Utilizing ^{1}H-NMR Spectroscopy to Measure the Octanol-Water Partition Coefficient of Hydantoin Compounds

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Introduction

- Hydantoin scaffolds are present in many antiseizure, antiviral, anticonvulsant, or antiulcer medications. Their topical applications have shown promise in treating chronic wounds.
- As with more drugs, hydantoin drugs are commonly found in a solid state and exhibit polymorphism (the existence of multiple crystalline structures) which decreases their pharmaceutical efficacy. By converting these solid-state drugs into a liquid state (ionic liquids), polymorphism can be prevented, and the new compounds can be used in developing new delivery strategies for hydantoin drugs.
- Hydantoin drugs are ideal anion precursors: they exist as either ionic (sodium salts) or neutral acidic compounds (which can be deprotonated to form the corresponding ionic form).

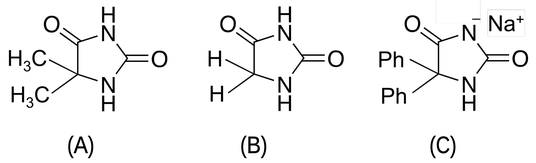

Figure 1. Hydantoin compounds:
(A) 5,5-dimethyl hydantoin; (B) Hydantoin; (C) Phenytoin

Objective

- The focus of this study was to investigate the solubility of ionic-liquid state hydantoin drugs through the determination of the octanol-water partition coefficient (K_{ow}).

Synthesis

- Dimethyl hydantoin (Figure 1) was reacted through acid-base reactions (Figure 2) with three cation sources, namely choline hydroxide (Cho OH), tetrabutylphosphonium hydroxide (PBu_4 OH), and tetrabutylammonium hydroxide (NBu_4 OH), in a 1:1 stoichiometric ratio. These reactions were carried out in acetone at room temperature and stirred for 24 hours. The remaining solvent and water product were removed using a Rotovap. As a result, three compounds, nearly colorless or highly viscous compounds, were obtained. The identity of the resulting liquid state compounds was investigated using Nuclear Magnetic Spectroscopy.

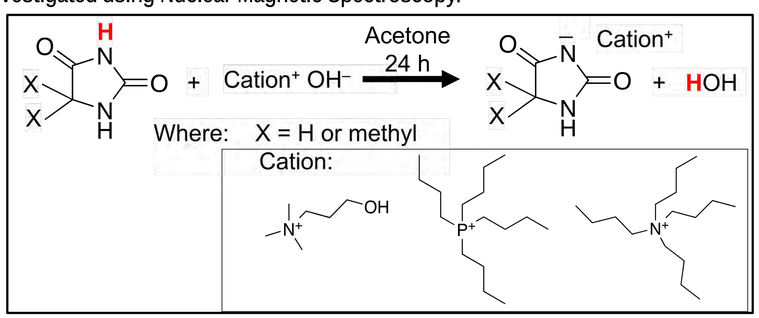

Figure 2. Synthesis of hydantoin compounds

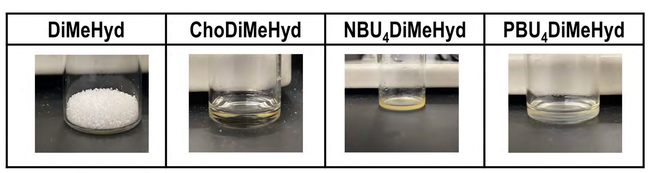

Figure 3. Liquid state dimethylhydantoin compounds

^{1}H-NMR Spectroscopic Characterization

- The identity of these products was confirmed using nuclear magnetic resonance (NMR) spectroscopy. ^{1}H-NMR spectra for dimethyl all compounds was collected for 0.058 M dmso-d6 solutions.
  - The most acidic hydrogen peak (H present on the N atom connected to the two carbonyl groups) from hydantoin starting materials is not present in the products
  - The next most acidic peak (H present on the N atom connected to only one carbonyl group) is shifted to lower ppm values in all the synthesized compounds. This is consistent with the removal of the most acidic hydrogen and with an increase in electron density on the hydantoin ring.

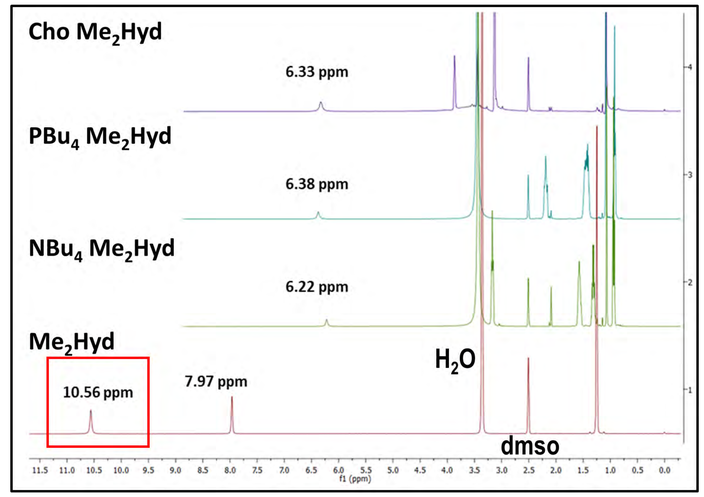

Figure 4. ^{1}H-NMR characterization of hydantoin (left) and dimethylhydantoin (right) compounds

