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The Lewis Acidity of Imidazole-derived Diaryliodonium Zwitterions

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The Lewis Acidity of Imidazole-derived Diaryliodonium Zwitterions

by

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Abstract:

Diaryliodonium salts can be used as effective aryl-transfer agents in reactions to form novel molecules with diverse applications including pharmaceuticals and agrochemicals without using harsh reaction conditions and transition metal reagents. In recent years, interest in the applications of the Lewis acidity of iodonium ion catalysts has increased. Despite this, the quantification of the Lewis acidities of diaryliodonium salts are scarce. Even rarer, there has not been much study into the Lewis acidities of zwitterionic diaryliodonium salts. For zwitterions, there is no counter anion that would come into consideration in regard to its Lewis acidity. To expand the understanding of the Lewis acidity of diaryliodonium salts, this work sought to quantify the binding of a variety of zwitterionic diaryliodonium salts. Multiple titrations of zwitterionic diaryliodonium salts and DABCO resulted in different ^{1}H NMR spectra for which the aromatic peaks with the greatest shift were recorded. Nonlinear regression was performed to afford a K_b value and a plot of $\Delta\delta$ vs. guest concentration. Of all the zwitterionic species, only the imidazole mesityl iodonium zwitterion could be dissolved at an appropriate concentration to do a binding study. Due to complications regarding pipetting and shimming of NMR spectra, the resultant binding constants could not reliably be determined. Further binding studies of zwitterionic species and their respective imidazole aryl iodonium acetates could allow quantification of binding constants in relation to the presence of a zwitterion.

Acknowledgements:

I would like to thank my advisor, the preeminent Dr. David R. Stuart, for accepting me into his organic chemistry laboratory despite being a biology major. He was the first organic chemistry professor that I had, and I believed my attendance in his class helped to foster a love for organic chemistry. He always helped me move on when I felt stuck and his guidance throughout has been indispensable. His reassurances about my project helped me to see things differently, and I wish to sincerely thank him for this past year.

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Introduction:

Diaryliodonium salts were first discovered in the late 1800s but did not receive much attention until the 1950s. In the past two decades, the scholarship regarding diaryliodonium salts have increased substantially (Figure 1)[3,8]. This is because diaryliodonium salts can be used as effective aryl-transfer agents in reactions to form novel molecules with diverse applications including pharmaceuticals and agrochemicals without using harsh reaction conditions and transition metal reagents[6,7,8]. Compared to other reagents such as transition metal reagents containing such substituents as tin, lead, and thallium, diaryliodonium salts are green alternatives which have comparatively lower toxicity, can be used at room temperature, and are more environmentally conscious[4,6,8].

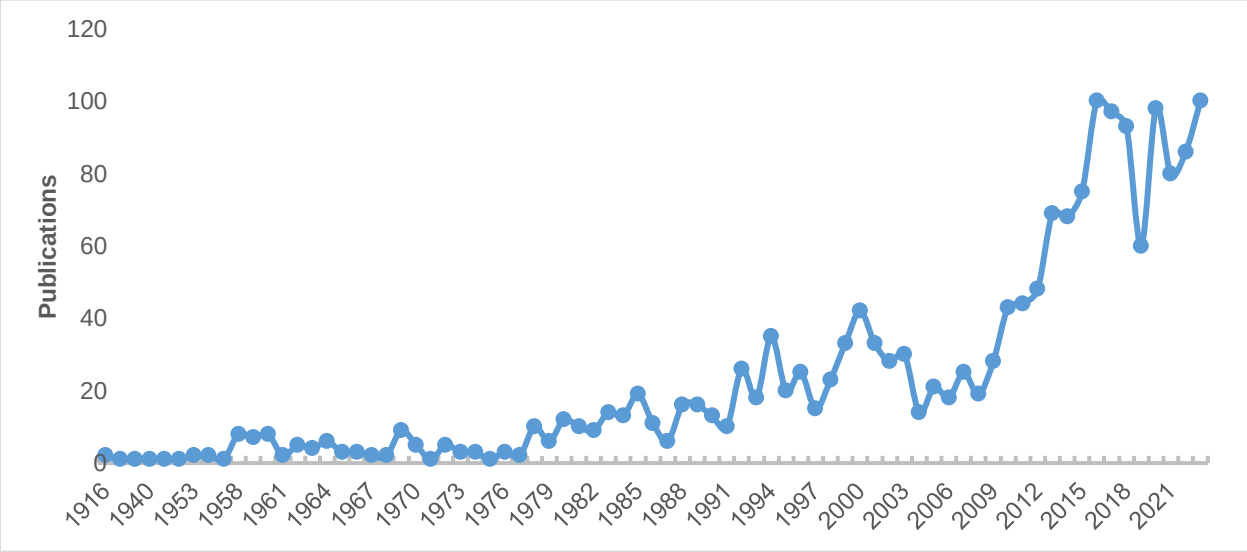


Figure 1: Diaryliodonium salt references in chemical literature[12].

