similar compounds in the Cambridge Structural Database (CSD) (ESI). Resulting Nc values of Br···O and Cl···O interactions are 0.86 and 0.92. These values are consistent with the relative HaB donor ability of the two elements and Ncs from calculations (M06-2X/DEF-2TZVPP) in acetonitrile solution (0.86 and 0.91; ESI, Table S2).

Literature reports have described the use of a variety of different techniques (e.g., NMR, IR and Raman, vapour-liquid equilibria, calculations) to study halothane adducts in solutions, cryosolutions, and in the gas phases.[19] These literature data demonstrated the presence of HB adducts in all cases studied via experimental techniques. In contrast, the presence of HaB adducts had been identified *in silico* only. The structure of halothane/HMPA cocrystal reported here is the first experimental confirmation that the HaB donor ability of bromine and chlorine can actually affect and drive aggregation phenomena involving halothane in the condensed phase.

To identify HaBs formed by halothane in solutions, we turned to NMR and UV-Vis studies of systems containing iodide anions and DABCO, two well-known HaB acceptors.[20] In general, formations of HB and HaB complexes result in distinct NMR and UV-Vis spectral changes.[21] For example, formation of HaB or HB between trihalomethanes and anions leads, in NMR spectra, to the opposite shift of proton signals and, in UV-Vis spectra, to the appearance of new absorption bands or shift of the absorption bands of reactants, respectively.[21,22]

Addition of DABCO or iodide (from TBAI) to a solution of halothane in acetonitrile resulted in a shifts of NMR signal of its proton to higher ppm values. The magnitude of this shift increases with the rise of concentration of nucleophile, and its direction indicates that halothane's proton is deshielded due to involvement in HB (ESI, Figure S13).

The UV-Vis measurements of the similar solutions containing halothane and iodide or DABCO showed increased absorption in the 250 – 280 nm range in comparison to the spectra of individual reactants. Subtraction of the absorptions of components revealed that this increase of absorption is related to appearance of new bands (Figure 2; ESI, Figures S14 and S15). Their intensities

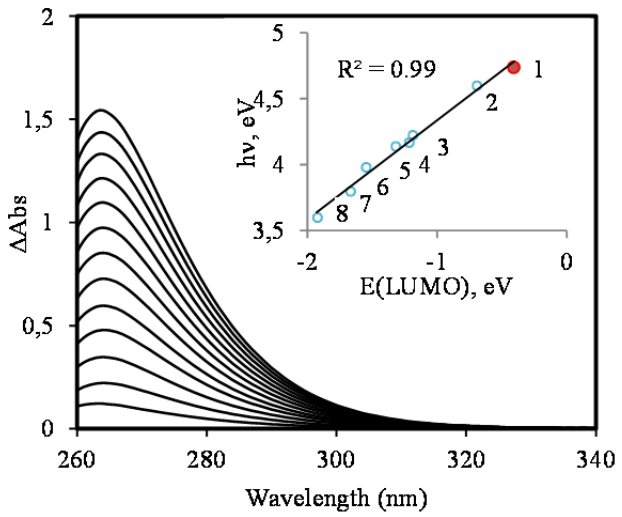


Figure 2. Differential spectra (obtained by subtraction of absorption of the components from spectra of the mixtures) of the solutions with constant concentrations of iodide (2 mM) and variable concentrations of halothane (from 0.08 to 1.5M, from the bottom to the top). Insert: Mulliken correlation between the energies of the absorption bands of HaB complexes of iodide with R-Br electrophiles and energies of their LUMOs. R-Br = Halothane (1), $C_3Br_2F_6$ (2), $CHBr_3$ (3), $CBrCl_3$ (4), CBr_3COOH (5) CBr_3F (6), CBr_3CN (7) and CBr_4 (8)).[23]

increase with the increase of concentration of iodide or DABCO in the solution with constant concentration of halothane and vice versa.

The dependencies of the intensities of the new bands on the fractions of components in the solutions with the constant sum of concentrations of reactants (Jobs plots) showed maxima at 1:1 molar ratios of halothane to nucleophile (ESI, Figure S16). This indicates 1:1 stoichiometry of the complexes formed in these solutions.

