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Monolignol lithium cation basicity estimates and lithium adduct ion optimized geometries

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ABSTRACT

Mass spectrometric analysis of lignin for developing biomaterials requires advances of characterization techniques. Positive ion mass spectrometry of lignin model compounds using lithium has recently been explored as a viable alternative to current negative mode techniques. To date, little is known about the impact of lithium adduct ion formation on relative response factors of lignin and lignin decomposition products. In this contribution, we report estimates of lithium cation basicity for synthetic monolignols H, G and S using Cooks' kinetic method on a linear quadrupole ion trap mass spectrometer. Optimized geometries and interaction energies have also been calculated by DFT methods to quantify the electrostatic cation coordination. Based on a combination of experimental and computational evidence, lithium appears to preferentially bind to the phenol and methoxy substituents on the aromatic ring of monolignols. The strength of this interaction increases with the number of methoxy substituents (S > G > H). This work serves as a basis of understanding for future work in developing lithium adducted lignin mass spectrometric analytical methods.

1. Introduction

Biomass is an abundant carbon-neutral resource for the production of bioenergy and biomaterials which has renewed interest in lignin chemistry for the generation of biofeuls [1,2]. Lignin is the most abundant carbon source on earth after cellulose and contains highly functionalized aromatic units that make it a potential source for the production of aromatics [3,4]. The processing of plant materials such as lignin into bio-derived materials and fuels requires the development of characterization techniques for analysis of degradation products [1,4]. Currently the largest challenge in this field is the structural elucidation of lignin oligomers and the ensemble of phenolic compounds for lignin biosynthesis [2].

There are various methods that reveal the details of lignin structure which focus on frequency of monolignols and main bond types [5]. The lignin polymer is composed of three aromatic ring types or monolignols H, G, and S (Fig. 1). These aromatic ring types are derived from the dominant monomers p-coumaryl alcohol (H, hydroxyphenyl), coniferyl alcohol (G, guaiacyl) and sinapyl alcohol (S, syringyl) [6,7]. Tandem mass spectrometry is the only analytical method for structural determination of complex mixtures of this polymer without extensive purification, and is one of the principle tools used for lignin characterization [2,6,8]. While mass spectrometric analysis provides information about the structure of lignin compounds, standard positive-ion or negative-ion mode analysis of lignin degradation products is hindered by poor ionization efficiency and extensive fragmentation which prevents the assignment of molecular weights [2,7,9]. The negative ion mode is slightly more successful and usually preferred because it is more sensitive to phenolics than the positive ion mode [9,10]. However, recently Haupert et al. demonstrated that positive ion mode electrospray ionization (ESI) is significantly more successful with the addition of sodium cations resulting in the formation of abundant adduct ions and limiting fragmentation [2,4].

The addition of alkali metal cations such as sodium makes positive-mode ESI of lignin an effective ionization technique due to the electrostatic interaction between the cation and lignin monomers [2,6]. Although sodium adducts are successful in ionizing lignin model compounds such as ß-O-4′ dimers, Asare et al. discusses the limitations in tandem mass spectrometry. In the analysis of ß-O-4′ dimers with sodium, only the fragment ion for the "B ring" sodium adduct of the dimer is observed in the tandem spectrum and no other structurally informative ions are observed

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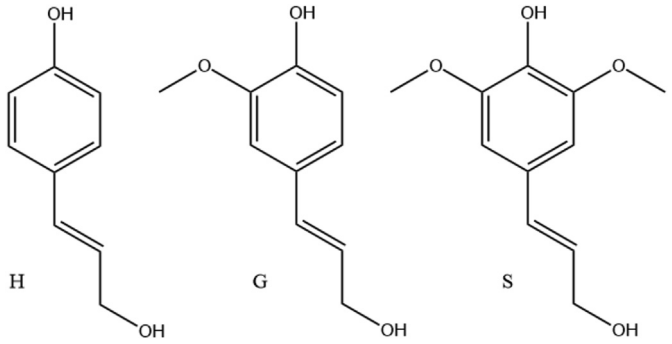

Fig. 1. Basic structure of monolignols H, G and S.

[11]. However, the tandem mass spectrometry of lithium adducted dimers shows fragment ions of both the A and B ring [11]. Therefore, the use of lithium for alkali metal cationization is the most promising for lignin analysis by mass spectrometry.

We will consequently focus on the tandem mass spectrometry of lithium cationized lignin because it allows for analysis of oligomers in the positive mode [11]. Adduct formation is improved by the more efficient binding of Li^+ due to its small ionic radius, high charge density, and shorter oxygen-cation binding distance [6,12]. One way to quantify the interaction of the Li^+ with monolignols is by experimental determination of the lithium cation basicity (LCB).