Diaryliodonium salts are often used as reagents for organic transformations and are useful in transferring aryl groups to nucleophiles without the use of metal catalysis. Because of the importance of the iodonium center and the nucleophile engage in the formation of pre-association complexes, Lewis acidity has a large influence on the reactivity diaryliodonium

salts[9]. In recent years, interest in the applications of the Lewis acidity of iodonium ion catalysts has increased. A few research groups have made use of the Lewis acidity of iodonium ions as catalysts for diverse applications such as for Mannich reactions and for catalyzing Diels-Alder reactions[9]. Despite this, the quantification of the Lewis acidities of diaryliodonium ions are scarce. Some of the work that has been done focuses on the binding constants of small sets of diaryliodonium 18-crown-6 and for nitrogen heteroarenes with $Ph_2I^+BF_4^-$ [9]. However, there has not been much study into the Lewis acidities of zwitterionic diaryliodonium salts[10]. Zwitterionic diaryliodonium salts may be accessed through NH-arylation of imidazole[2]. In the case of Ph_2IOTf ion pairing, Ph_2I^+ and OTf^- as a counter anion plays a role in interpreting the Lewis acidity of the salt. For zwitterions, there is no counter anion that would come into consideration. Additionally, the bond angles seen between the phenyl and imidazole in the zwitterion is less than in diphenyl iodonium. This reduced bond angle suggests that an increase in p-character would increase the Lewis acidity in the imidazole zwitterion over diphenyl iodonium. Are diaryliodonium zwitterions stronger Lewis acids than the more common diaryliodonium salts?

The ability of these zwitterionic species to act as Lewis acids can be studied using an NMR titration experiment to determine their binding constant, K_b[5]. For studying molecules in a supramolecular chemistry context, binding constants can quantify the complexation between a host, the diaryliodonium of interest, and a guest, some Lewis base[5]. These 1:1 interactions between the host, H, and the guest, G, can be modeled using a simple equation (equation 1):

Equation 1: $H + G \overset{K_b}{\rightleftharpoons} HG$

Using further applications of related acid-base equilibria equations, a more practical equation based on the ^{1}H NMR ppm shift observed in a fast exchange system can be used for the purpose of quantifying K_b[5]:

Equation 2: $$\Delta\delta = \frac{\delta_{\Delta HG}}{[H]_0}\left(\frac{1}{2}\left\{\left([G]_0 + [H]_0 + \frac{1}{K_b}\right) - \sqrt{\left([G]_0 + [H]_0 + \frac{1}{K_b}\right)^2 + 4[G]_0[H]_0}\right\}\right)$$

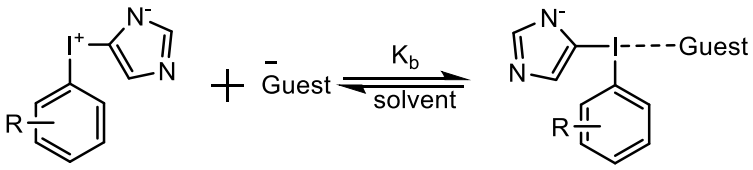
This equation is particularly useful for quantifying the binding of the zwitterionic species because it leaves only one unknown variable, K_b. Thus, this equation allows one to quantify the change in physical property which accompanies the formation of the host-guest complex. Known initial concentrations of host, $[H]_0$, and guest, $[G]_0$, are dissolved in a solvent with varying ratios. In this equation, the observed NMR resonance (δ) is the weighted average of the bound HG and unbound H species. Using Δδ between titrations containing no guest and those containing varying concentrations of guest, the change in physical property can be defined[5]. All that is left is to solve for K_b using the Solver function in Excel.

