Supporting Information for

"An Experimental and Theoretical Investigation of the Decomposition of Lithiated Hydroxyl Side Chain Amino Acids" by S. J. Ye and P. B. Armentrout

Descriptions of the isomers of the $(AA - F)$, $Li^+(AA - F)$, and $(F)Li^+(AA - F)$ species where AA = Ser and Thr and F = H_2O, CO_2, and XCHO (X = H for Ser and CH_3 for Thr) as well as the transition states and intermediates along the potential energy surfaces for elimination of F from the lithiated amino acid complexes. Tables S1 and S2 provide the relative energies and key geometric parameters of all species lying along these potential energy surfaces. Figure S1 shows the optimized structures of $(AA - F)$ and $(H_2O)Li^+(AA - F)$. Additional figures show alternate potential energy surfaces for elimination of H_2O (S3 and S4), CO_2 (S6), HCHO (S9), and the rearrangements of the $(H_2O)Li^+Aca$ (S2), $(CO_2)Li^+May$ (S5), and $(HCHO)Li^+Cay$ products (S7 and S8). This information is available free of charge via the Internet at http://pubs.acs.org.

      S1. Dehydration products: $(AA - H_2O)$, $Li^+(AA - H_2O)$, and $(H_2O)Li^+(AA -H_2O)$.
The neutral Apa and cis-Aba (where the C_4 backbone has a cis orientation) have almost identical backbone structures, Figure S1, with an intramolecular NH···O=C hydrogen bond formed between the amino hydrogen and carboxylic oxygen. However, cis-Aba is calculated to be 18 – 20 kJ/mol higher than the trans-Aba ground structure, Table 2, which is lower in energy mainly because repulsion between the OH and CH_3 groups in cis-Aba is relieved. When the double bond is located at the end of the C_4 chain, an alternative isomer, 2-amino-3-butenoic acid (3-Aba), lying 50 – 59 kJ/mol above the trans-Aba ground structure, is obtained. The four-membered ring lactone molecules, Abl and Ambl, have only one isomer and lie 70 – 81 kJ/mol and 64 – 74 kJ/mol above the Apa and trans-Aba isomers, respectively. The three-membered ring aziridine molecules, Aca and Amca, have two isomers distinguished by whether the carboxylic hydroxyl group is cis or trans to the carbonyl. Aca-trans-OH (Amca-trans-OH) lies lower in energy because an OH···N hydrogen bond is formed, Figure S1, and lies 77 – 91 (75 – 90) kJ/mol above the ground state Apa (Aba) isomers. Aca-cis-OH (Amca-cis-OH) lies another 5 – 8 (6 – 9) kJ/mol higher in energy and is stabilized by an internal OH···OC hydrogen bond.

      In Li^+Apa and Li^+Aba, the Li^+ binds directly to the amino nitrogen and carbonyl oxygen atom after disrupting the NH···O=C hydrogen bond. A similar bidentate binding motif is seen in

the M^+Gly system.[1-3]   Upon binding of Li^+, the intramolecular hydrogen bond in the carboxylic group becomes 0.03 – 0.04 Å longer than the corresponding neutral Apa or Aba, Figure 3. Such elongation is mainly because of electron delocalization from the carbonyl oxygen to the lithium cation, which weakens this hydrogen bond. Also note that the relative energies among the three isomers of Li^+Aba are smaller than those in neutral Aba system, Tables 2 and S1. For the cyclic lactone and aziridine species, lithium cations bind in [N,CO] bidentate conformations, Figure 3. This requires only that the amine group rotate for Abl and Ambl, but the constrained geometry of the lactone ring leads to relatively long Li^+–O and Li^+–N bond lengths, Table S2. For Aca and Amca, lithium cation binding also leads to elongation of the hydrogen bond in the carboxylic acid group relative to the Aca-cis-OH and Amca-cis-OH neutrals. In the zwitterionic form of these complexes, formed by attaching Li^+ to the trans-OH isomers, the hydrogen bond is retained but shifted to a NH···O configuration. These $ZW[CO_2^-]$ complexes are 20 – 22 and 16 – 17 kJ/mol higher in energy than the charge-solvated [N,CO] Li^+Aca and Li^+Amca complexes, respectively, Table S1. The corresponding M3[COOH] structures of the $ZW[CO_2^-]$ complexes are not stable when optimized and collapse to M6[CO] structures, which lie 37 – 43 and 40 – 46 kJ/mol above the ground M1[N,CO] structures.