Computations of lithium cation affinity (LCA) have previously been directly compared to experimental results of gas-phase LCB measurements [13]. Empirical determinations of lithium interactions are referred to as lithium cation basicity, while computational work to deduce the energy change upon a lithium interaction is referred to as lithium cation affinity. Due to the complexity of the monolignol systems and multiple sites of chelation, the calculated lithium affinity at isolated positions cannot be directly associated to experimentally determined LCB. Instead, the electrostatic interaction energy at the primary and most stable coordination points will be compared across monolignols H, G and S to elucidate molecular characteristics that have the largest impact on experimental LCB. Energy calculations of cation-pi interactions with alkaline earth cations using DFT optimizations have been studied extensively and will be applied for the theoretical determination of electrostatic interaction energy [12,14]. Computational predictions of primary binding motifs of lignin dimers with Li^+ have been reported, and will be applied to predict the most probable locations of alkali metal coordination [6]. In the more complex monolignol systems, this computational theory will elucidate strength of coordination for the cation-pi, dipole, and coulomb interactions of H, G and S with a lithium cation [12,15].

Here we present LCB measures of synthetic monolignols H, G and S by Cooks' et al. kinetic method on a linear quadrupole ion trap mass spectrometer (LTQ). The kinetic method uses gas-phase transfer equilibrium and rates of competitive dissociation of a mass-selected cluster ion to provide information on the electrostatic behavior of chemical compounds [16–18]. The LCB findings will be supplemented by quantum chemical computations of the interaction or electrostatic energy using density functional theory (DFT) to optimize the geometry of the lignin monomers and study trends in the strength of electrostatic interactions for comparison with experimentally determined lithium cation basicity [19,20]. This work will begin to address if the location of a lithium cation and its high charge density explains the retention of sequencing features in tandem MS, and how LCB may be impacting response factor. From computational results we will also propose the most probable coordination positions for each monolignol.

2. Materials and methods

2.1. Mass spectrometry methods of lithium cation basicity determination

The synthesis of the monolignols has been reported previously [21].

Lithium Cation Basicity determination was carried out by a ThermoScientific LTQ linear ion trap mass spectrometer (ThermoScientific, Waltham, MA, USA) in the positive-ion mode equipped with an ESI source. The sample was infused directly for MS/MS analysis. First the instrument was tuned to optimize the signal of the monolignol lithium adduct ions. The best signal for H, G and S lithium adducts was obtained with the instrument operating at a spray voltage of 4.0 kV, sheath gas flow of 4.0, capillary voltage of 45.0 V and temperature of 250 °C, and tube lens charge of 78.0 V. This tune method was applied for all subsequent experimentation.

The validity of the kinetic method in our laboratory was evaluated by carrying out experimentation on references treated as unknowns. Isophorone with an LCB in the expected range for the G monolignol was treated as an unknown. Reference compounds including 1,2-dimethylimidazole, glycine and pyridazine were chosen to bracket the expected LCB of isophorone. A solution that consisted of 0.3 mg/mL isophorone, 0.3 mg/mL reference, 3.3 mM LiCl and was approximately 50% aqueous, 50% MeOH was directly infused. The $[B + Ref + Li^+]$ complex was isolated and fragmented by CID with collision energies appropriate to retain ~30% of the precursor ion (typically 15–25% normalized collision energy, NCE). Data was acquired and analyzed using the ThermoScientific Xcalibur software (ThermoScientific, Waltham, MA, USA) and a minimum of 70 scans were averaged to find the abundance of the lithiated reference and monolignol. The experimental LCB by the kinetic method was then compared with the reported value.

Further method validation was performed by determining the LCB of cysteine, isoleucine and S monolignol with the structurally unrelated compound trimethylphosphine oxide as a reference. The tune method was applied, and solutions were prepared at 0.05 mg/mL trimethylphosphine oxide and 0.5 mg/mL 'unknown' of cysteine, isoleucine or S. The solution was adjusted to 50% aqueous, 50% MeOH and 5 mM lithium chloride.

The above tune method was applied to each lithium bound cluster ion of monolignol and reference. For electrostatically bound cluster ions that were difficult to isolate, the tune method was held constant and the concentration of reference and monolignol in solution was varied to improve complex formation and electrospray efficiency. The monolignol of interest was prepared in methanol and the reference compounds in water or methanol depending on their solubility. References for S include proline, isoleucine and cysteine; for G include glycine, 1,2-dimethylimidazole, and methylimidazole; and for H include dimethyl isophthalate, methyl benzoate and 3-methylpyridine. Generally, isolation of S complexes was successful at a final concentration of 0.2 mg/mL S and 0.4 mg/mL reference, G complexes at 0.4 mg/mL G and 0.2 mg/mL reference, and H complexes at 0.4 mg/mL H and 0.2 mg/mL reference. All solutions were adjusted when needed to approximately 50% aqueous, 50% MeOH and 5 mM LiCl.