Methodology:

To study the Lewis acidity of the zwitterion diaryliodonium species, the iodonium salts of interest were synthesized based on existing procedures[1,2,11]. The zwitterion species are not commercially available and must be synthesized through multiple steps which give isolated products. The procedure to synthesize diacetoxy iodoarene species can be done in just ten minutes at room temperature with sodium hypochlorite pentahydrate and glacial acetic acid (Scheme 1). The penultimate procedure was for the overnight synthesis of the imidazole aryl iodonium acetate where the iodine has an acetyl counter anion (Scheme 2). Finally, the procedure for the synthesis of the zwitterionic species of interest is done in a water suspension starting from the imidazole aryl iodonium acetate precursor (Scheme 3).

The syntheses were conducted under varying reaction conditions detailed across multiple general procedures for the goal of isolating the zwitterionic salts. Upon the completion of the procedure, the salts were thoroughly dried, and their structures were confirmed by comparison of ^{1}H NMR spectra to literature. Further, the solubility of the isolated zwitterionic salts were taken in multiple solvents including chloroform, dichloromethane, and acetonitrile.

The resultant ^{1}H NMR chemical shifts are used to calculate their binding constants to determine their effectiveness as a Lewis acid. The equilibrium equation which can be used to model the binding of the host and guest in the binding study is based on the 1:1 fast exchanging equilibrium system in Equation 1 as Binding Scheme 1:



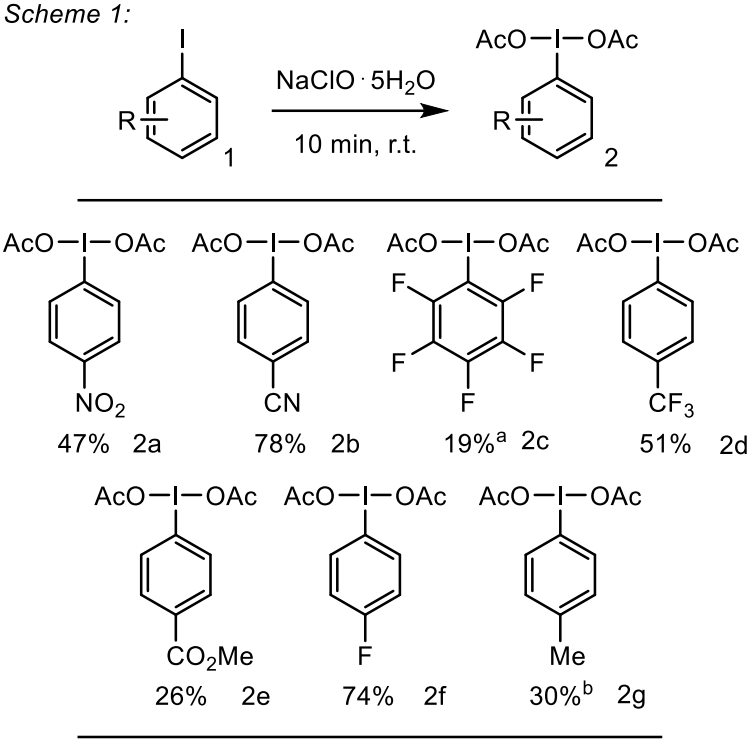
Binding Scheme 1: This is a rewriting of equation 1 with imidazole aryl iodonium zwitterion binding with some base (Guest).

The binding studies were performed by producing twelve different titrations of imidazole aryl iodonium species (Host) and a DABCO (Guest), a Lewis base. The titrations were produced by creating stock solutions of host and guest with deuterated solvents and micro-pipetting precise volumes of solution into NMR tubes. The concentration of the host remained constant across the twelve titrations while the guest was changed by varying equivalences from: 0, 0.1, 0.2, 0.5, 0.7, 1, 1.5, 2.5, 5, 10, 15, and 20. The volume of each tube was adjusted by addition of more deuterated solvent to afford equal total volumes of solvent in each tube. The tubes are promptly capped to reduce dissipation which would affect concentrations of the host and guest.

The twelve titrations result in twelve different ^{1}H NMR spectra. The aromatic peaks with the greatest shift were recorded and a nonlinear regression was performed using the Solver add-in in Excel. The function affords a K_b value and a plot of $\Delta\delta$ vs. guest concentration. The binding studies were performed such that the host concentration fell between one to two orders of magnitude from the millimolar (mM) region to allow for a better calculation of the binding constant[5]. As such, if the salt of interest does not readily solubilize in the specific concentration range, the binding study could effectively be scrapped.