For the hydrated systems, $(H_2O)Li^+(AA – H_2O)$, the water binds directly to the other side of Li^+ while keeping the rest of the molecule nearly unchanged, Table S2. Both the Li^+–O and Li^+–N distances increase by ~0.04 Å as compared to those of the corresponding $Li^+(AA – H_2O)$ conformers, Table S2. Similar elongation (by ~0.03 Å) of these distances was found upon hydration of Na^+Gly.[4]   For hydrated Li^+Aca and Li^+Amca complexes, the charge-solvated [N,CO] form is again more stable and favored over the $ZW[CO_2^-]$ by 24 – 25 and 18 – 22 kJ/mol.

S2. Products of Carbon Dioxide Elimination: (AA – CO₂), Li^+(AA – CO₂), and $(CO_2)Li^+$(AA –CO₂). The lowest energy isomers for (AA – CO_2) are ethanol-2-amine (Eam) in the Ser system and propanol-2-amine (Pam) in the Thr system, respectively, Figure S1, where an intramolecular N···HO hydrogen bond (2.27 and 2.23 Å, respectively) is formed between the amine nitrogen and hydroxyl hydrogen. A zwitterionic isomer of E(P)am is $HOCH_2C^-HN^+H_3$, methoxy ammonium ylide (May) for Ser, and $HOCH(CH_3)C^-HN^+H_3$, ethoxy ammonium ylide (Eay) for Thr, where the nitrogen is positively charged and the alpha carbon is negatively charged. There are two conformers close in energy for these zwitterionic molecules. The lower

energy conformer, May(Eay)-cis-OH, has two relatively long-range hydrogen bonds, $N^+H\cdots OH$ and $OH\cdots C^-$ (2.42 and 2.45 Å for May and 2.41 and 2.39 Å for Eay, respectively), Figure S1. Not surprisingly, the zwitterionic ylide isomer is much less stable than the corresponding alcohol amine isomer, lying 240 – 248 (247 – 253) kJ/mol above Eam (Pam). The May(Eay)-trans-OH conformer has only the $N^+H\cdots OH$ hydrogen bond (2.27 and 2.13 Å for May and Eay, respectively) and lies 13 – 15 (16 – 17) kJ/mol above the cis conformer. The shorter hydrogen bond distances in both cis and trans Eay conformers as compared to those of May are clearly a result of a methyl group inductive effect.

Li$^+$ binds to the alcohol amine and its zwitterionic ylide form in [N,OH] and [C$^-$,OH] bidentate configurations, respectively, as shown in Figure 3, after disrupting the hydrogen bonds in neutral E(P)am and M(E)ay. Li$^+$May lies 197 – 206 kJ/mol above Li$^+$Eam and Li$^+$Eay lies 203 – 210 kJ/mol above Li$^+$Pam, Table S1. It is worth noting that the relative energy of Li$^+$M(E)ay compared to Li$^+$E(P)am is smaller than the excitation energy of M(E)ay vs. E(P)am by about 40 kJ/mol. This is because the negatively charged alpha carbon is stabilized by complexation to the lithium cation. The TS for transformation between Li$^+$May and Li$^+$Eam is calculated to lie 325 – 342 kJ/mol above the ground Li$^+$Eam structure, and 127 – 136 kJ/mol above Li$^+$May. Thus, although the latter complex is relatively unstable, it cannot spontaneously rearrange to the lower energy form.

In the (CO_2)Li$^+$(AA – CO$_2$) bis-ligand complexes, CO$_2$ preferentially binds directly to the other side of the lithium cation of the Li$^+$(AA – CO$_2$) complexes mentioned above in an end-on orientation. Among these complexes, (CO_2)Li$^+$Eam has the lowest energy, followed by (CO_2)Li$^+$May, which is 137 – 164 kJ/mol higher in energy. Likewise, (CO_2)Li$^+$Pam is lower than (CO_2)Li$^+$Eay by 145 – 171 kJ/mol.