In accordance with the earlier studies, the appearance of such absorption bands is symptomatic of formation of HaB complexes. This suggestion is supported by the UV-Vis changes resulting from the addition of the other HaB or HB donors to the solutions containing the same (DABCO or iodide) nucleophiles. In particular, addition of 1,2-dibromohexafluoropropane (which is exclusively an HaB donor with characteristics similar to that of halothane) to the solutions of DABCO or iodide resulted in appearance of a new absorption band in the UV-Vis spectra (ESI, Figure S17). The maximum of this absorption band was close to that observed in the solutions with halothane. Most importantly, the energy of the absorption bands of the complex of halothane with iodide followed the same Mulliken correlations (insert in Figure 2) as the HaB complexes of these nucleophiles with the other bromo-substituted nucleophiles, such as CBr_4, CBr_3F, etc. On the other hand, analogous addition of the solely HB donor, methanol, to the solutions of DABCO or iodide in acetonitrile resulted in hypsochromic (blue) shift of the absorption bands of these nucleophiles. Subtraction of the absorption of components resulted (in contrast to the similar solutions with halothane) in a dip in the differential absorbance in the 240 – 270 nm range (ESI, Figure S18).

Thus, while the NMR measurements indicated the presence of the HB complexes in the acetonitrile solutions of halothane and DABCO or iodide, the UV-Vis measurements pointed out the formation of HaB associates in the same systems. Simultaneous fitting of the NMR and UV-Vis spectral data measured in the solutions with constant concentration of halothane and variable concentrations of iodide led to formation constants of HaB and HB complexes of about 0.2 M^{-1} and 0.5 M^{-1}, respectively (ESI, Figure S13).[22] Similar treatment of the data obtained in solutions of halothane with DABCO led to formation constants of about 0.2 and 0.4 M^{-1} for their Hab and HB complexes, respectively. Such observations are consistent with the results of the quantum-mechanical computations which produced both HaB and HB complexes between halothane and these nucleophiles with a greater strengths for the latter interaction (ESI, Table S2).

In conclusion, our results demonstrate that HaB complements and/or competes with HB in the interactional landscape of halothane in the solid and in solutions. The halothane/HMPA cocrystal shows that the HaB donor ability of bromine and chlorine affects and drives aggregation phenomena involving halothane. The appearance of new UV-Vis absorption bands on addition of DABCO and TBAI to halothane solutions indicates that not only oxygen, but also nitrogen and anions may mediate halothane recognition and binding processes via HaB. This interaction can thus play a role in the binding of this agent to specific moieties in biomolecules, e.g., to basic nitrogen sites in proteins or to P=O groups in phospholipids (a major component of cell membranes). X-ray structures of halothane bound to apoferritin[24] and human serum albumin[25] show the possible presence of HaB with Leu-24 oxygen and Cys-438 sulfur. The small Nc values obtained for the Br···O and Cl···O interactions in the halothane/HMPA cocrystal suggest that the HaBs observed in the protein adducts mentioned above are not induced by the binding, but play an active role in inducing, or driving, the binding. This is consistent with the emerging evidences on the general relevance of specific interactions involving halogen atoms in securing ligand-protein binding.[26] Finally, the proven ability of hydrogen, bromine and chlorine atoms of halothane to act as electrophilic sites, namely the possibility for the agent to form two or three interactions, affords an atomic rational for the different pharmacological activity[8] and catabolism of its enantiomers.[9]

Acknowledgements

J.T.B. and S.V.R thank the National Science Foundation (grant CHE-1607746) for financial support We thank Slade Kepler for assistance with the UV-Vis measurements.

Conflict of interest

The authors declare no conflict of interest.

Keywords: anesthetics • halothane • halogen bond • hydrogen bond • cryocrystallography

[1] https://www.who.int/medicines/publications/essential medicines/en/.

[2] T. Cui, V. Bondarenko, D. Ma, C. Canlas, N. R. Brandon, J. S. Johansson, Y. Xu and P. Tang, *Biophys. J.* **2008**, *94*, 4464–4472.

[3] (a) G. A. Manderson, J. S. Johansson, *Biochemistry* **2002**, *41*, 4080–4087; (b) A. H. Sawas, S. N. Pentyala, M. J. Rebecchi, *Biochemistry* **2004**, *43*, 12675–12685; (c) K. Solt, J. S. Johansson, D. E. Raines, *Biochemistry* **2006**, *45*, 1435–1441; (d) R. G. Eckenhoff, *J. Biol. Chem.* **1996**, *271*, 15521–15526; (e) G. Ghirlanda, S. A. Hilcove, R. Pidikiti, J. S. Johansson, J. D. Lear, W. F. DeGrado, R. G. Eckenhoffc, *FEBS Letters* **2004**, *578*, 140–144; (f) Sandorfy C. *Collect. Czech. Chem. Comm.* **2005**, *70*, 539–549.