All investigated complexes were fragmented with a CID setting of typically 15–25% NCE. The CID setting was plotted vs. the natural log of the ratio of unknown to reference to quantify the dependence of fragmentation on the degree of excitation (equation (3)). The slope of this plot is the T_{eff} value. An average of at least five ratios of unknown to reference at corresponding CID were averaged to calculate the change LCB (kcal/mol) using the corresponding $1/RT_{eff}$ factor (equation (3)). The change was then applied to the known reference LCB to estimate the lithium cation basicity of the

unknown component of the selected cluster ion. A linear least squares regression of reference LCB vs. observed change was performed to evaluate the error in estimated LCB of unknowns.

2.2. Quantum chemical computations

All calculations were done using Gaussian 09 on a DLX supercomputer cluster. The study considered optimized structures of H, G and S monolignols and their interactions with Li^+ cations. Multiple Li^+ starting points for each monolignol were chosen based on previous reports of Lithium coordination tendencies [6,22,23]. The positions were first optimized using a classical molecular mechanics method with a UFF force field, then using a quantum chemical ab initio density functional theory with B3LYP functional and a 6311G + basis set [6]. The DFT computations provided three primary lithium coordination patterns consistent across all three monolignols.

The three primary coordination motifs were further optimized using DFT/B3LYP methods with increasing basis sets to improve results including 6311G+(d,p) and 6311G+(2d,2p) [24]. Each monolignol independent of lithium and a lithium ion were similarly optimized for subsequent calculations. After optimization, the vibrational frequencies were calculated at the same level to ensure there were no imaginary frequencies and that the computation had reached a true minimum [14].

Optimization energies of the monolignols and the monolignols coordinated by lithium were then used to calculate the interaction energy of the three lithium coordination motifs. The interaction energy or lithium cation affinity of H, G and S was calculated by subtracting the energy of the monolignol and lithium ion from the total energy of the $[monolignol\text{-}Li]^+$ complex [12,14]. Zero point energy (ZPE) correction was also calculated with the corresponding method [14]. The ZPE was added to the interaction energy to determine a final interaction energy estimation. No corrections for basis set superposition error (BSSE) were made due to previous reports that BSSE corrections are negligible for lithium cation affinity calculations [13,25].

3. Theory

3.1. Kinetic method

The gas-phase lithium cation basicity is defined as the negative of the Gibbs free energy associated with the reaction:

$$B_{(g)} + Li^+_{(g)} \rightarrow B - Li^+_{(g)} \quad (1)$$

Using the kinetic method, the LCB is determined by the rates of competitive dissociation of a mass-selected cluster ion [16,17]. Lithium cations can form chelate clusters by coordinating to two or more basic centers easily, because of the flexible nature of the electrostatic interaction and the long optimum Li^+ to base distance [18,26]. The cluster is composed of a reference compound, the compound of interest, and the ion to which binding occurs. For LCB determination of monolignols (H, G, and S) the cluster will consist of a monolignol (B), Li^+, and reference (Ref) with known LCB. Assuming the reference compound is structurally similar to the compound of interest and there is no reverse activation energy, dissociation of the mass selected cluster gives rise to two ions via two competitive dissociation pathways [17].

$$[BLiRef]^+ \begin{matrix} \nearrow\ [BLi]^+ + Ref \\ \searrow\ [B]^+ + LiRef \end{matrix} \quad (2)$$

The competitive dissociation occurs from a common ion, therefore the logarithm of the ratio of rate constants can be expressed as [16,26]:

$$ln\frac{k_B}{k_{Ref}} = \ln\left[\frac{BLi^+}{RefLi^+}\right] \approx \frac{\Delta LCB}{RT_{eff}} \quad (3)$$

Where T_{eff} is the effective temperature or an indication of the degree of excitation of the complex that undergoes competitive fragmentation [17]. Reference bases were chosen during preliminary experimentation that roughly estimated an expected LCB range for each monolignol and three bases were chosen based on their reported LCB to best bracket the unknowns [18].

Analysis was carried out on a ThermoScientific LTQ linear ion trap mass spectrometer in the positive-ion mode with an ESI source. Previous studies have debated the use of ion traps for the kinetic method due to gas-phase interactions of the adduct ions with water left over in the trap that could alter the observed ratio of ions via the competitive dissociation of the activated cluster [27]. Despite these claims, some of the original work by Cooks et al. was performed on a quadrupole ion-trap mass spectrometer, therefore we expected the LTQ mass spectrometer to provide adequate data [28].

The shortcomings of Cooks' kinetic method are extensively discussed in Armentrout's commentary on the use of the kinetic method as a thermodynamic method [29]. The most apparent inadequacy of Cooks' kinetic method according to Armentrout is that T_{eff} should not be considered a thermodynamic quantity which reflects a Maxwell-Boltzman distribution because it varies from cluster to cluster, depends on relative enthalpies for competitive dissociations, and is impacted by experimental parameters [29]. While we recognize T_{eff} as a measurable perturbation, the impact of T_{eff} on the estimation of LCB by the kinetic method does not have an apparent effect on the experimental results. The kinetic method is dependent on the accuracy of the reported LCB of the reference compounds, and this error masks any impact of T_{eff} in the experimentally determined value.

