COMMUNICATION

Lipophilicity modulations by fluorination correlate with membrane partitioning

Zhong Wang,[a] Hannah R. Felstead,[a] Robert I. Troup,[a] Bruno Linclau,*[a,b] Philip T. F. Williamson*[c]

(a) Prof B. Linclau, Dr Z. Wang, H. Felstead, R. Troup
School of Chemistry, University of Southampton, Highfield, Southampton SO17 1BJ, UK.
E-mail: bruno.linclau@soton.ac.uk. ORCID 0000-0001-8762-0170
(b) Prof B. Linclau
Department of Organic and Macromolecular Chemistry, Ghent University, Campus Sterre, Krijgslaan 281-S4, 9000 Ghent, Belgium.
(c) Dr P. T. F. Williamson
Centre for Biological Sciences, University of Southampton, Southampton, United Kingdom, SO17 1BJ.
E-Mail: P.T.Williamson@soton.ac.uk. ORCID 0000-0002-0231-8640

Supporting information for this article is given via a link at the end of the document.

Abstract: Bioactive compounds generally need to cross membranes to arrive at their site of action. The octanol-water partition coefficient (lipophilicity, logP_{OW}) has proven to be an excellent proxy for membrane permeability. In modern drug discovery, logP_{OW} and bioactivity are optimized simultaneously, for which fluorination is one of the relevant strategies. The question arises to which extent the often subtle log$P$ modifications resulting from different aliphatic fluorine-motif introductions also lead to concomitant membrane permeability changes, given the difference in molecular environment between octanol and (anisotropic) membranes. We find that for a given compound class, there is excellent correlation between logP_{OW} values with the corresponding membrane molar partitioning coefficients (K_p); a study enabled by novel solid state ^{19}F NMR MAS methodology using lipid vesicles. Our results show that the factors that cause modulation of octanol-water partition coefficients similarly affect membrane permeability.

The lipophilicity of a compound has been shown to be an excellent proxy for a host of physical parameters related to ADMET (absorption, distribution, metabolism, excretion and toxicity).[1] It relates to a compound's ability to partition into the cell membrane, and as such it provides a valuable metric to describe the ability of a pharmaceutical to permeate the various cell membranes required to access its site of action.[1-2] Lipophilicity is measured as the octanol/water partition coefficient (logP_{ow}) of a compound, or by indirect methods based on correlations with chromatographic retention times.[3]

Despite the success of lipophilicity as a parameter in the drug discovery process, the octanol phase is clearly a drastically simplified model for the complex composition and chemical environment of the cell membrane.[4] In contrast to the isotropic octanol environment, the anisotropic cell membrane presents a highly complex environment composed of many lipid species each with their own physicochemical properties that determine the spatial organization and dynamics of the lipids within the lipid bilayer.[5] To reflect these differences, correlation studies between logP_{OW} and the membrane molar partition coefficient (K_P), a unitless value describing the ratio of the mole fractions of a compound in bilayer to that in the aqueous phase, have been carried out[6]. Although these studies show a general correlation between logP_{OW} and partitioning in lipid vesicles (logK_P), significant variations are observed.[7] These differences arise due to the differences in the physicochemical properties of octanol and the cell membrane that influence their interaction with the drug.[4-5, 8] Typically compounds show a higher affinity for the cell membrane than for octanol, with the magnitude of these discrepancies depending on enthalpic and entropic contributions to the partitioning.[9] This is explained by charged species being well tolerated in the high-dielectric lipid headgroup region. In addition, steric effects contribute, with octanol accommodating bulky groups that would otherwise disrupt the packing of the lipids within the bilayer.[4b]

Fluorination of drug candidates is a much-employed strategy to modify both biological and physical properties of drug candidates, and the resulting impact on logP_{OW} can be significant. Hence, much research has been carried out in investigating how fluorination motifs modulate lipophilicity.[10] However, to the best of our knowledge, a detailed study on the influence of fluorination on water-membrane partitioning is not available. Zhang *et al*. have determined the K_p values of trifluoroethanol, hexafluoro-2-propanol and nonafluoro-*t*-butanol using fluorescence quench methods as part of a study of their bilayer modifying properties.[11] While not specifically mentioned, a qualitative agreement between log$P$ (clog$P$ in the case of C_4F_9COH) with logK_p is apparent. Hence, this calls for further research regarding the effect of aliphatic fluorination on membrane permeability.