Octanol-Water Partition Coefficient

- Each sample was prepared in a 0.01 M concentration and dissolved in 500 μL water (Optima™ LC/MS Grade).
- ^{1}H-NMR spectrum of each sample was obtained using a coaxial tube containing D_2O as the internal standard and used to determine the relative ^{1}H-NMR peak integration of analyte in H_2O ($RI_W^{initial}$)
- 500 μL 1-octanol was added to each tube and inverted approximately 50 times.
- The samples were allowed to phase separate for approximately one hour.
- A final ^{1}H-NMR spectrum was obtained to determine the relative ^{1}H-NMR peak integration of analyte in H_2O after equilibrium with 1-octanol ($RI_W^{equilibrium}$)

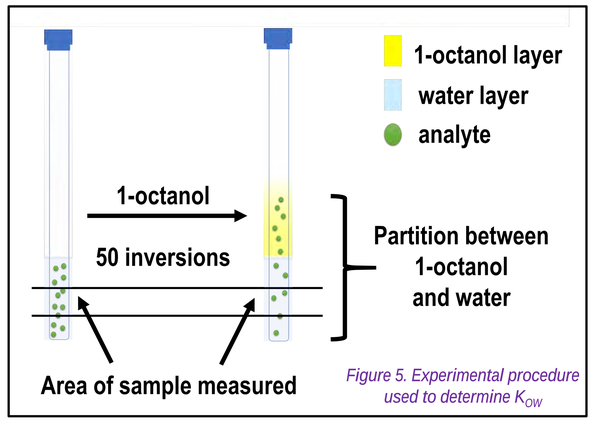

Figure 5. Experimental procedure used to determine K_{OW}

$$K_{OW} = \frac{RI_W^{initial} - RI_W^{equilibrium}}{RI_W^{equilibrium}}$$

K_{OW} = octanol-water partition coefficient
$RI_W^{initial}$ = relative NMR peak integration of analyte in H_2O before equilibrium
$RI_W^{equilibrium}$ = relative NMR peak integration of analyte in H_2O after equilibrium with 1-octanol

log K_{OW} < 0: higher affinity for H_2O (more hydrophilic)
log K_{OW} > 0: higher affinity for 1-octanol (more lipophilic)

Table 1. K_{OW} and log K_{OW}

	Sample #	K_{ow}	log K_{ow}
Me_2Hyd	1	-0.12092	–
	2	-0.61579	–
	3	–	–
	4	-0.62044	–
	5	-0.68465	–
NBu_4 Me_2Hyd	1	0.17856	-0.74821
	2	0.10442	*-0.98120*
	3	0.03605	*-1.44304*
	4	0.18746	-0.72708
	5	0.19142	-0.71800
PBu_4 Me_2Hyd	1	0.57602	*-0.23956*
	2	0.26965	-0.56920
	3	–	–
	4	0.19526	-0.70938
	5	0.27891	-0.55452
Cho Me_2Hyd	1	-0.01537	–
	2	-0.05336	–
	3	–	–
	4	-0.05290	–
	5	-0.07592	–

Conclusions

- The method is not suitable for the more hydrophilic compounds, Me_2Hyd and Cho Me_2Hyd (K_{OW} < 0) BUT it is suitable for the more hydrophobic compounds, NBu_4 Me_2Hyd and PBu_4 Me_2Hyd (K_{OW} > 0)
- NBu_4 Me_2Hyd and PBu_4 Me_2Hyd: log K_{OW} < 0 → higher affinity for H_2O phase
  - Outliers still present in the obtained data (2/5 for NBu_4 Me_2Hyd and 2/5 for PBu_4 Me_2Hyd)

Future Work

- To decrease the number of outliers, re-assessing the hydrophilicity of the synthesized compounds by using a higher number of samples (*e.g.*, 10 *vs.* 5) and a higher number of inversions (*e.g.*, 75 *vs.* 50)
- Investigating the thermal behavior of the synthesized hydantoin derivatives using Thermal Gravimetric analysis (TGA, for determining the decomposition temperatures) and Differential Scanning Calorimetry (DSC, for determining melting points)
- Investigating the transdermal delivery potential of the synthesized compounds

References

(1) https://kuscholarworks.ku.edu/bitstream/handle/1808/1175/SC08_R_Prankerd.pdf;sequence=1. Last Accessed 09/06/21. (2) Shaw, J.; Hughes C.M.; Lagan K.M.; Bell P.M.; The clinical effect of topical phenytoin on wound healing: a systematic review. *British Journal of Dermatology.* 2007, 997-1004. DOI: 10.1111. (3) Cumming H.; Rücker C.; Octanol-Water Partition Coefficient Measurement by a Simple ^{1}H-NMR Method. *ACS Omega.* 2017, 2, 9, 6244-6249

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