It is also important to note that the kinetic method relies on the assumption that the competing dissociations involve species that are chemically similar so that entropic effects can be considered negligible [17,29]. However, since there are very few compounds that are structurally similar to the monolignols with LCBs in the appropriate range, the reference bases are comparable, but only chemically similar in some respects [26]. To ensure that the method still holds in the case of the dissociation of a cluster composed of somewhat dissimilar species, multiple validity tests were performed. The effect of using a reference compound that is very structurally different from the unknown is also investigated in the LCB range of the S monolignol using trimethylphosphine oxide. By understanding the possible entropic contributions when using dissimilar compounds, we can more comprehensively represent the accuracy of our LCB estimations.

3.2. Computational methods

Density functional theory has been used to study the structure and thermodynamic properties of the interaction between lithium cation and neutral bases due to previous reports that DFT methods are appropriate for aromatic systems with electrostatic interactions like the monolignol-Li^+ complex [30]. Then the interaction energy (ΔE_{int}) is calculated by optimizing structures and subtracting the energy of monomers from its complex [12,14]. For computations of the lithium cation affinity and electrostatic interaction energy, the most common methods used are ab initio MP2 or DFT methods [13,24,30]. To reproduce experimentally measured LCB values, it has been reported that inclusion of electron correlation effects and the use of sufficiently large polarized diffuse split-valence basis sets

is required [30]. Rodgers et al. provides an extensive evaluation of theoretical computations of lithium cation affinity, effected by computationally challenging perturbations of the ligands due to lithium's high charge density and short metal-ligand bond lengths [24]. The short metal cation-ligand binding distance allows for the interaction of closed-shell core electrons that can be relieved if the core electrons are permitted to polarize and correlate [24]. Therefore the most appropriate method for LCA calculation is the intensive MP2(full)/aug-cc-pVTZ(Li–C)//MP2(full)/cc-pVDZ(Li–C) approach [24].

However, the focus of the computational portion of this research is to show general coordination motif trends based on stability of the primary chelation positions. Since we are not attempting to estimate LCB with these computations, DFT methods are sufficient. Among the simpler approaches, multiple sources including Rodgers et al. confirm that DFT B3LYP gives the best results for LCA/LCB and interaction energy computations and is therefore suitable for this study [13,24,25,30].

4. Results and discussion

4.1. Lithium cation basicity

Using Cooks' kinetic method, the monolignols H, G and S were each evaluated by three reference compounds to determine their relative lithium cation basicity's. The values reported in Table 1 were obtained using tandem MS and CID to dissociate each electrostatically bound cluster and produce a ratio of monolignol to reference. The uncertainty of the average LCB is calculated by a linear least squares regression and the overlap of values is reasonable for the estimated LCB of H, G and S monolignols. There is approximately an 11% increase with each methoxy addition, which suggests that the lithium cation basicity of these hydroxyphenyl based compounds is highly dependent on the number of methoxy groups on the aromatic ring.

The isolation of H, G and S under the established tune method was successful with LTQ tandem mass spectrometry (Fig. 2). A CID energy of only 15–25% NCE is necessary to dissociate these electrostatically bound clusters, producing the two competitive ions of dissociation almost exclusively and limiting fragmentation. In some cases, a higher CID setting was required, and other fragments were observed, but the additional fragmentation did not appear to have an impact on the observed ratio. As discussed in the methods, at times one component had more affinity for Li^+ or was more successfully ionized under the electrospray conditions and aqueous percentage. Accordingly, the concentration of one component was adjusted to force complex formation and improve signal. In some cases, it was also challenging to isolate the cluster exclusively. When a higher CID setting was necessary for fragmentation, it was evident that there was more than one compound under the selected m/z and isolation window. The window was adjusted for the best isolation in a range of 1–3 (arbitrary units) until the fragments produced were primarily representative of the electrostatically bound cluster ion.

In addition to primarily producing the two competitive ions of dissociation, the spectra also reveal very few interactions between the adduct ions and neutral water in the trap (Fig. 3). The addition of water to the lithiated adduct ions impacts the ratios of monolignol to reference. However, the impact of interactions is well within the LCB margin of error. As an example, the effect of water addition has been calculated for the $[S + Ile + Li]^+$ (m/z 348) complex dissociation (Fig. 3). The relative proportion of hydrated adduct ions was minimal compared to the desired ion dissociation.

When the addition of hydrated ions is included in the ratio of monolignol to reference for S and Isoleucine, there is a 0.02 kcal/mol increase in the calculated LCB of S which is well within the associated error implying the impact of the addition of water in the trap is insignificant. With effective isolation of the desired complex, secondary fragmentation at the low CID energy used and addition of water or other gas-phase interactions in the trap are consistently negligible.