S3. Products of Aldehyde Loss: (AA – XCHO), Li$^+$(AA – XCHO), and (XCHO)Li$^+$(AA – XCHO). The neutral molecules formed upon aldehyde elimination from Ser and Thr are the same. The lowest energy isomer is glycine (Gly) where two intramolecular $N(H)_2\cdots OC$ hydrogen bonds (2.84 Å) are formed between the amino hydrogen atoms and carbonyl oxygen. More detailed information about Gly calculated at the same level of theory has been elucidated elsewhere.[1] The next higher energy isomer considered is 2-amino-1,1-dihydroxy-ethene (Ade). There are two conformers close in energy for this diol molecule. The Ade-trans-NH conformer has $HN\cdots HO$ and $HO\cdots HO$ intramolecular hydrogen bonds (2.12 and

2.20 Å, respectively), Figure S1. It is calculated to lie 86 – 96 kJ/mol above Gly. The cis conformer has NH···OH and HO···HO hydrogen bonds, where the former is about 0.3 Å longer than the HN···HO hydrogen bond in the trans conformer. Therefore, the cis conformer lies 19 – 22 kJ/mol higher in energy than the trans conformer. The highest energy isomer considered is carboxy ammonium ylide (Cay), $HO(CO)C^-HN^+H_3$. Similar to May and Eay, Cay also has two conformations. Cay-cis-OH lies 113 – 124 kJ/mol above Gly and has N^+H···OC and OH···OC hydrogen bonds (1.78 and 2.26 Å, respectively). It is therefore 15 – 16 kJ/mol lower in energy than the trans conformer, which has only the first hydrogen bond (1.72 Å). The Cay-cis-OH structure can be formed by shifting the hydroxyl hydrogen in the Ade-trans-NH structure to the amine nitrogen. The TS for this transformation is calculated to be 39 – 48 kJ/mol above Ade-trans-NH or 1 – 7 kJ/mol below Cay-cis-OH once ZPE is included (2 – 7 above Cay-cis-OH without ZPE).

For all of these (AA –XCHO) isomers, Li^+ favors binding in a bidentate configuration: [N,CO] for Gly, [N,OH] for Ade, and [COOH] for Cay, Figure 3. Li^+Gly has the lowest energy of all three isomers, with Li^+Ade and Li^+Cay being higher in energy by 114 – 117 and 111 – 117 kJ/mol, respectively. For Li^+Ade, the [OH,OH] bidentate conformer lies 29 – 32 kJ/mol above the [N,OH] conformer, which is consistent with the fact the $-NH_2$ group has stronger bonds to alkali metal cations than the –OH functional group.[1]

The aldehydes prefer binding via their carbonyl group directly on the other side of Li^+ in the Li^+(AA –XCHO) complex. The lowest energy structure is (XCHO)Li^+Gly, followed by (XCHO)Li^+Ade and (XCHO)Li^+Cay, where the latter are comparable in energy. In all three cases, the $(CH_3CHO)Li^+(Thr – CH_3CHO)$ complexes are 21 – 42 kJ/mol more stable than the analogous $(HCHO)Li^+(Ser – HCHO)$ complexes. This is because the more polarizable acetaldehyde binds more strongly to Li^+(AA – XCHO) than formaldehyde, by calculated differences (without BSSE corrections) of 17 – 18 kJ/mol for Li^+Gly, 17 – 19 kJ/mol for Li^+Ade, and 12 – 16 kJ/mol for Li^+Cay.