Table 1. Synthesis of diacetoxy iodoarene

Scheme 1:



Reaction conditions: General procedure 1 for diacetoxy iodoarene where iodoarene (10 mmol) with $NaClO \cdot 5H_2O$ (1 eq.) and glacial AcOH (7.5 mL), r.t., air, 10 min; [a]Slight modification of general procedure 1 where $NaClO \cdot 5H_2O$ (2 eq.) was used; [b]General procedure 2 for diacetoxy iodoarene where AcOH (3 eq.) in MeCN (7.5 mL) was used; All ^{1}HNMR spectra was recorded in $CDCl_3$.

General Procedure 1 (without solvent) for synthesizing diacetoxy iodoarenes:

Diacetoxy iodoarene was prepared using a known literature procedure[1]. To a 20 mL vial with vigorously stirring $NaClO{\cdot}5H_2O$ (10mmol, 1 eq.), iodoarene (10 mmol, 1 eq.) and glacial AcOH (7.5 mL) was added at room temperature under air. The mixture was stirred for 10 minutes. DCM (~20 mL) was added to the mixture to precipitate NaCl and other solids. The mixture was vacuum filtered and washed several times with DCM. The filtrate solvent was evaporated under reduced pressure using a rotary evaporator to give a solid. The solid was washed several times with hexanes and vacuum filtered to give diacetoxy iodoarene. Further

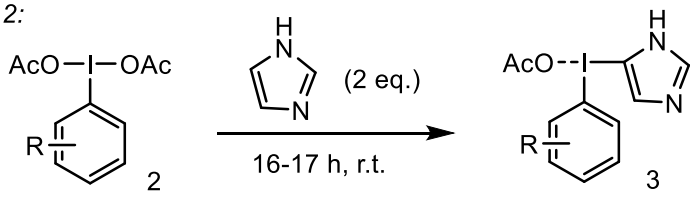
purification can be achieved by redissolving in DCM and re-triturating with hexanes a second time.

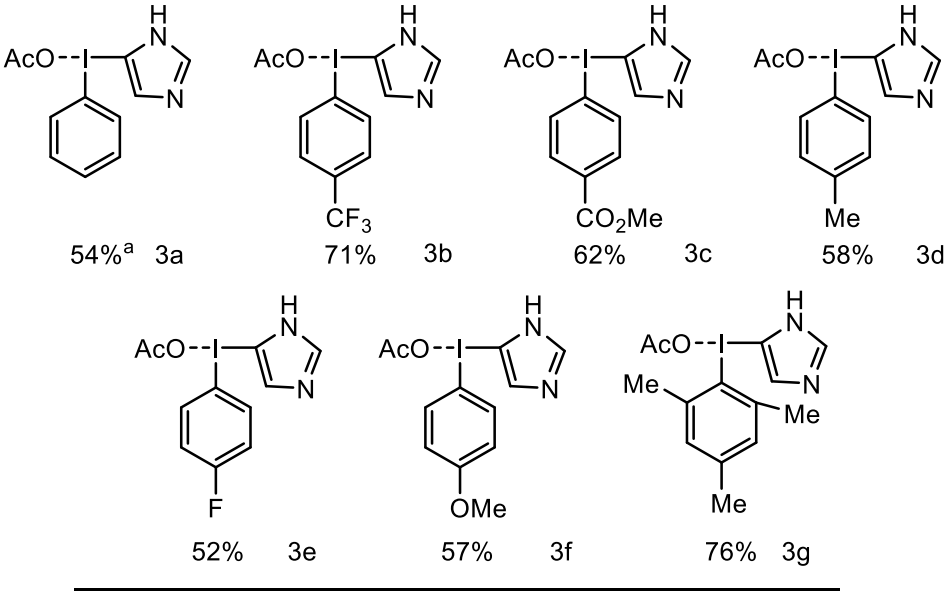
General Procedure 2 (with solvent) for synthesizing diacetoxy iodoarene:

Diacetoxy iodoarene was prepared using a known literature procedure[1]. To a 20 mL vial containing a vigorously stirred mixture of $NaClO{\cdot}5H_2O$ (10mmol, 1 eq.) in either MeCN or DCM (7.5 mL), iodoarene (10 mmol, 1 eq.) and AcOH (1.715 mL, 30 mmol) was added at room temperature under air. The mixture was filtered under vacuum and washed several times with DCM. The filtrate solvent was evaporated under reduced pressure using a rotary evaporator to give an off-white solid (generally pale yellow). The solid was washed several times with hexanes and filtered over vacuum to give diacetoxy iodoarene. Further purification can be achieved by redissolving in DCM and re-triturating with hexanes.