To evaluate the accuracy of the lithium cation basicity, a linear least squares (LLS) regression fit was performed. The relationship between reference LCB and the change in LCB calculated by the natural log of the ratio of unknown to reference (equation (3)) is linear and can be evaluated by LLS. The uncertainty was most likely largest for the H monolignol because the reference compounds cover a small LCB range of 1.05 kcal/mol compared to references used for the LCB determination of G and S which cover a range of 1.6 kcal/mol and 2.3 kcal/mol respectively. To further evaluate the accuracy of our estimation we experimentally determined the LCB of isophorone for comparison with the published value because it falls in the middle of the investigated LCB range for the monolignols. As depicted in Table 2, the experimentally determined LCB of isophorone was within 0.1 kcal/mol of the reported value. We obtained the LCB using reference bases that are comparable in some ways but structurally dissimilar. Using dissimilar compounds to obtain an LCB analogous to the reported value for isophorone further validates this method and its application to the monolignols.

For H and G monolignols, a structural range of compounds was used for experimentation. Based on the results and the method validation using isophorone, the kinetic method provided an effective estimation of the lithium cation basicity. In the case of the S monolignol there are few compounds that are structurally comparable with published LCBs in the appropriate range, so we were only able to use amino acids as reference compounds. The results for H and G suggest our LCB determination of S is very reasonable

Table 1
Lithium Cation Basicity of Monolignols H, G and S. All values are reported in kcal/mol. The estimate LCB is an average of resultant LCB from each reference comparison [18]. *Entropic contributions and the error in the LCB of S monolignol is further investigated by trimethylphosphine oxide.

Compound (B)	Reference (Ref)	LCB Ref [18]	ΔLCB	LCB (B)	Estimate LCB
H	Dimethyl Isophthalate	37.55	−0.77	36.78	
	Methyl Benzoate	36.81	−0.04	36.77	36.9 ± 0.3
	3-Methylpyridine	36.50	0.67	37.18	
G	Glycine	41.60	−0.58	41.02	
	1,2-Dimethylimidazole	41.80	−0.28	41.52	41.0 ± 0.2
	Methylimidazole	40.20	0.36	40.56	
S	Proline	47.50	−0.96	46.54	
	Isoleucine	45.30	0.38	45.68	46.1 ± 0.2*
	Cysteine	45.20	0.94	46.14	