S4. Intermediates and Transition States: H_2O Loss. From PC_N, Figure 4, the loosely bound water molecule can easily move to a more stable position by binding directly to the lithium cation to form $(H_2O)Li^+$Aca[ZW], Figure S2. Transfer of a proton from the nitrogen to the carboxylate group occurs by passing TS_Z and requires little energy because of the short

NH···O hydrogen bond involved. This forms IM_Z in which Aca is bound to Li^+ through its carbonyl, with the water ligand on the opposite side. Rotation about the $C–C_\alpha$ bond consumes 43 – 45 kJ/mol of energy (44 – 47 kJ/mol for Thr system) and leads to the rate-limiting step in this transformation, TS_{ZR1}, which lies 80 – 92 kJ/mol below TS_{NPT} (72 – 85 kJ/mol in the Thr case). Thus, this transformation has enough energy to occur at the threshold for elimination of water. The IM_{ZR1} intermediate binds to Li^+ in an [N,CO] binding mode, but the carboxylic acid hydrogen is trans to the carbonyl. Rotation of this group passes TS_{ZR2} and forms the ground conformer of $(H_2O)Li^+Aca$, in which the hydroxyl group is cis to the carbonyl, Figure S2.

An alternative pathway found for generating $Li^+(AA – H_2O)$ is the transfer of a hydrogen atom from the side-chain hydroxyl oxygen of Ser to the hydroxyl group of the carboxylic acid. The complete potential energy surface including all transition states and intermediates along this pathway for the Li^+Ser case is presented in Figure S3. (Li^+Thr is very similar both in energetic and structural information and is therefore not shown.) Relative energies and some critical geometric parameters for the transition states and intermediates of both systems are included in Tables S1 and S2, respectively. The mechanism starts as in Figure 4 to form IM_{N2}, but instead of rotating the hydroxyl group of the carboxylic acid, the side-chain hydroxyl group is rotated to form IM_O (where the subscript indicates the atom from which the hydrogen atom used to form the water originates), in which there is a long-range OH···OH hydrogen bond (2.42 Å). TS_O and IM_O are nearly isoenergetic lying 50 – 61 kJ/mol above the reactant complex (54 – 64 kJ/mol in the Thr case). From IM_O, the hydrogen is transferred from the carboxylic acid group to the side-chain hydroxyl in a four-center TS to form a water molecule and a new CO bond, yielding the four-membered ring lactone. Because the hydrogen transfer is long range and there are considerable steric constraints associated with the formation of the lactone ring, the energy of TS_{OPT} is 263 – 281 kJ/mol above the reactants, 87 – 109 kJ/mol above TS_{NPT}. (For the Thr case, the energies are 259 – 275 and 85 – 112 kJ/mol, respectively.) Other placements of the lithium cation were also considered, but we found none that yielded a lower barrier for this rearrangement. Once past TS_{OPT}, the system falls into a product-like complex that can easily lose water, PC_O. PC_O lies 66 – 72 kJ/mol above the ground state of the $(H_2O)Li^+Abl$ complex (66 – 71 kJ/mol for the analogous species in the Thr case). Loss of the bidentate Abl and Ambl ligands requires ~60 and ~70 kJ/mol, respectively, more energy than loss of water, but both product asymptotes lie below the energy of TS_{OPT}. Thus, the thresholds for observation of the

products of reactions 4a, Li$^+$(AA – H$_2$O), and 4b, Li$^+$(H$_2$O) should be the same, but the experimental observations discussed in the manuscript do not support this conclusion.