The extensive recent research into aliphatic lipophilicity prompted us to investigate whether the often small log$P$ modifications caused by subtle changes in fluorination substitution are actually replicated in membrane partitioning, or in other words, whether 1-octanol is still a valid model for membrane permeability when considering purely aliphatic fluorination modifications. For this purpose, closely related compound analogues with subtly different fluorination motifs are employed, using aqueous solutions of multilamellar lipid vesicles composed of 1-palmitoyl-2-oleoyl-glycero-3-phosphocholine (POPC) and a mixture of POPC/cholesterol as a mimic of the eukaryotic cell membrane. Mindful of membrane anisotropy and steric factors, three different compound series **A**–**C** (Figure 1) with varying steric demands and lipophilicity range (1.49 log$P$ units) were selected. The cyclopropyl methyl compounds and the carbohydrate derivatives are models for relatively rigid compounds, whereas

the 1,5-pentanediol derivatives are models for conformationally flexible compounds.

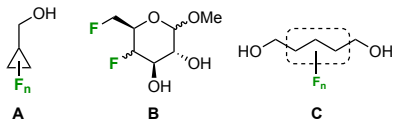


Figure 1. Compounds used in this study.

We also describe the development of convenient magic-angle spinning (MAS) ^{19}F solid-state NMR methodology to determine the partitioning of these (non-UV-active) fluorinated compounds into lipid vesicles without the need for separation of the vesicles. Solution-state ^{1}H and ^{19}F NMR methods for K_p measurement have been developed that rely on the detection of the free compound in solution by exploiting perturbations in resonance position, linewidth and/or T_1 relaxation arising from the rapid exchange between the free and membrane bound states.[12] Typically this necessitates titration across a range of lipid concentrations, making such an approach labour intensive and time consuming, but it benefits from not relying on accurate quantitation of the concentration of the compounds in the free and membrane bound state.[4a, 8] NMR techniques that are able to measure compounds partitioned into a membrane are more challenging to use, as the restricted motion in a membrane environment leads to a broadening of the line-shape due to the chemical shielding anisotropy, susceptibility effects and dipolar couplings present. While solid-state NMR methods are widely used to determine the localisation of drugs within a cell membrane[13], its application for the determination of logK_p is more limited. A ^{2}H solid-state NMR method has been developed for logK_p determination, where both the free and bound deuterated species can be analysed. Partitioning of deuterated molecules into membranes results in the formation of the broad quadrupolar Pake pattern in the ^{2}H-NMR spectrum, which can be deconvoluted from the isotropic signal arising from the free compound, allowing the ratio of free to membrane bound compound to be determined.[14] Nevertheless, this method requires isotope labelling whilst quantitation is challenging as the signal from the motionally restricted deuterium spectrum which is low in intensity and distributed across a broad range of frequencies must be integrated against the sharp intense peak of the free compound.

Given this work deals with investigating the effects of fluorination on membrane partitioning, we considered ^{19}F solid-state NMR methodology, in which the exquisite sensitivity of the ^{19}F chemical shift to changes in electrostatic environment would be exploited.[15] We postulated that application of magic-angle spinning with proton decoupling would sufficiently average the anisotropic nuclear spin interactions that become apparent in the spectrum upon partitioning in the membrane to obtain baseline-separated resonances of the compound in water and in the lipid environment. The absence of fluorine in naturally occurring lipids further simplifies any spectrum, eliminating any spectral ambiguity and facilitating the accurate integration of the resonances necessary for the calculation of the molar partition coefficient K_P.

The principle of the method is explained in Figure 2 (with a detailed description of the protocol provided in Supplementary Information). The method utilizes ^{19}F MAS-NMR to quantitate the partitioning of the fluorinated compounds between the aqueous and membrane phases. To our delight, two resolved resonances were observed, which not only shows that the sensitivity of the ^{19}F resonance to the local environment is able to distinguish between the compound in the aqueous and in the membrane phase, but also that exchange between the aqueous and membrane pools is slow on the NMR timescale, i.e. $k_{exch} \ll \Delta\delta$ (for a detailed discussion see Supplementary Information). Experimentally, it was determined that only moderate spinning speeds (10 kHz) and low power decoupling (10 kHz decoupling field) were required to obtain well resolved spectra, even at these high magnetic fields; with motional processes within the liquid crystalline lipid bilayer averaging the potentially large chemical shielding anisotropy and dipolar couplings experienced by the fluorine spins. The application of low spinning speeds and radiofrequency decoupling fields also reduces sample heating, whilst minimising the pelleting of the vesicles against the rotor wall. The absence of any discernable sidebands, resulting from incomplete averaging, simplifies the analysis, as this precludes the need to integrate the entire family of sidebands.