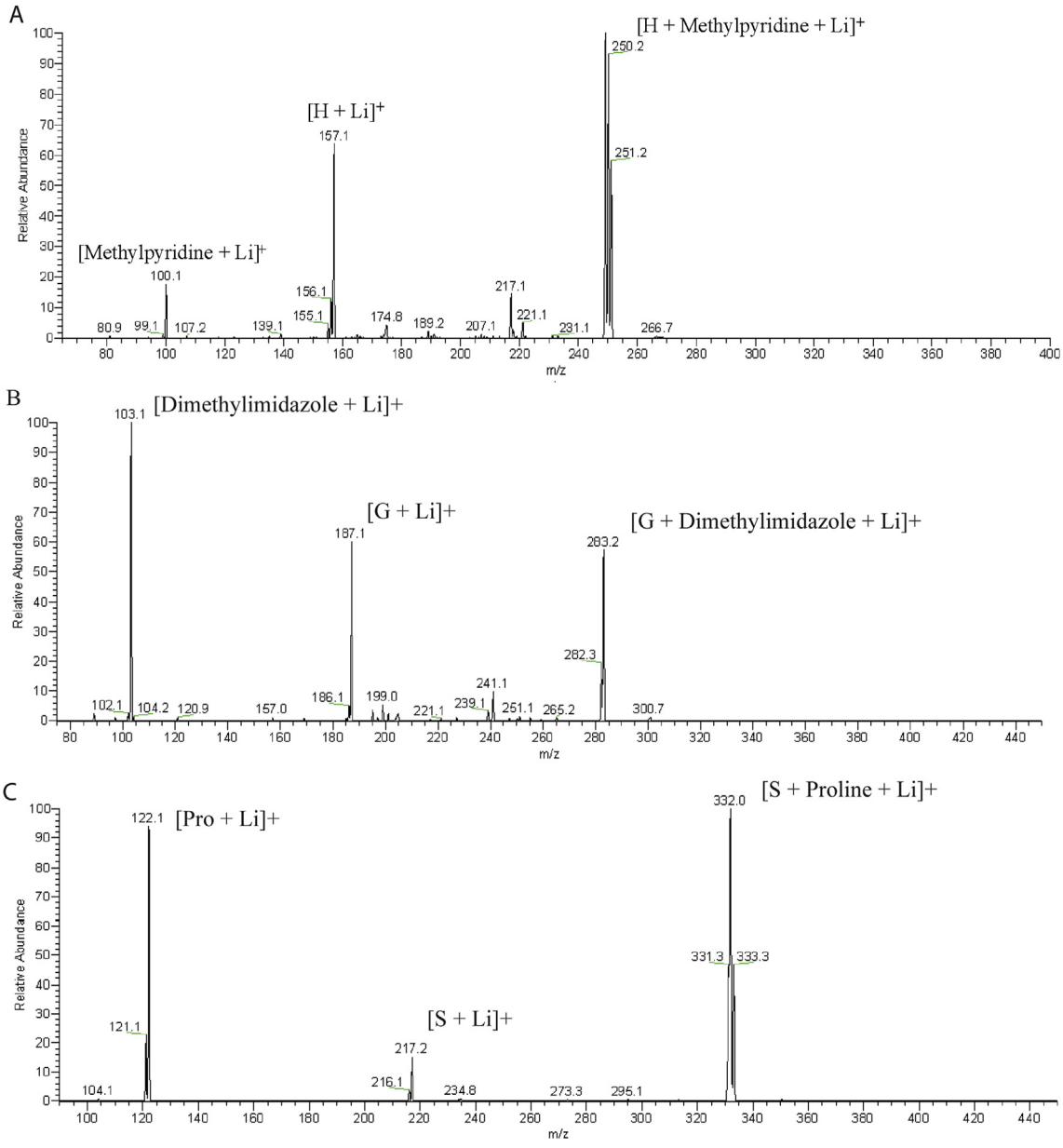

Fig. 2. LTQ CID/MS^2 spectra of lithiated monolignol, reference and complex post CID with depletion of complex ion. **A**. H monolignol lithium adduct (*m*/*z* 157) with 3-methylpyridine lithium adduct (*m*/*z* 100) reference to form complex (*m*/*z* 250), **B.** G monolignol lithium adduct (*m*/*z* 187) with 1,2-dimethylimidazole lithium adduct (*m*/*z* 103) reference to form complex (*m*/*z* 283) and **C.** S monolignol lithium adduct (*m*/*z* 217) with proline lithium adduct (*m*/*z* 122) reference to form complex (*m*/*z* 332).

with a consistent 11% increase. However, we felt it would be beneficial to further investigate the LCB of S using an additional reference base that is not an amino acid.

Trimethylphosphine oxide (Me_3PO) is one of the few compounds with a published lithium cation basicity in the range of S monolignol that is not an amino acid. This compound is very structurally different from both S monolignol and the amino acids used as reference bases. Based on the results shown in Table 3, the LCB determination for cysteine and isoleucine using Me_3PO resulted in an LCB about 2.0 kcal/mol different than the reported values. This is most likely because these compounds are so structurally unrelated that the entropic contribution in cluster dissociation affects the accuracy of results. When determining the LCB of S monolignol using trimethylphosphine oxide as reference, a very similar skew is observed with a resultant LCB about 1.8 kcal/mol lower than the estimation provided using amino acids (Table 1). Based the consistent skew for Cys, Ile, and S, we can conclude that the amino acids used to estimate the LCB of S appear to be sufficiently structurally similar for a reasonable result using the kinetic method. Nevertheless, if we were to consider the results from structurally unrelated trimethylphosphine oxide, the LCB of S would be 45.2 ± 0.6 kcal/mol. While this is lower than the estimation by amino acids, it is still significantly larger than the LCB estimate for G. Therefore, we confidently conclude that the addition of a methoxy group has a large impact on the lithium cation basicity for monolignols, and has the potential to create a variance in response factor for H, G and S.

4.2. Interaction energy computations

The quantum chemical computational results support LCB findings that the addition of methoxy groups to the aromatic has a