[4] R. Liu, R. Pidikiti, C.-E. Ha, C. E. Petersen, N. V. Bhagavan, R. G. Eckenhoff, *J. Biol. Chem.* ***2002***, *277*, 36373–36379.

[5] R. Liu, J. Yang, C.-E. Ha, N. V. Bhagavan, R. G. Eckenhoff, *Biochem. J.*, **2005**, *388*, 39–45.

[6] D. Scharf, K. Laasonen, *Chem. Phys. Lett.* **1996**, *258*, 276–282.

[7] A. Olejniczak, A. Katrusiak, P. Metrangolo, G. Resnati, *J. Fluorine Chem.* **2009**, *130*, 248–253.

[8] (a) B. D. Harris, E. J. Moody, P. Skolnick, *Eur. J. Pharm.* **1998**, *341*, 349–352; (b) M. M. Sedensky, H. F. Cascorbi, J. Meinwald, P. Radford, P. G. Morgan, *PNAS* **1994**, *91*, 10054–10058.

[9] J. L. Martin, J. Meinwald, P. Radford, Z. Liu, M. L. M. Graf, L. R. Pohl, *Drug Metab. Rev.* **1995**, *27*, 179–189.

[10] S. K. Nayak, G. Terraneo, A. Forni, P. Metrangolo, G. Resnati, *CrystEngComm* **2012**, *14*, 4259–4261.

[11] B. Czarnik-Matusewicz, D. Michalska, C. Sandorfy, T. Zeegers-Huyskens, *Chem. Phys.* **2006**, *322*, 331–342.

[12] The ‘‘normalized contact’’ Nc for an interaction is the ratio Dij/(rvdWi + rvdWj), where Dij is the experimental distance between atoms i and j and rvdWi and rvdWj are the van der Waals radii for i and j (A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441−451). If the electron donor j is an anionic atom, rvdWj is substituted by rPj, the Pauling ionic radius of anion atom j (R. D. Shannon, *Acta Crystallogr., Sect. A* **1976**, *32*, 751−767). Nc is a useful indicator because it allows for a more rigorous comparison of distances between different interacting partners than when absolute values of separations are used.

[13] A. Streitwieser, D. Holtz, G. R. Ziegler, J. O. Stoffer, M. Lee Brokaw, F. Guibé, *J. Am. Chem. Soc.* **1976**, *98*, 5229−5234.

[14] (a) G. Trogdon, J. S. Murray, M. C. Concha, P. Politzer, *J Mol. Model.* **2007**, *13*, 313–318; (b) Z. P.-I. Shields1, P. G. Seybold, J. S. Murray, *J. Mol. Model.* **2018**, *24*, 19.

[15] (a) S. M. Melikova, K. S. Rutkowski, M. Rospenk, *J. Mol. Struct.* **2018**, *1160*, 434−439; (b) B. Michielsen, J. J. J. Dom, B. J. van der Veken, S. Hesse, Z. Xue, M. A. Suhm, W. A. Herrebout, *Phys. Chem. Chem. Phys.* **2010**, *12*, 14034–14044; (c) J. J. J. Dom, B. Michielsen, B. U. W. Maes, W. A. Herrebout, B. J. van der Veken, *Chem. Phys. Lett.* **2009**, *469*, 85–89.

[16] (a) B. Michielsen, W. A. Herrebout, B. J. van der Veken, *ChemPhysChem* **2007**, *8*, 1188–1198; (b) Z. Liu, Y. Xu, A. C. Saladino, T. Wymore, P. Tang, *J. Phys. Chem. A* **2004**, *108*, 781–786; (c) M. Tkadlecova, V. Dohnal, M. Costas, *Phys. Chem. Chem. Phys.* **1999**, *1*, 1479–1486; (d) V. Dohnal, K. Kratochvilova, M. Bureš, M. Costas, *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 1877–1886.