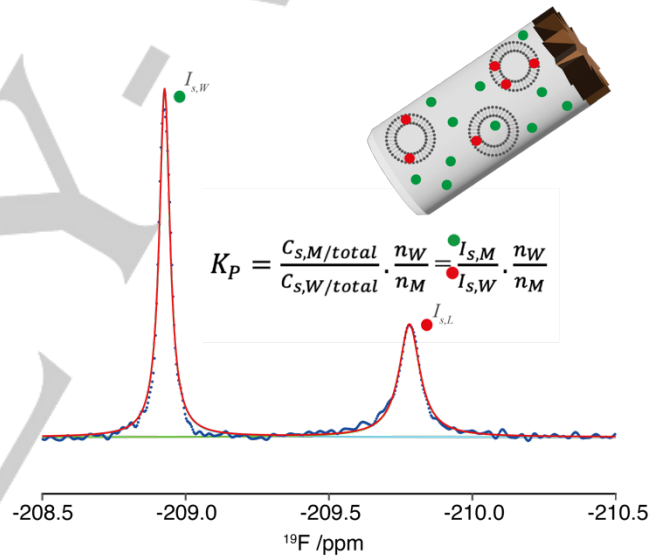


Figure 2. Schematic explaining ^{19}F MAS-NMR (850 MHz) is utilized to calculate molar partition coefficient (K_P). ^{19}F MAS-NMR spectra of fluorinated compounds exhibit two resonances arising from the populations in the water (W) and membrane phases (M), whose intensities ($I_{s,W}$) and ($I_{s,M}$) reflect the concentrations ($C_{s,W}$and $C_{s,M}$) of the compounds in each environment. With knowledge of the number of water (n_W) and lipid (n_M) molecules, the molar partition coefficient (K_P) is readily determined.

To determine how the the concentration of the compound and bilayer hydration influenced the measured logK_P, a systematic study of these parameters was undertaken for compound **10** (Figure S2, Table S1). Samples were prepared where the lipids were hydrated at levels between 10 to 30%(w/v), a range widely used to study the physical properties of lipid bilayers. This resulted in a mean logK_P of 1.85±0.06 across the range of compound concentrations studied. Similarly, variation of compound concentration from 1 to 10 mol% (with respect to total lipid) showed similar reproducibility with a mean logK_P of 1.85±0.02 across all levels of hydration. On the basis of the reproducibility of these figures, all subsequent experiments were conducted at 20% (w/v) hydration with a compound/lipid ratio of