An additional pathway explored for generating Li$^+$(AA – H$_2$O) is the transfer of a hydrogen atom from C$_\alpha$ to the side-chain hydroxyl oxygen of Ser or Thr. The complete potential energy surface including all transition states and intermediates along this pathway for the Li$^+$Ser case is presented in Figure S4. (Li$^+$Thr is very similar both in energetic and structural information and is therefore not shown.) Relative energies and some critical geometric parameters for the transition states and intermediates for both systems are included in Tables S1 and S2. Starting from the ground structure of the reactants, M1[N,CO,OH]-cis-OH, the side-chain oxygen rotates ~50° along the C$_\alpha$–C$_\beta$ bond (Table S2) to reach transition state TS$_C$ (where the subscript C stands for the atom supplying the hydrogen atom), which costs 53 – 65 kJ/mol (56 – 66 for Li$^+$Thr), Table S2. The system then further rotates in the same direction for ~40°, while keeping the rest of the amino acid backbone nearly unchanged, to reach intermediate IM$_C$, lying 31 – 39 kJ/mol (35 – 42 for Li$^+$Thr) higher than the reactants. It is worth noting that the hydroxyl oxygen forms a C$_\beta$O$\cdots$HN hydrogen bond with the amino hydrogen (2.15 and 2.03 Å for Li$^+$Ser and Li$^+$Thr, respectively) in IM$_C$, which is similar to that in M1[N,CO], Figure S4. In IM$_C$, the hydroxyl oxygen is situated fairly close to the alpha carbon hydrogen (HO$\cdots$HC$_\alpha$ distance of ~2.7 Å). Next, the hydroxyl oxygen further rotates ~50° in the same direction to bring the oxygen atom even closer to the C$_\alpha$ hydrogen, which induces cleavage of the C$_\alpha$–H bond (extended C$_\alpha$–H distances of 1.56 and 1.54 Å for Li$^+$Ser and Li$^+$Thr, respectively), transfer of the hydrogen to the hydroxyl oxygen forming a H$_2$O moiety, and elongation of the C$_\beta$–OH bond (by ~0.15 Å). Because the proton transfer is fairly long range and also involves the disruption of the C$_\beta$O$\cdots$HN hydrogen bond in IM$_C$, the corresponding transition state, TS$_{CPT}$, sits 231 – 254 kJ/mol (241 – 265 for the corresponding Li$^+$Thr TS$_{CPT}$ case) above reactants. This TS also lies 44 – 56 (56 – 71) kJ/mol above TS$_{NPT}$, the lowest energy TSs found for dehydration. After TS$_{CPT}$ proton transfer, the ion falls into a relatively stable product-like complex, PC$_C$, where the H$_2$O moiety forms a hydrogen bond with one of the amino group hydrogens (bond distances of 1.94 and 1.96 Å for Li$^+$Ser and Li$^+$Thr, respectively). PC$_C$ is situated 25 – 42 kJ/mol (30 – 56 for Li$^+$Thr) above the reactants and 53 – 58 kJ/mol higher than the ground conformer of (H$_2$O)Li$^+$Apa (67 – 71 kJ/mol higher than the (H$_2$O)Li$^+$(trans-Aba) ground conformer in the Li$^+$Thr system). Because of

the large energy release from TS_{CPT} to PC_C and the short distance between the H_2O ligand and Li^+, it seems likely that the ground conformers of $(H_2O)Li^+Apa$ and $(H_2O)Li^+(trans-Aba)$ could be formed transiently. In any event, H_2O elimination from the $PC(H_2O)$ complexes or the lower energy $(H_2O)Li^+Apa$ and $(H_2O)Li^+(trans-Aba)$ complexes is calculated to be more favorable than the elimination of the bidentate Apa and Aba ligands by ~80 and 100 kJ/mol, Table S1, respectively. However, the rate-limiting transition states lie above both product asymptotes, Figure S4, indicating that the thresholds for observation of the products of reactions 4a, $Li^+(AA - H_2O)$, and 4b, $Li^+(H_2O)$ should be the same. This contrasts with the experimental observations.

For the Li^+Thr system, there is another possible pathway for water elimination that involves proton transfer from the methyl group to the side-chain hydroxyl oxygen. The energy of the transition state for this pathway, TS_{CPT2}, is calculated to be comparable to the one discussed above, TS_{CPT}, Table S1. Briefly, the proton transfer process starts from the M1[N,CO,OH]-cis-OH ground conformer of Li^+Thr. One of the methyl hydrogen atoms rotates ~50° along the C_β-C_α bond to align itself with the hydroxyl oxygen. In addition, rotation of the hydroxyl hydrogen along the O–C_β bond by ~40° facilitates abstraction of the methyl hydrogen atom. Formation of the tight TS_{CPT2} transition state involves cleavage of the HO–C_β bond (bond distance of 2.26 Å) and elongation of the H–C_α distance (from 1.09 to 1.24 Å). TS_{CPT2} lies 244 – 277 kJ/mol above the ground reactant complex. After passing through this transition state, the ion falls into a stable product-like complex, $(H_2O)Li^+(3-Aba)$, which is only 4 – 25 kJ/mol above the ground conformer of Li^+Thr. This complex can easily eliminate either H_2O or 3-Aba, but again the rate-limiting transition state lies above both product asymptotes, Table S1.

