A combined experimental and theoretical study of radon solubility in fat and water

Elvira P. Sanjon¹, Andreas Maier², Annika Hinrichs²,³, Gerhard Kraft², Barbara Drossel¹ & Claudia Fournier²

Radon is a radioactive noble gas that can enter the human body, thus increasing the risk of lung cancer. But it is also used for treatment of various ailments, most notably rheumatoid arthritis. The accumulation of radon differs between tissues, with particularly high concentrations in fat tissue. To understand the underlying mechanisms, a combination of γ-spectroscopy and molecular dynamics simulations were performed, to study the accumulation of radon gas in contact with several liquids (water, fatty acids). The solubilities, specific for a defined radon activity concentration, are in good agreement and differ by two orders of magnitude between water and fat, caused by radon disrupting the hydrogen bond network of water. In contrast, the energy cost of introducing radon atoms into fat is low due to the dispersive interaction between radon and fat, which is a non-polar solvent. This correlation was also explicitly demonstrated in our simulations by changing the polarization of the solvent.

Radon is a naturally occuring radioactive noble gas. Its most stable isotope ²²²Rn has a half-life of 3.8 days. Exposure to radon and its decay products accounts for the largest proportion of annual radiation dose from natural sources¹². The highest dose is deposited in the lung and is caused mainly by the short-lived radon daughter nuclei ²¹⁸Po and ²¹⁴Po³⁴ which are α-emitters, thus increasing the risk of lung cancer⁵⁶. Radon is inhomogeneously distributed in different tissues⁷⁸, resulting in significant doses to other organs⁹. Despite this risk, radon has beneficial effects when used for therapy of inflammatory diseases such as rheumatoid arthritis and ankylosing spondylitis, but the underlying molecular mechanisms are not fully understood⁹¹⁰.

Radon enters the body via the epithelial tissues of lung, skin and the gastrointestinal tract, diffuses into the bloodstream and accumulates in fatty tissue⁷¹². The physical and chemical reasons behind this inhomogeneous distribution in the human body have not been explored yet, although this is of great interest for understanding the effect of radon therapy as well as the potential health risks. In order to fill this gap, we propose that radon diffuses slower into liquid water due to the strong polar interaction between the water molecules. Fat in contrast is non-polar, which leads to an energetic lower threshold for radon to enter in fatty tissue. To check this hypothesis, we used a combination of γ-spectroscopy and molecular dynamics (MD) simulation to investigate the concentration specific solubility of radon in water and fat.

The sample/air partition coefficient of radon or concentration specific solubility (S) is defined by the relation

\[ S = \frac{C}{D_{Rn}} \]

where C is the concentration of radon in the liquid and D_{Rn} is the radon density in the surrounding gas, which has been chosen in the simulations as a pure radon gas at room temperature and normal pressure. Previous simulations¹³⁻¹⁸ studied the diffusion of a small number (2–5) of noble gas atoms (He, Ne, Ar, Kr, Xe) in water in order to investigate the hydrophobic effect. They found that the bigger the atom, the more distorted is the local structure of the surrounding water molecules. Since the radon atom is even larger than these atoms used in previous studies, its presence in water must considerably disturb the local structure. There exist no comparable studies for the diffusion of a noble gas in a non-polar solvent.

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In the simulations, we had to use fat molecules with shorter chains in order to achieve equilibration. Two types of fat and water-salt solutions were used. In addition, we also used hexane as well as pure water (labelled as $Q_0$) and water with a polarization that was artificially reduced ($Q_+\backslash$) or enhanced ($Q_\backslash$) by 15%.

Table 1 shows the density and nearest-neighbour distances for the different liquids used in the computer simulations. The attraction between water molecules is dominated by the electrostatic interaction, and therefore density decreases with decreasing polarity. The densities obtained for water $Q_0$ (0.995 $g \cdot cm^{-3}$) and for water $Q_+$ (1.058 $g \cdot cm^{-3}$) are close to the empirical value of 1.000 $g \cdot cm^{-3}$.