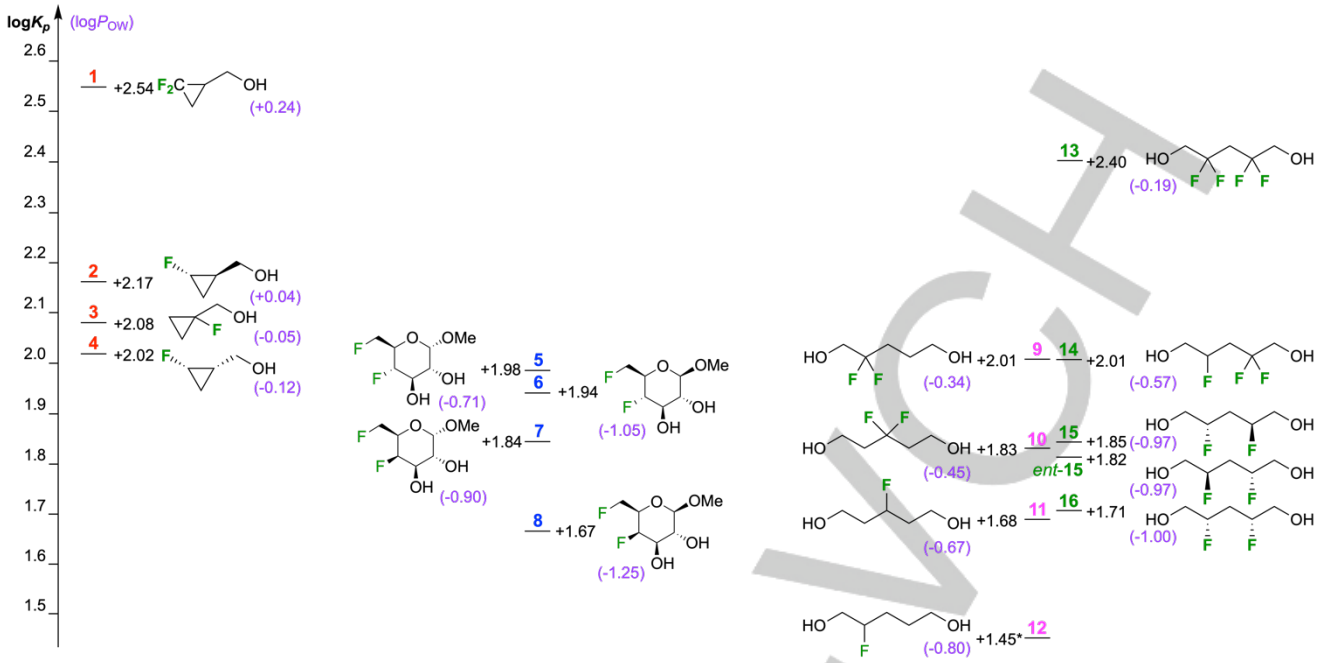


Figure 3. The structures of the compounds used, with their log(K_p) values (values reported are a mean of 3 independent experiments). Octanol-water lipophilicities are shown in blue.

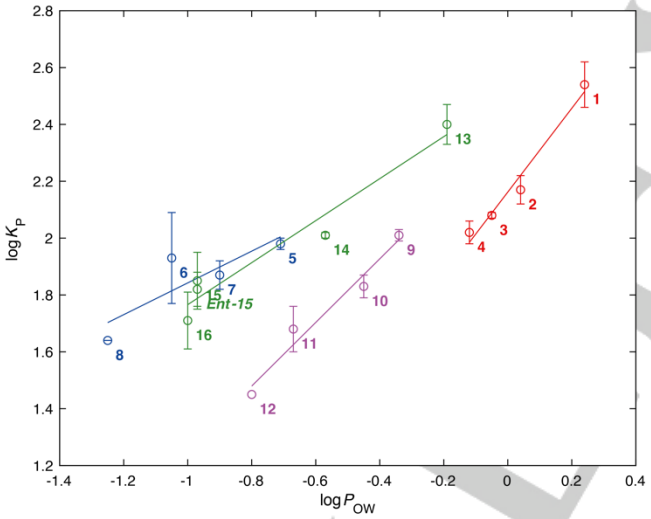


Figure 4. logK_p / logP_{OW} correlation for each series of compounds. The labelling and the structures of each compound is the same as for Figure 3.

0.033. In addition to providing excellent reproducibility, these concentrations afforded good signal to noise ratios with sensible spectral acquisition times.

The structures of the studied compounds and the obtained logK_p values are shown in Figure 3. The corresponding logP_{OW} values are provided in purple, with a range of 0.36 log$P$ units for the cyclopropyl derivatives,[16] and 0.54 and 0.81 log$P$ units for the carbohydrate and 1,5-pentanediol[17] derivatives. Overall, the correlation between the logK_p and logP_{OW} values (Figure S3) is only moderate, with a correlation coefficient of 0.59. However, when each series is considered individually, excellent logK_p – logP_{OW} correlations are obtained (Figure 4).