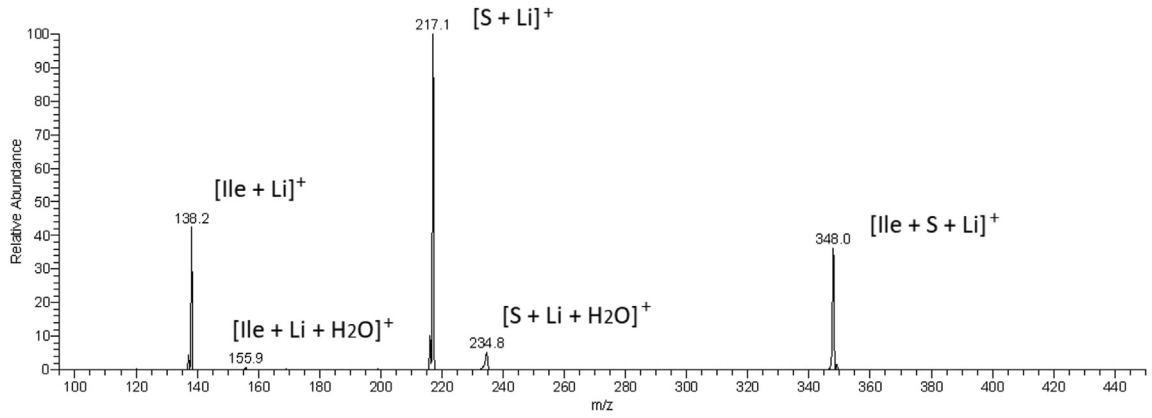

Fig. 3. LTQ CID/MS^2 spectrum of S lithium adduct (m/z 217) and isoleucine lithium adduct (m/z 138) dissociation product ions from complex [Ile + S + Li]$^+$ (m/z 348) CID fragmentation. Evidence of neutral water addition to complex dissociation product ions [S + Li + H_2O]$^+$ (m/z 235) and [Ile + Li + H_2O]$^+$ (m/z 156).

Table 2
Method validation using isophorone as an unknown for comparison with reported lithium cation basicity [13]. Reported in kcal/mol.

Compound	Ref	LCB Ref	LCB Iso	Average	Reported
Isophorone	1,2-Dimethylimidazole	41.80	41.77		
	Glycine	41.60	41.51	41.6 ± 1.2	41.5 ± 1.2
	Pyridazine	41.40	41.67		

Table 3
Using trimethylphosphine oxide as a reference base to determine the experimental LCB of cysteine, isoleucine and S monolignol. Reported in kcal/mol.

Compound	Expected LCB	LCB (Me_3PO ref)	Ob-Ex	Average Skew
Cysteine	45.20	43.16	−2.04	
Isoleucine	45.30	43.54	−1.76	−1.88
S Monolignol	46.13	44.29	−1.84	

large impact on the electrostatic coordination of lithium. In the empirical determination of LCB using the kinetic method, the lithium is also coordinated to a reference compound. Therefore, the total coordination of the lithium cation is dependent on the complex system and available coordination sites on each reference compound and monolignol. In order to discern the lithium cation affinity of the monolignols, Fig. 4 depicts the most probable electrostatic interaction sites. The interaction energy (ΔE_{int}) is calculated by subtracting the energy of the monolignol and lithium from its complex [12]. More negative interaction energy values correspond to stabilization due to lithium interaction. There are three main coordination motifs of lithium to the monolignols including chelation at the tail phenol (Fig. 4, C), the aromatic (Fig. 4, A), and the aromatic phenol and methoxy substituents (Fig. 4, B).

The geometry optimization of monolignol-Li^+ interactions provided expected chelation positions. The cation-pi interaction (Fig. 4, A) has little effect on the optimized geometry of the monolignol and sits directly above the aromatic ring at a distance dependent on the number of electron donating groups on the aromatic. For the optimized structures of monolignols G and S, the chelation of Li^+ with the phenol and a methoxy of the aromatic ring creates an electrostatic five membered ring and aromatic bicyclic structure that is essentially planar as expected. Coordination position C is consistent across the monolignols following the scorpion-effect where the cation sits perpendicular to the plane of the tail phenol above the alkene for optimum stability [31]. This interaction at the tail oxygen has a difference in stability between H, G and S less than 1.2 kcal/mol and is consistent across all three monolignols, therefore it is not a large contributor to the variability in LCB.

The addition of methoxy groups on the aromatic ring also improves the monolignol pi-cation coordination. Cation-pi interaction energies are very sensitive to the electronic nature of the substituent and the number of substituents [12,15]. The effects of multiple substituents has been shown to follow additivity, or that the total substituent effect on interaction energy is the sum of the individual contributions [12]. The methoxy and phenol groups are electron donating and therefore increase the stability of the cation-pi interaction energy. This is verified by DFT results shown in Table 4 where the increase in substituents on the hydroxyphenyl increases stability.

The largest contribution based on interaction energy calculations is lithium chelation to the methoxy and phenol substituents on the aromatic ring (coordination B). The computational estimations show (Table 4) the substantial increase in stability with the addition of a methoxy from H to G across all basis sets. Comparatively the change in interaction energy is minimal at the other major sites of chelation. The preferable interaction of two sites on the aromatic is possible for both G and S monolignols which greatly improves the coordination distance and stability of the complex. The stability at this site appears to be similar for G and S because the lithium can only interact with one methoxy group and phenol at a time (Table 4). However, there is an additional methoxy group available for interaction in the case of S. Therefore, it can be argued based on probability of collision and successful interaction that it is twice as likely for the methoxy-phenol coordination to form successfully on the S monolignol. These computational results support the experimental findings that there is a significant increase in lithium cation basicity with each addition of a methoxy group.

Based on the optimization results of the monolignols with lithium, we propose that lithium adducts have sufficient stability to reach a true energetic minimum with the lithium coordinated at many positions to produce a population distribution of interaction sites. The energies of the intermediate geometries are high enough that the lithium does not act as a diffuse charge like other alkali metal cations. There is some barrier of energy to move from one coordination position to the next, which results in a population distribution of low and high probability lithiated geometries. We can conclude from experimental and computational results that the interaction between lithium and the methoxy and phenol on the aromatic ring (Fig. 4, B) is the largest contributor to the population of coordination positions.