The concentration of radon in the different liquids is shown in Table 2. Radon is hardly soluble in water $Q_0$ and water $Q_+$, but accumulates to some extent in water $Q_\backslash$. More radon accumulates in alkaline solutions than in pure water, indicating that the effect of adding salt is similar to the effect of changing the polarity of water.

The experimental results obtained with oelie and linolic acid and isotonic salt solution are shown in Table 3. The experiments for the salt solution and oleic acid were repeated three times, and four times for linolic acid. The final results for concentration specific solubility of radon obtained from experiment and simulation are summarized in Table 4. They agree very well with each other for all the fatty acids, with concentration specific solubility values around 2. These values are of the same order of magnitude as measured by Nussbaum and Hursh. The concentration of solved radon is so low that it could not be distinguished from 0 in the simulations. Because of this sensitive dependence of concentration specific solubility of radon on water polarization, we think that the difference between simulation and experiment is due to the fact that water molecules used in simulations have fixed partial charges that cannot respond to different types of interaction partners. In any case, the computer simulations confirm that concentration specific solubility of radon differs vastly between polar and non-polar liquids.
Table 3. Experimentally determined radon concentration in the sample for the different nuclide $^{214}$Pb ($C_{\text{pb}}$) and $^{214}$Bi ($C_{\text{Bi}}$) and radon activity-concentration $D_{\text{Rn}}$ during experiments. The assumed densities are 1.000 g · cm$^{-3}$ for the isotope solution, 0.895 g · cm$^{-3}$ for oleic acid and 0.900 g · cm$^{-3}$ for linoleic acid. The experiments were done at an air pressure of 1001 ± 9 mbar and a temperature of 295.2 ± 0.4 K (with standard deviation).

| Liquid           | Concentration specific solubility of radon | 
|------------------|-------------------------------------------|
|                  | ($C_{\text{pb}}$) (Bq/cm$^3$) | ($C_{\text{Bi}}$) (Bq/cm$^3$) | $D_{\text{Rn}}$ (Bq/cm$^3$) |
| H$_2$O +0.9% NaCl | 0.11 ± 0.08 | 0.09 ± 0.07 | 3.97 ± 0.11 |
| C$_{18}$H$_{32}$O$_2$ | 3.65 ± 0.08 | 3.62 ± 0.08 | 2.12 ± 0.07 |
| C$_{18}$H$_{34}$O$_2$ | 7.76 ± 0.22 | 7.36 ± 0.22 | 3.91 ± 0.11 |
| C$_{10}$H$_{20}$O$_2$ | 8.86 ± 0.22 | 8.36 ± 0.22 | 2.88 ± 0.08 |
| C$_{10}$H$_{20}$O$_2$ | 6.73 ± 0.21 | 7.07 ± 0.21 | 3.76 ± 0.10 |
| C$_{10}$H$_{20}$O$_2$ | 7.15 ± 0.21 | 6.90 ± 0.21 | 3.76 ± 0.10 |

Table 4. (a) Measured concentration specific solubility of radon in oleic acid (C$_{18}$H$_{34}$O$_2$), linolic acid (C$_{18}$H$_{32}$O$_2$), and an isotope solution (with standard deviation). (b) Computer simulation results for concentration specific solubility of radon in pure water, pure water with increased (Q$^+$) or reduced (Q$^-$) polarization, two types of water-salt solutions, hexane (C$_6$H$_{14}$), butyric acid (C$_4$H$_8$O$_2$), and capric acid C$_{10}$H$_{20}$O$_2$ with standard error. [For more details, see the methods section].

In the following, we used the computer simulation data in order to explore how this concentration specific solubility difference emerges from the interaction of radon with the respective liquids. Since radon is a large atom, its presence interrupts the structure of the solvent molecules. Figure 1(a) shows the radial distribution functions (i.e., the distribution of intermolecular distances) of the different solvents in the absence of radon. The first peak of each curve gives the nearest-neighbour distance in the non-distorted case. This distance is substantially smaller for water than for fat (which has larger molecules), and it decreases with increasing polarity, i.e., with increasing attractive interaction.