Table 2. Synthesis of imidazole aryl iodonium acetate

Scheme 2:





54%[a] 3a | 71% 3b | 62% 3c | 58% 3d

52% 3e | 57% 3f | 76% 3g

Reaction Conditions: General procedure 1 for imidazole aryl iodonium acetate where diacetoxy iodoarene (2.5 mmol) and imidazole (2 eq.) added after 5 min in MeOH (2.5 mL), r.t., air, 16-17 h; [a]General procedure 2 for imidazole aryl iodonium acetate where diacetoxy iodoarene (2.5 mmol) and imidazole (2 eq.) in MeCN (7.5 mL), r.t., N_2 atmosphere, 17 h; All ^{1}HNMR spectra was recorded in MeOD.

General procedure 1 for synthesizing imidazole aryl iodonium acetate:

Imidazole aryl iodonium acetate was prepared using a modification to known literature procedures[2,11]. To a round bottom containing vigorously stirred MeOH (2.5 mL), diacetoxy iodoarene (2.5 mmol, 1 eq.) is added at room temperature under air. The mixture is allowed to stir for 5 minutes. To the stirred suspension, imidazole is added (5 mmol, 2 eq.). The mixture was allowed to stir overnight (16-17 hours) at room temperature under air. After 16-17 hours had elapsed, the solvent was removed under reduced pressure. To the residue MeCN (~20 mL) was

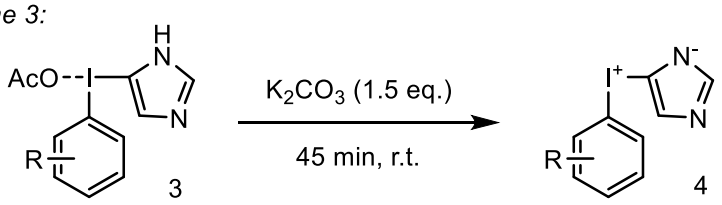
added and allowed to stir for 1-2 hours at room temperature under air until precipitate forms. The solid was filtered and washed with MeCN several times and dried under vacuum filtration to give imidazole aryl iodonium acetate.

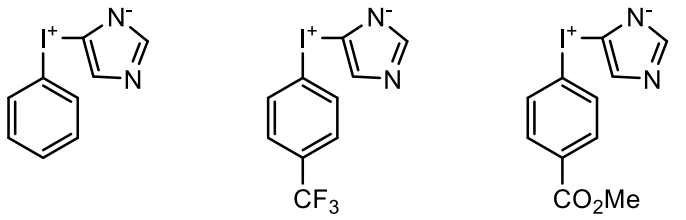
General procedure 2 for synthesizing imidazole aryl iodonium acetate:

Imidazole aryl iodonium acetate was prepared using a known literature procedure[2]. A round bottom flask was charged with a stir bar, diacetoxy iodoarene (2.5 mmol) and imidazole (5 mmol, 2 eq.). The flask was flushed with N_2 and MeCN (7.5 mL) was added, and the mixture was allowed to stir at room temperature overnight for 17 h. The mixture slowly accumulated a white precipitate. After 17 h had elapsed, the solid was filtered and washed several times with MeCN and DCM. The solid was dried under vacuum filtration to give imidazole aryl iodonium acetate.

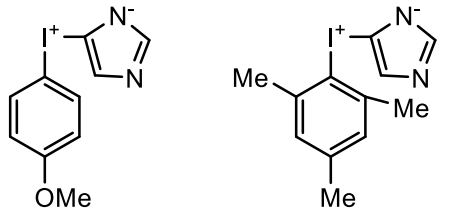
Table 3. Synthesis of imidazole aryl iodonium zwitterion

Scheme 3:





79% 4a 18% 4b 31% 4c



4% 4d 46% 4e

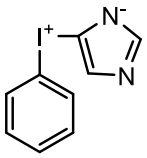
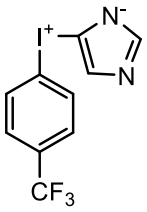
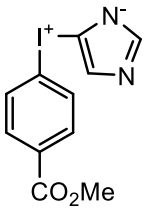
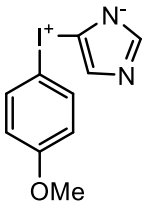
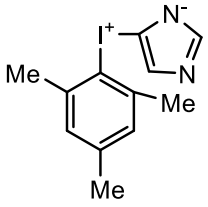
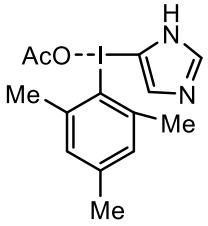
Reaction Conditions: General procedure for imidazole aryl iodonium zwitterion where imidazole aryl iodonium acetate (1 mmol) and K_2CO_3 (2 eq.), r.t., air, 45 min; ^{1}HNMR spectra were recorded in either MeOD or $CDCl_3$.