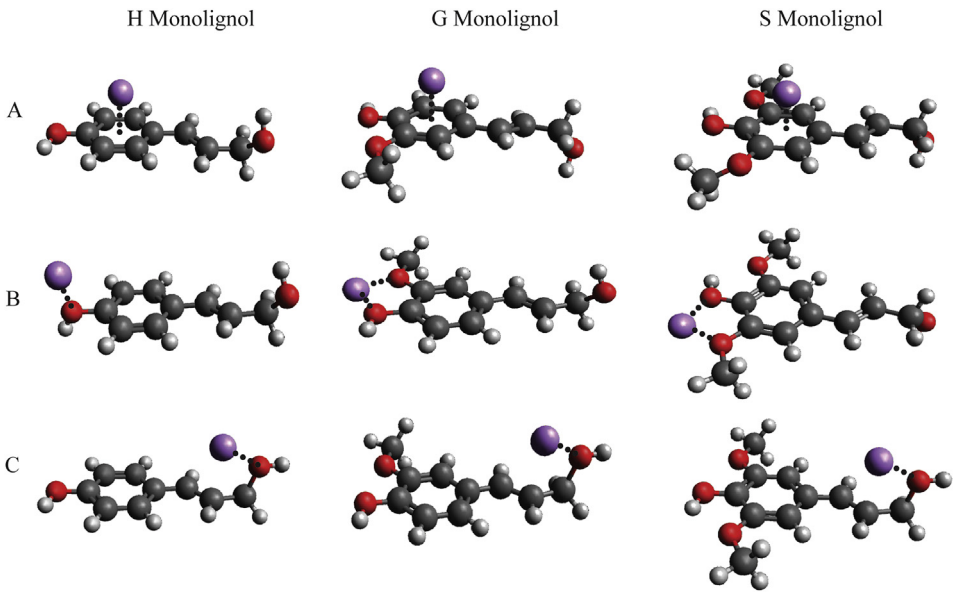

Fig. 4. DFT 6311G+(2d,2p) optimized structures of monolignols H, G and S. Lithium cations are shown in purple, oxygen atoms are shown in red. Dashes represent electrostatic bonds or coordination sites.

Table 4
Computed DFT B3LYP interaction energies reported in kcal/mol. Comparison across basis sets and monolignols H, G and S.

Coordination	Basis Set	Interaction Energy		
		H	G	S
A	6311G+	−33.6	−35.9	−38.5
	6311G + d,p	−37.4	−40.7	−42.6
	6311G+2d,2p	−38.0	−41.3	−43.1
B	6311G+	−41.8	−67.1	−70.2
	6311G + d,p	−36.1	−57.8	−61.7
	6311G+2d,2p	−35.7	−56.6	−60.7
C	6311G+	−55.9	−55.8	−55.6
	6311G + d,p	−51.3	−52.2	−53.3
	6311G+2d,2p	−50.9	−51.8	−53.2

5. Conclusion

Recently the mass spectrometry of lithium adducted model lignin compounds has shown promise for the improvement of analytical methods for the structural elucidation of lignin. To improve our understanding of using lithium to form stable adduct ions, the lithium cation basicity of H, G and S monolignols has successfully been estimated for the first time. The large increase in LCB with the addition of each methoxy group is supported by the computational results which show that the largest change in stability for H, G and S occurs at the methoxy-phenol position (Table 4, B).

The geometry optimizations and interaction energy calculations also confirm that there is some population distribution of lithium coordinated across low and high probability positions. In the tandem mass spectrometry of lignin model compounds such as β-O-4′ dimers discussed in our previous work, a distribution of chelation positions would produce a spread of fragments with the abundance of each fragment dependent on the strength of its lithium interaction [11]. When lignin model compounds are ionized using other alkali metal ions such as sodium, comparatively weak electrostatic interactions are formed due to the lower charge density. The sodium ion acts as a diffuse charge that can reach a consistent equilibrium position and does not produce a distribution of sodium adducted fragments. This explains why only one ring fragment is observed in the tandem mass spectrometry on a sodium adducted β-O-4′ dimer, but both rings are observed in the tandem spectrum of the lithium adducted dimer [11]. Based on our LCB and interaction energy results, the population distribution produced by lithium cationization clarifies the tandem MS results reported in our previous work by Asare et al. and supports the finding that lithium adduct ionization for tandem mass spectrometry is the most promising for the analysis of lignin [11]. The lithium cation basicity clearly has an impact on the response factor in tandem mass spectrometry, and in future work we plan to determine the lithium cation basicity of the β-O-4′ dimers.

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Appendix A. Supplementary data

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