Figure 1(b) shows the radial distribution function of solvent molecules around radon atoms. The distance to the closest solvent atom is ≈0.4 nm, which is comparable to the radius of a radon atom. It is of the same order of magnitude as the distance between fatty acid molecules and considerably larger than the distance between water molecules. A visual impression of how the radon atom is embedded in the local structure is given in Fig. 2, which shows snapshots of the equilibrated system configurations obtained with MD simulations. The left panel shows capric acid molecules surrounding a radon atom, which is located in a void in the hydrocarbon arrangement. The right panel displays radon surrounded by water molecules. The surrounding water molecules are connected to each other by hydrogen bonds. In order to create space for the radon atom, the hydrogen bonds around it form a cage that has a different structure from the usual hydrogen bond network of pure water and thus this network is disturbed in the vicinity of the radon atom. Altogether, these observations indicate that the local structure of water is much more distorted by the presence of a radon atom than the structure of fatty acids. In order to penetrate water, the radon atom must modify the hydrogen bond network structure so that enough space for the radon atom is created, which goes along with an energy cost. Furthermore, in order to change from one location in water to a neighbouring one, the radon atom must break hydrogen bonds of its cage. A straightforward comparison between hydrogen bonds strength in water (between 21–24 kJ/mol)$^{19,20}$ and the inter-molecular energy in hydrocarbons (related to the London dispersion energy on the order of 1–8 kJ/mol) suggests that the energy cost
of breaking a bond is larger by one order of magnitude in water than in fat. Introducing radon in water thus comes with a high cost of free energy, leading to a low solubility. This low solubility is accompanied by a slow diffusion. Using our simulation data, we compared the diffusion of a radon atom in water with the diffusion of radon in hexane (see Table S1 of the Supplementary Information). The diffusion coefficient is at least four times lower in water compared to hexane. This supports our above finding that the diffusion of radon in water is hampered by a higher energy barrier due to the necessity of breaking hydrogen bonds. These two effects explain the much lower concentration specific solubility of radon in water compared to fat.

The amount of radon solved in water increases when the energy of the hydrogen bonds is reduced (Q_{water}) or when the tetrahedral short range order of water is reduced by dissolving salt in water (see the concentration specific solubility data in Table 4(b)). A deeper theoretical understanding of the solvation of hydrophobic solutes is conveyed in the work of Sedlmeyer et al.21.

**Figure 1.** (a) Radial distribution function of the different types of water used in the simulations (based on the location of the oxygen atoms) and of fatty acids (based on the location of the first carbon atom). (b) Radial distribution function of the different solvent molecules around a solved radon atom, based again on the oxygen resp. carbon atoms.

**Figure 2.** Snapshots showing the local structure of liquid molecules surrounding a radon atom, obtained when the system is equilibrated. Left: Capric acid molecules around a radon atom. Right: Water molecules surrounding a radon atom.
In contrast to water, hydrocarbon aggregates provide free volume in which radon can enter without disrupting the molecular structure in a noticeable way. In the Supplementary Information (Fig. S1), we demonstrated this explicitly by showing the radial distribution of carbon in butyric and capric acid in two different cases: first in the liquid structure and second in the liquid after accumulation of radon. The effect of radon in the local structure of hydrocarbons is almost not visible, apart from a slight move of the shoulder of the first neighboring shell peak to larger distances. Interestingly, radon accumulates more in fatty acids than in linear oily chains. This may be related to the fact that fatty acids contain larger atoms (C and O), and that they have a heterogeneous structure with aliphatic groups that can form hydrogen bonds. In contrast, the difference between saturated and unsaturated fat molecules plays only a minor role for concentration specific solubility of radon (when taking into account the size of the error bars).

To conclude, our study explains the much better concentration specific solubility of radon in fat compared to water, and it has thus laid the ground for a more detailed exploration of the accumulation of radon in various tissues.