General Procedure for synthesizing imidazole aryl iodonium zwitterion:

Imidazole aryl iodonium zwitterions were prepared using a known literature[2]. To a stirred suspension of iodoarene imidazole acetate (1 mmol) in water (1.6 mL), K_2CO_3 (1.5 mmol, 1.5 eq) was added at room temperature under air. The mixture was allowed to stir for 45 minutes. The precipitate was washed with water several times, vacuum filtered and allowed to air dry to give imidazole aryl iodonium zwitterion. For ease of isolation, the filtrate flask may be exchanged for a clean flask after thorough air drying of solid. The solid was washed several

times and allowed to dissolve with MeOH into the filtrate flask. The filtrate solvent was evaporated under reduced pressure to give an off white solid.

Table 4. Solubility of imidazole aryl iodonium (mM)

imidazole aryl iodonium		$CHCl_3$	DCM	MeCN	MeOH
	4a	0.07	0.01	0.1	>10
	4b	<1.25	<1.25	n.d.	>10
	4c	<0.625	<0.625	<0.625	>10
	4d	n.d.	n.d.	<<2.5	>10
	4e	2	n.d.	n.d.	>10
	3g	4	n.d.	n.d.	>10

This table details the tested solubilties of synthesized species as candidates for determining binding. The values listed in the columns are represented as the lowest concentration (mM) observed in different solvents. Each test involved measuring an appropriate mass of salts to be dissolved in solvents (1 mL). N.d. label means that the solubility was not determined for that solvent.

Results:

The solubilities of the salts were determined through a simple process and began from a starting concentration of 20 mM. An appropriate amount of salt was placed into a test tube and 1 mL of solvent was added. The volume of solvent was adjusted by addition of 50 μL until the solution became clear, was free from particulates, and solid did not settle to the bottom over time. The aim was for a solubility between 1-10 mM. If the salt solubilized at too low of a concentration to effectively determine a K_b, the binding study was not followed through with. The solubilities of the zwitterionic species were catalogued in Table 4. Favorable solubility was aided by a fixed speed vortexer and/or a sonicator device.

The solubility of the unsubstituted **4a** was quite low in the target solvents. However, it did dissolve well in methanol. Methanol could not be used to test the titrations and thus determine the binding constant because it competitively interacted with Lewis acids in solution. Because the goal was to find any of those three solvents (chloroform, dichloromethane, and acetonitrile), it was not necessary to further test solubility in other solutions if it had already been determined to have favorable solubility. Subsequently, solubility testing of all zwitterions aside from **4e** and **3g** resulted in solutions which persistently precipitated. **4e** and **3g** appeared to have a low, yet favorable, solubility in chloroform which resulted in a slightly yellow clear solution free or particulates. However, these two both appeared to require time to dissolve upwards of 20 minutes. Particles which appeared **4d** was perhaps the most visually remarkable of these low solubility zwitterions as it remained an opaque milky white seemingly no matter how dilute the solution became.

Binding studies were parallelly attempted for **4e** and **3g** with DABCO in deuterated chloroform. The resultant calculations for K_b yielded data which could not be conclusively

quantified. The ongoing solubility issue may have contributed to the difficulty producing conclusive data near to the end of the project timeline. Ultimately, there was naught time to remedy the issue or to try the other solvents. Overall, solubility was a major obstacle.

Future Directions:

The zwitterionic species still leave much to be investigated and the results were lacking due to the complications mostly arising from lack of solubility of many of the zwitterionic species. By adjusting the temperature some of the zwitterionic species may become soluble in a high enough concentration to do binding studies in the solvents used. The substituted zwitterionic species do not appear in literature and are therefore novel. Their physical properties had not been determined prior to this project and it was difficult to predict whether they would be viable. With further research, these novel salts can be fully categorized. More of these zwitterionic species could be synthesized and subsequently tested for binding.