For the cyclopropylmethyl derivatives **1** – **4**, the logK_p – logP_{OW} correlation (r^2 = 0.97) includes comparisons between substrates having different relative fluorine stereochemistries (**2** vs **4**), fluorination position (**2**,**4** vs **3**), and number of fluorines on a given carbon atom (**2**,**4** vs **1**). For the glycosides **5** – **8**, which also involve changes at a non-fluorine containing stereocentre, log$P$ changes between epimers are reproduced in the corresponding logK_p values (**5** vs **6**; **7** vs **8**; **5** vs **7**; **6** vs **8**), but this is not the case when two stereocentres are inverted simultaneously: the methyl-β-4,6-difluorinated glucoside derivative **6** has a lower log$P$ value compared to methyl-α-4,6-difluorinated galactoside derivative **7**, but a higher logK_p value. This results in a moderate logK_p – log$P$ correlation (r^2 = 0.72). For the more flexible pentane-1,5-diol derivatives, excellent logK_p – logP_{OW} correlations were also obtained when two separate series were considered: compounds **9** – **12** with fluorination at a single position (r^2=0.97), and compounds **13** – **16** with a skipped fluorination motif (r^2=0.95). For both series, lipophilicity differences arising from positional, fluorination number and diastereochemical changes are nicely reflected in their corresponding logK_p values. An interesting case concerns the enantiomers **15**/*ent*-**15**. A fundamental difference between 1-octanol and POPC vesicles (or membranes) is that the former is achiral, while the latter are composed of enantiomerically pure constituents. By definition, enantiomers have identical log$P$ values, but could be expected to have different logK_p values. The measured logK_p values for **15** and *ent*-**15** however, are virtually identical, and within error of each other.

It is interesting to note that there is an apparent difference in the ability of octanol/water and liposome systems to discriminate between the lipophilicity, as captured by the slope of the

correlations (Figures 4 and S4). For the glycosides **5** – **8**, logP_{OW} provides greater discrimination with a slope of 0.56, whilst the lipophilicity of cyclopropyl derivatives are best discriminated by the liposome based model, with a slope of 1.47. Surprisingly, even the two very similar series of pentane-1,5-diols **9** – **12** with a fluorination and a single site and compounds **13** – **16** with a skipped fluorination motif exhibited differing lipophilicity dependencies with slopes of 1.20 and 0.74 respectively. Such variations have been explained by the relative ability of the two hydrophobic phases to accommodate incoming molecules, with the 'malleable' octanol environment and the more structured bilayer environment responding differently to molecular shape and range of interactions.[4]

Cellular membranes exhibit significant variations in lipid composition, a property that is also not reflected in octanol/water partition experiments. A major advantage of the method presented here compared to log*P* determination is that it can be applied to membranes of arbitrary complexity, enabling the analysis of the influence of such properties as headgroup size/charge and chain length/saturation. As naturally occurring lipids are devoid of fluorine and do not contribute to spectral complexity, our solid state ^{19}F NMR MAS methodology is readily extended to natural lipid extracts, and in principle, with appropriate attention paid to data interpretation, to intact cells. As an example of this kind of investigation, a mixed lipid system was employed. In particular, we investigated how increasing concentrations of cholesterol, a commonly found sterol in eukaryotic cell membranes, influenced the membrane partitioning of **9** and **10** (Figure 5, Table S3). In contrast to pure POPC membranes, increasing levels of cholesterol up to 50 mol%, a level found in native membranes,[18] resulted in a reduction in the partitioning of the compound into the membrane, with the logK_P of **9** and **10** falling by 0.24 and 0.17 respectively. The fall in logK_P mirrors earlier studies where a reduction in membrane partitioning for small molecules has been observed.[19] This reduction has been attributed to the disruption of the acyl chain packing and their favourable interactions with the cholesterol.[20]

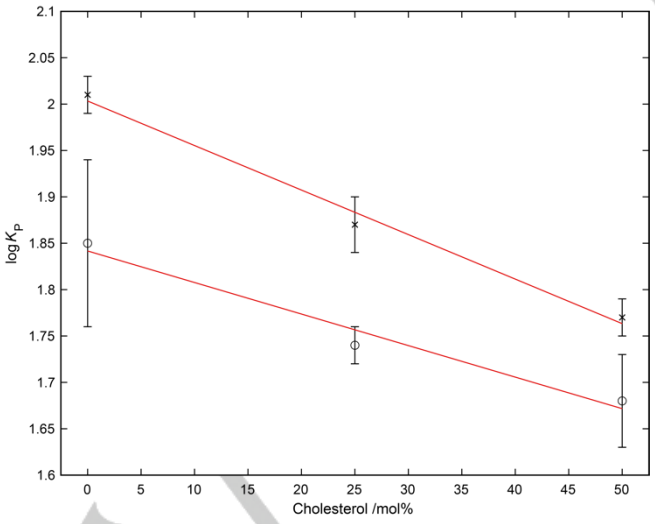


Figure 5. Influence of membrane cholesterol concentration on the partitioning of compounds A and B into POPC bilayers.