**Methods**  
**Experimental methods.** The experiments were conducted in a radon chamber, and the samples were exposed at room temperature (295.2 ± 0.4 K) and atmospheric pressure (1001 ± 9 mbar) under controlled conditions (radon activity concentration, temperature and relative humidity)\(^2\). The most abundant fatty acids in the human body, oelic acid (C\(_{18}\)H\(_{34}\)O\(_2\)), linolic acid (C\(_{18}\)H\(_{32}\)O\(_2\))\(^3\) and isotonic salt solution (0.9 mass percent NaCl) were exposed in the liquid phase. The radon activity concentration was constant during exposure.

The experimental scheme is shown in Fig. 3. Samples were placed in dishes with a layer thickness of around one centimetre and covered with a fibre glass filter for protection from contamination with radon decay products. Samples were exposed for one hour, in which saturation with \(^{222}\)Rn was reached, which was in agreement with diffusion measurements conducted in parallel\(^2\).

After exposure the radon chamber was flushed with air for five minutes to remove most of the radon. Then the specimen were transferred into uncontaminated glass jars and sealed. After approximately four hours a radioactive equilibrium between \(^{222}\)Rn and its daughter nuclei \(^{214}\)Pb and \(^{214}\)Bi could be reached. Subsequent measurement of the activities via \(\gamma\)-spectroscopy and by determining the activity at \(t = 0\), the concentration specific solubility of radon could be determined by normalizing to the mass of the sample and the radon activity concentration during experiment.

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The \(\gamma\)-spectra of the radioactive nucleides \(^{214}\)Pb and \(^{214}\)Bi were measured with a high purity Ge-detector. Data were analysed with commercial available software. After calibration for energy and efficiency, a background subtraction of an unexposed sample with the same geometry was performed. For efficiency calibration, the sample geometry was considered, as this has an impact on the self-absorption of the \(\gamma\)-quanta inside the specimen and on the solid angle of the emitted photons in relation to the detector. For analysis, the most prominent \(\gamma\)-lines at 242 keV, 295 keV, 352 keV (all \(^{214}\)Pb) and 609 keV (\(^{214}\)Bi) were taken into account. Subsequently the results were plotted over the time after exposure. The intersection of the extrapolated activity with the \(\gamma\)-axis gives the initial activity of the measured isotopes and therefore the initial \(^{222}\)Rn concentration. By normalizing to the mass of the sample and considering the density of the sample material, the activity inside the specimen was determined. Taking into account the radon activity concentration during the experiment, the concentration specific solubility of \(^{222}\)Rn in the sample was calculated.
density of radon gas. Some simulation using the parameters suggested by other authors have been performed, using the Langevin-Piston method. Whereas the temperature is fixed to room temperature (T = 298 K) using a Langevin thermostat with a coupling coefficient of 1.0 ps$^{-1}$. An integration time step of 1 fs is utilized in order to accurately follow the motion of fast radon atoms. The simulations have been run for approximately 10 ns for the equilibration of each pure liquid, meanwhile the accumulation of radon in each liquid has been observed during a time interval of at least 2 ns. We used periodic boundary conditions, allowing the calculation of the long-range contributions.

### Computational methods

Classical MD simulations are performed with the NAMD25 2.10 simulation package. The SPC/E (extended simple point charge) model is used to model liquid water, where a water molecule is represented by three atom sites. The partial charge attached to the oxygen atom is $Q_{\text{O}} = -0.8476$ e and half i.e $0.423e$ is attached to the hydrogen atoms. In order to vary the polarity, the partial charges attached on the oxygen atom are varied and values $Q_{\text{O}} = -0.8476 e$, $Q_{\text{O}} = Q_{\text{H}} = 0.009 e$, and $Q_{\text{O}} = Q_{\text{H}} = 0.0560 e$ are the ones generally used in MD simulations to characterize dynamical properties of ions in salt solutions.

Interaction parameters of the alkaline ions were extracted from the work of Luo and Aqvist. Additionally, fat is mimicked by simulating the linear isomer of hexane (C$_6$H$_{14}$), butyric (C$_4$H$_8$O$_2$) and capric (C$_{10}$H$_{20}$O$_2$) acid. The parameters used to simulate hexane are taken from the CHARMM22 force field, and those for butyric and capric acid from the work of Clifford et al.