It would be useful to see which types of substituents and what positions on the ring opposite the imidazole lend themselves most to binding, whether they be electron donating groups or electron withdrawing groups. Considering the spotty solubility, the imidazole zwitterions may have a lower binding than when there is a counter anion to the iodine. Additionally, the position of the negative charge on the imidazole could be affecting the binding. The charge on the nitrogen may go through resonance structures which act similarly to an ylide between the imidazole ring and the iodine. Further, the imidazole can be changed to a different nitrogen heterocycle, for example pyrazole. There are also cyclic diaryliodonium species which have zwitterions which may have a higher solubility or greater Lewis acidity. Diaryliodonium zwitterions have a vast potential for being effective Lewis acid reagents for building further

complexity. Continuing to explore this avenue of diaryliodonium chemistry is important and the areas of research open at this stage are quite large.

References:

(1) Watanabe, A.; Miyamoto, K.; Okada, T.; Asawa, T.; Uchiyama, M. Safer Synthesis of (Diacetoxyiodo)Arenes Using Sodium Hypochlorite Pentahydrate. *J. Org. Chem.* **2018**, *83* (23), 14262–14268. https://doi.org/10.1021/acs.joc.8b02541.

(2) Wu, Y.; Izquierdo, S.; Vidossich, P.; Lledós, A.; Shafir, A. NH-Heterocyclic Aryliodonium Salts: Synthesis and Access to N1- Aryl-5-Iodoimidazoles. *Angew. Chem. Int. Ed.* **2016**, *55*, 7152–7156. https://doi.org/10.1002/anie.201602569

(3) Merritt, E. A.; Olofsson, B. Diaryliodonium Salts: A Journey from Obscurity to Fame. *Angew. Chem. Int. Ed.* **2009**, *48* (48), 9052–9070. https://doi.org/10.1002/anie.200904689.

(4) Aradi, K.; Tóth, B.; Tolnai, G.; Novák, Z. Diaryliodonium Salts in Organic Syntheses: A Useful Compound Class for Novel Arylation Strategies. *Synlett* **2016**, *27* (10), 1456–1485. https://doi.org/10.1055/s-0035-1561369.

(5) Thordarson, P. Binding Constants and Their Measurement. In *Supramolecular Chemistry*; Gale, P. A., Steed, J. W., Eds.; Wiley, 2012. https://doi.org/10.1002/9780470661345.smc018.

(6) Villo, P.; Olofsson, B. Arylations Promoted by Hypervalent Iodine Reagents. In *Patai's Chemistry of Functional Groups*; Wiley, 2018; pp 1–61. https://doi.org/10.1002/9780470682531.pat0950.

(7) Seidl, T. L.; Stuart, D. R. An Admix Approach To Determine Counter Anion Effects on Metal-Free Arylation Reactions with Diaryliodonium Salts. *J. Org. Chem.* **2017**, *82* (22), 11765–11771. https://doi.org/10.1021/acs.anionjoc.7b01599.

(8) Stuart, D. R. Aryl Transfer Selectivity in Metal-Free Reactions of Unsymmetrical Diaryliodonium Salts. *Chem. Eur. J.* **2017**, *23*, 15852–15863. https://doi.org/10.1002/chem.201702732.

(9) Mayer, R. J.; Ofial, A. R.; Mayr, H.; Legault C.Y. Lewis Acidity Scale of Diaryliodonium Ions toward Oxygen, Nitrogen, and Halogen Lewis Bases. *J. Am. Chem. Soc.* **2020**, *142* (11), 5221–5233. https://doi.org/10.1021/jacs.9b12998

(10) Montgomery, C. A.; Murphy, G. K. Exploring the Role of Halogen Bonding in Iodonium Ylides: Insights into Unexpected Reactivity and Reaction Control. *Beilstein J. Org. Chem.* **2023**, *19*, 1171–1190. https://doi.org/10.3762/bjoc.19.86.

(11) Antonkin, N. S.; Vlasenko, Y. A.; Yoshimura, A.; Smirnov, V.I.; Borodina, T.N. Preparation and Synthetic Applicability of Imidazole-Containing Cyclic Iodonium Salts. *J. Org. Chem.* **2021**, *86* (10), 7163–7178. https://doi.org/10.1021/acs.joc.1c00483.

(12) Based on a May 24, 2024 SciFinder search for “diaryliodonium salts”.