Where the ^{19}F chemical shifts of multiple compounds are spectrally resolved, it is also possible to investigate the relative partitioning of compounds in a mixture. Such measurements allow the determination of ΔlogK_p between the compounds studied and are potentially useful if complex lipid mixtures are being studied and the partial molecular volume of the lipid is unknown. To demonstrate this, equimolar mixtures of two pairs of compounds (**9**/**10** and **10**/**13)** were added to multilamellar POPC vesicles. As the compounds in each pair are spectrally well resolved, it is possible to integrate the free and the bound species as described for the individual components and determine the logK_p directly. Overall, excellent agreement was found between the the logK_P measured for each compound alone and that measured in equimolar mixtures (Table 1); with both the absolute logK_p and ΔlogK_p maintained when the compounds were studied in combination. The largest deviation was found for a mixture of compounds **9** and **10** which at 3.3 mol% resulted in a increase in logK_p of 0.2 units for both species. Interestingly, a reduction in the concentration to 1.65 mol%, such that the overall concentration mirrored those used to obtain logK_P in isolation, resulted in closer agreement.

Table 1. Summary of molar partition coefficients determined from studies containing mixtures of fluorinated substrates. Partitioning studied in POPC bilayers hydrated at 20% w/v for a given compound to lipid ratio.

		logK_p Measured as equimole mixture	logK_p Measured as single compound(3.30 mol%)
9 + 10	1.65 mol% each	1.99 ± 0.09 (**9**) 1.84 ± 0.01 (**10**)	2.01 ± 0.02 (**9**) 1.83 ± 0.04 (**10**)
	3.30 mol% each	2.18 ± 0.07 (**9**) 2.01 ± 0.04 (**10**)	
10 + 13	3.30 mol% each	1.88 ± 0.11 (**10**) 2.50 ± 0.10 (**13**)	1.83 ± 0.11 (**10**) 2.40 ± 0.07 (**13**)

In conclusion, it has been demonstrated that for different sets of fluorinated aliphatics, the changes in logP_{OW} arising from variation in fluorination motif are also observed in their respective water-membrane partition coefficients (logK_p). However, excellent correlations were only obtained if each series is considered separately, which is attributed to steric effects arising from molecules entering the lipid environment. It was interesting to note that for some families of isomers which exhibited little variation in log*P*, greater discrimination was observed in logK_p. An efficient and convenient experimental solid state MAS ^{19}F NMR protocol was developed that permits the accurate determination of the molar partition coefficient of fluorinated compounds in membranes of arbitrary complexity was described. This technique exploits the exquisite sensitivity of the ^{19}F chemical shift to the local electrostatic environment, far greater than that experienced by protons or deuterons, to allow the resolution of the free and membrane bound fluorinated compounds. Given the sensitivity of current spectrometers, this provides access to the study of logK_p across approx. 5 units. Our results will be of interest in drug discovery optimisation programmes, as our results clearly indicate that logP_{OW} modulation via fluorination is translated in concomitant membrane permeability changes. Furthermore, from the perspective of membrane biophysics, these methods enable us to ascertain how the composition and physicochemical

properties of the membrane modulate the partitioning of fluorinated compounds, providing opportunities to tailor fluorination motifs that favour partitioning into particular classes of membranes.

Acknowledgements

BL and PTFW are grateful to EPSRC for a project (EP/P019943/1) and core capability grant (EP/K039466/1). The UK 850 MHz solid-state NMR Facility instruments used in this research were funded by EPSRC and BBSRC, as well as the University of Warwick, including via part funding through Birmingham Science City Advanced Materials Projects 1 and 2 supported by Advantage West Midlands (AWM) and the European Regional Development Fund (ERDF). BL acknowledges the Research Foundation Flanders (FWO, Belgium) for an Odysseus Type I grant (G0F5621N).

Keywords: membrane partitioning • lipophilicity • fluorination • NMR • aliphatic

[1] M. J. Waring, *Expert Opin. Drug Discov.* **2010**, *5*, 235-248.