Radon atoms interact with the atoms of each liquid via Van der Waals interaction, implemented as Lennard-Jones (LJ) potential

$$U_{\text{LJ}} = 4\epsilon \left[ \frac{\sigma^12}{r_{ij}} - \frac{\sigma^6}{r_{ij}^6} \right].$$

(1)

The isotope $^{222}\text{Rn}$ is used to model radon. In order to obtain the LJ parameters corresponding to the gaseous phase of radon, the well depth $\epsilon$ is derived from the radon bulk cohesive energy ($U_{\text{coh}}$) using $\frac{U_{\text{coh}}}{N_0} = -(2.15) \cdot 4\epsilon$ for $^{222}\text{Rn}$. The value of $\sigma$ used in the present study has been chosen accordingly in order to reproduce the correct density of radon gas. Some simulation using the parameters suggested by other authors have been performed, but the resulting density at room temperature was at least 5% higher than the empirical radon density.

The interaction of radon with other atoms occurs also via the LJ potential, with parameters calculated using the Lorentz-Berthelot mixing rules.

Table 5 shows all LJ parameters as well as partial charges assigned to the different atom types. All runs have been carried out within the NPT ensemble keeping the pressure constant and equal to 1 bar using the Langevin-Piston method. Whereas the temperature is fixed to room temperature (T = 298 K) using a Langevin thermostat with a coupling coefficient of 1.0 ps$^{-1}$. An integration time step of 1 fs is utilized in order to accurately follow the motion of fast radon atoms. The simulations have been run for approximately 10 ns for the equilibration of each pure liquid, meanwhile the accumulation of radon in each liquid has been observed during a time interval of at least 2 ns. We used periodic boundary conditions, allowing the calculation of the long-range contributions.

### Table 5. LJ parameters for each atomic site used in the simulation.

| Atoms | $\epsilon$ (Kcal/mol) | $\sigma$ (nm) | $Q$ (e) |
|-------|----------------------|--------------|--------|
| O$_{\text{w}}$ | 0.155 | 0.317 | $-$0.847 |
| H$_{\text{w}}$ | 0.000 | 0.179 | 0.423 |
| C$_{\text{w}}$ | 0.078 | 0.363 | $-$0.270 |
| C$_{\text{w}}$ | 0.0560 | 0.358 | $-$0.180 |
| H$_{\text{w}}$ | 0.024 | 0.238 | 0.009 |
| H$_{\text{w}}$ | 0.035 | 0.238 | 0.009 |
| C | 0.081 | 0.390 | 0.750 |
| O(=C) | 0.156 | 0.305 | $-$0.550 |
| O(=H) | 0.184 | 0.302 | $-$0.610 |
| H | 0.000 | 0.179 | 0.009 |
| CH$_2$ | 0.091 | 0.395 | $-$0.180 |
| CH$_3$ | 0.194 | 0.375 | $-$0.270 |
| N$_{\text{w}}$ | 0.046 | 0.251 | 1.000 |
| Cl | 0.150 | 0.404 | $-$1.000 |
| C$_{\text{w}}$ | 0.023 | 0.324 | 2.000 |
| Rn | 0.541 | 0.453 | 0.000 |

Table 5. LJ parameters for each atomic site used in the simulation. O$_{\text{w}}$ and H$_{\text{w}}$ stand for the oxygen and hydrogen atoms of water. C$_{\text{w}}$ and C$_{\text{w}}$ are the carbons of the hexane chain linked respectively to 2 (H$_{\text{w}}$) and 3 (H$_{\text{w}}$) hydrogens. C, O(=C) and O(=H) are the atoms of the fatty acids carboxylic group. CH$_2$ and CH$_3$ are the carbons of the fatty acids linked respectively to 2 and 3 hydrogen atoms, and H represent the hydrogens. Na, Ca and Cl represent the sodium, calcium and chloride ions.
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Author Contributions

E.P. performed the computer simulations; A.M., A.H. conducted the experiments; G.K. and C.F. directed the experiments and, with B.D., helped analysing and discussing the data; E.P., A.M. and B.D. wrote the paper. All authors reviewed the manuscript.
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