[17] (a) S. M. Melikova, K. S. Rutkowski, M. Rospenk, Optics Spectrosc. **2017**, *123*, 30–37; (b) W. Zierkiewicz, R. Wieczorek, P. Hobza, D. Michalska, *Phys. Chem. Chem. Phys.* **2011**, *13*, 5105–5113; (c) V. Dohnal, D. Fenclova, M. Bureg, M. Costas, *J. Chem. Soc. Faraday Trans.* **1993**, *89*, 1025–1033.

[18] (a) K. S. Rutkowski, S. M. Melikova, R. E. Asfin, B. Czarnik-Matusewicz, M. Rospenk, *J. Mol. Struct.* **2014**, *1072*, 32–37; (b) B. Michielsen, C. Verlackt, B. J. van der Veken, W. A. Herrebout, *J. Mol. Struct.* **2012**, *1023*, 90–95; (c) B. Michielsen, J. J. J. Dom, B. J. van der Veken, S. Hesse, M. A. Suhm, W. A. Herrebout, *Phys. Chem. Chem. Phys.* **2012**, *14*, 6469–6478.

[19] (a) L. Avram, A. Bar-Shir, *Org. Chem. Front.* **2019**, *6*, 1503–1512; (b) L. Avram, M. A. Irona. A. Bar-Shir, *Chem. Sci.* **2016**, *7*, 6905–6909.

[20] (a) C. Weinberger, R. Hines, M. Zeller, S. V. Rosokha, *ChemCommun.* **2018**, 8060–8063; (b) T. M. Beale, M. G. Chudzinski, M. G. Sarwar, M. S. Taylor, *Chem. Soc. Rev.* **2013**, *42*, 1667–1680; (c) P. Metrangolo, T. Pilati, G. Resnati. A. Stevenazzi, *Curr. Opinion Coll. Interface Sci.* **2003**, *8*, 215–222.

[21] (a) N. Schulz, S. Schindler, S. M. Huber, M. Erdelyi, *J. Org. Chem.* **2018**, *83*, 10881−10886; (b) C. C. Robertson, R. N. Perutz, L. Brammer, C. A. Hunter, *Chem. Sci.* **2014**, *5*, 4179–4183;
(c) R. S. Mulliken, W. B. Person, Molecular Complexes. A Lecture and Reprint Volume Wiley: New York, **1969**; (d) R. D. Green, J. S. Martin, *J. Am. Chem. Soc.* **1968**, *90*, 3659–3668; (e) J. F. Bertrán, M. Rodríguez, *Org. Magn. Resonance* **1979**, *12*, 92–94.

[22] B. Watson, O. Grounds, W. Borley, S. V. Rosokha, *Phys. Chem. Chem. Phys.* **2018**, *17*, 4989–4999.

[23] S. V. Rosokha, C. L. Stern, A. Swartz, R. Stewart, *Phys. Chem. Chem. Phys.* **2014**, *16*, 12968–12979.

[24] R. Liu, P. J. Loll, R. G. Eckenhoff, *FASEB J.* **2005**, *19*, 567–576.

[25] A. A. Bhattacharya, S. Curry, N. P. Franks, *J. Biol. Chem.* **2000**, *275*, 38731–38738.

[26] F. Y.Lin, A. D. MacKerrel, *J. Phys. Chem. B* **2017**, *121*, 6813–6821.

10.1002/anie.201907829

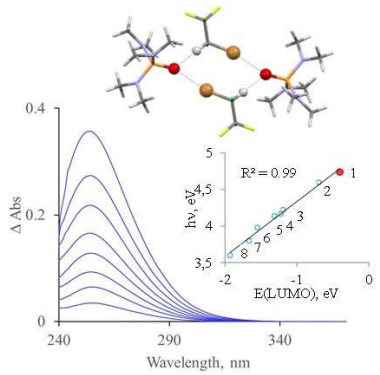
WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Halothane binding: Experimental proof is given of the ability of volatile anesthetic halothane to form halogen bonds and hydrogen bonds with lone pair possessing atoms and anions in solid and in solution. This affords new vistas in the understanding of halothane-membrane interactions as well as other features of the agent, e.g., its eudismic ratio.



Susanta K. Nayak, Giancarlo Terraneo, Quirino Piacevoli, Federica Bertolotti, Patrick Scilabra, John T. Brown, Sergiy Rosokha, Giuseppe Resnati**

Page No. – Page No.

Molecular bases for anesthesia: Halothane as halogen and hydrogen bonds donor