[2] a) J. A. Arnott, S. L. Planey, *Expert Opin. Drug Discov.* **2012**, *7*, 863-875; b) P. D. Leeson, S. A. St-Gallay, *Nat. Rev. Drug Discov.* **2011**, *10*, 749-765.

[3] a) S. Ritter, W. H. Hauthal, G. Maurer, *J. Chem. Eng. Dat.* **1994**, *39*, 414-417; b) A. Kaune, M. Knorrenschild, A. Kettrup, *Fresenius J. Anal. Chem.* **1995**, *352*, 303-312.

[4] a) G. P. van Balen, C. Martinet, G. Caron, G. Bouchard, M. Reist, P. A. Carrupt, R. Fruttero, A. Gasco, B. Testa, *Med. Res. Rev.* **2004**, *24*, 299-324; b) A. Avdeef, in *Absorption and Drug Development*, 2nd ed., **2012**, pp. 220-250.

[5] a) X. Liu, B. Testa, A. Fahr, *Pharmaceut. Res.* **2011**, *28*, 962-977; b) S. D. Krämer, D. Lombardi, A. Primorac, A. V. Thomae, H. Wunderli-Allenspach, *Chem. Biodivers.* **2009**, *6*, 1900-1916.

[6] a) R. Welti, L. J. Mullikin, T. Yoshimura, G. M. Helmkamp, Jr., *Biochem.* **1984**, *23*, 6086-6091; b) K. Kitamura, M. Yamamoto, S. Takegami, M. Sugiura, *Talanta* **1999**, *49*, 261-265; c) K. Kitamura, N. Imayoshi, T. Goto, H. Shiro, T. Mano, Y. Nakai, *Anal. Chim. Acta* **1995**, *304*, 101-106; d) N. C. Santos, M. Prieto, M. A. Castanho, *Biochim. Biophys. Acta* **2003**, *1612*, 123-135.

[7] a) G. P. van Balen, G. Caron, G. Ermondi, A. Pagliara, T. Grandi, G. Bouchard, R. Fruttero, P. A. Carrupt, B. Testa, *Pharm. Res.* **2001**, *18*, 694-701; b) A. Avdeef, K. J. Box, J. E. A. Comer, C. Hibbert, K. Y. Tam, *Pharm. Res.* **1998**, *15*, 209-215; c) C. Ottiger, H. Wunderli-Allenspach, *Eur. J. Pharm. Sci.* **1997**, *5*, 223-231.

[8] S. D. Kramer, in *Pharmacokinetic Optimization in Drug Research*, Wiley, **2000**, pp. 401-428.

[9] B. Testa, P.-A. Carrupt, P. Gaillard, R.-S. Tsai, in *Lipophilicity in Drug Action and Toxicology*, **1996**, pp. 49-71.

[10] a) S. Saphier, S. Katalan, G. Yacov, A. Berliner, O. Redy‐Keisar, G. Fridkin, L. Ghindes‐Azaria, I. Columbus, A. Pevzner, E. Drug, H. Prihed, E. Gershonov, Y. Eichen, S. Elias, G. Parvari, Y. Zafrani, *Chem. Eur. J.* **2023**, *29*, e202202939; b) K. P. Melnykov, O. Tavlui, A. Skreminskiy, Y. O. Kuchkovska, O. O. Grygorenko, *Chem. Eur. J.* **2022**, *28*, e202201601; c) Q. Jia, Y. Ni, Z. Liu, X. Gu, Z. Cui, M. Fan, Q. Zhu, Y. Wang, J. Ma, *J. Chem. Inf. Model.* **2022**, *62*, 4928-4936; d) S. Holovach, K. P. Melnykov, A. Skreminskiy, M. Herasymchuk, O. Tavlui, D. Aloshyn, P. Borysko, A. B. Rozhenko, S. V. Ryabukhin, D. M. Volochnyuk, O. O. Grygorenko, *Chem. Eur. J.* **2022**, *28*, e202200331.

[11] M. Zhang, T. Peyear, I. Patmanidis, D. V. Greathouse, S. J. Marrink, O. S. Andersen, H. I. Ingólfsson, *Biophys. J.* **2018**, *115*, 679-689.

[12] a) A. A. Omran, K. Kitamura, S. Takegami, M. Kume, M. Yoshida, A. A. Y. El-Sayed, M. H. Mohamed, M. Abdel-Mottaleb, *J. Pharm. Biomed. Anal.* **2002**, *30*, 1087-1092; b) S. Takegami, K. Kitamura, M. Ohsugi, A. Konishi, T. Kitade, *AAPS PharmSciTech* **2016**, *17*, 1500-1506.

[13] a) S. E. Feller, C. A. Brown, D. T. Nizza, K. Gawrisch, *Biophys. J.* **2002**, *82*, 1396-1404; b) H. A. Scheidt, D. Huster, *Acta Pharmacol. Sin.* **2008**, *29*, 35-49; c) T. Kimura, K. Cheng, K. C. Rice, K. Gawrisch, *Biophys. J.* **2009**, *96*, 4916-4924; d) D. Ntountaniotis, T. Kellici, A. Tzakos, P. Kolokotroni, T. Tselios, J. Becker-Baldus, C. Glaubitz, S. Lin, A. Makriyannis, T. Mavromoustakos, *Biochim. Biophys. Acta* **2014**, *1838*, 2439-2450; e) O. Engberg, H. A. Scheidt, T. K. M. Nyholm, J. P. Slotte, D. Huster, *Langmuir* **2019**, *35*, 11902-11911; f) J. Kremkow, M. Luck, D. Huster, P. Muller, H. A. Scheidt, *Biomolecules* **2020**, *10*.

[14] D. A. Middleton, D. G. Reid, A. Watts, *J. Pharm. Sci.* **2004**, *93*, 507-514.

[15] a) S. E. Chambers, E. Y. Lau, J. T. Gerig, *J. Am. Chem. Soc.* **1994**, *116*, 3603-3604; b) E. Y. Lau, J. T. Gerig, *J. Am. Chem. Soc.* **1996**, *118*, 1194-1200; c) E. Y. Lau, J. T. Gerig, *J. Am. Chem. Soc.* **2000**, *122*, 4408-4417.

[16] B. Jeffries, Z. Wang, R. I. Troup, A. Goupille, J.-Y. Le Questel, C. Fallan, J. S. Scott, E. Chiarparin, J. Graton, B. Linclau, *Beilstein. J. Org. Chem.* **2020**, *16*, 2141-2150.

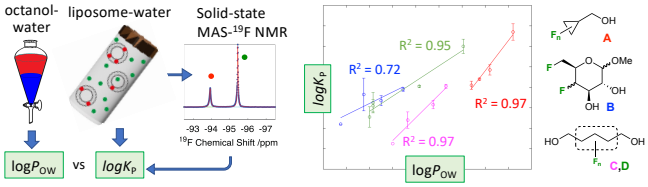
[17] R. I. Troup, B. Jeffries, R. E. Saudain, E. Georgiou, J. Fish, J. S. Scott, E. Chiarparin, C. Fallan, B. Linclau, *J. Org. Chem.* **2021**, *86*, 1882-1900.

[18] a) R. Lipowsky, E. Sackmann, *Structure and dynamics of membranes: I. from cells to vesicles/II. generic and specific interactions*, Elsevier, **1995**; b) G. van Meer, *Trends Cell Biol.* **1998**, *8*, 29-33.

[19] a) K. Korten, T. J. Sommer, K. W. Miller, *BBA Biomem.* **1980**, *599*, 271-279; b) R. A. Smith, E. G. Porter, K. W. Miller, *BBA Biomem.* **1981**, *645*, 327-338; c) W. K. Subczynski, J. S. Hyde, A. Kusumi, *P Natl Acad Sci* **1989**, *86*, 4474-4478; d) W. K. Subczynski, A. Wisniewska, J.-J. Yin, J. S. Hyde, A. Kusumi, *Biochem.* **1994**, *33*, 7670-7681.

[20] C. L. Wennberg, D. van der Spoel, J. S. Hub, *J. Am. Chem. Soc.* **2012**, *134*, 5351-5361.

Entry for the Table of Contents



A novel solid-state ^{19}F MAS-NMR method was developed to accurately and easily measure water-membrane partitioning values (K_p). Given the very different octanol and membrane environments, a remarkable correlation between K_p and log*P* was found, but only for a given compound series. This work indicates that even minor lipophilicity modulations by aliphatic fluorination can have true relevance for the drug discovery optimization process.

Institute and/or researcher Twitter usernames: @sotonbiosci, @WE07_UGent

WILEY-VCH