S5. Intermediates and Transition States: CO_2 Loss. $(CO_2)Li^+M(E)ay$ is the product complex formed by CO_2 elimination after passing the rating-limiting TS_{DCC}, Figure 5. However, this product is calculated to lie 202 – 211 (208 – 215) kJ/mol above its stable $(CO_2)Li^+E(P)am$ isomer. Calculations were performed to investigate possible rearrangements of $(CO_2)Li^+May$ to $(CO_2)Li^+Eam$. The complete PES including all TSs and intermediates along this pathway for the Ser case is presented in Figure S5. (Li^+Thr is similar both in energetic and structural information and therefore is not shown.) Relative energetics and critical geometric parameters for the TSs and intermediates are included in Tables S1 and S2, respectively.

Briefly, starting from $(CO_2)Li^+May$, the ion reaches TS_{EPT} by transferring one of the ammonium hydrogen atoms toward the anionic carbon while still maintaining $[C^-, OH]$ bidentate binding with lithium cation. This 1,2-hydrogen shift consumes $120 - 130$ kJ/mol of energy and then the ion forms a stable intermediate, IM_{EPT}, in which Li^+ interacts primarily with the hydroxyl group of Eam, although there is an agostic interaction with the CH_2 group as well. Therefore, IM_{EPT} lies $85 - 92$ kJ/mol above the ground $(CO_2)Li^+Eam$ structure. The rest of the PES involves rotation of the amino group along the N–C bond followed by rotation along the C-C bond to allow both the NH_2 and OH functional groups to interact with Li^+, Figure S5. Similar to rotational transitions in other reaction pathways considered here, this requires a small activation energy, only $6 - 9$ kJ/mol, for IM_{EPT} to reach $(CO_2)Li^+Eam$, Table S1.

Another reaction pathway found for generating $Li^+(Ser - CO_2)$ involves the transfer of a hydrogen atom from the carboxylic acid to the C_α of Ser, as shown in Figure S6. Briefly, starting from $IM_{DR1} = M1[N,CO,OH]$-trans-OH, the four-centered rate-limiting TS_{DPT2} involves a direct shift of a hydrogen atom from the carboxylic acid to C_α and is calculated to be $319 - 330$ kJ/mol above the Li^+Ser ground state. Although this pathway generates the stable Eam fragment, TS_{DPT2} is over 130 kJ/mol higher than the experimental measurement and $131 - 152$ kJ/mol higher than TS_{DCC}, Table S1.

S6. Intermediates and Transition States: XCHO Loss. The lowest energy process for loss of an aldehyde from Li^+Ser is shown in Figure 6 of the main text with the rate-limiting TS_{APT}. Two other higher energy TSs (not depicted) that also lead to $(HCHO)Li^+Cay$, TS_{APT2} and TS_{APT3}, were located. TS_{APT2} is almost identical to TS_{APT} except the carboxylic acid hydrogen atom is in a trans position. It is situated only $7 - 12$ kJ/mol above TS_{APT}. TS_{APT3} involves a 1,4-hydrogen shift from a structure that resembles IM_{NTC}, Figure 4, except the $C_\beta O \cdots OH$ hydrogen bond is formed on the same side as the amine group. This TS leads to a [COOH] bidentate configuration of $(HCHO)Li^+Cay$, i.e. 1A-ZW[COOH], where A and ZW stand for aldehyde and zwitterion, respectively, Figure S1. TS_{APT3} lies $47 - 57$ kJ/mol above TS_{APT}.

The complete PES for the transformation of $(XCHO)Li^+Cay$ to a slightly more stable charge-solvated complex, $(XCHO)Li^+Ade$, including all TSs and intermediates along this pathway for the Ser case (X = H) is presented in Figure S7. (The PES for Li^+Thr is not shown because it is similar both in energetic and structural information except that all energies relative to the ground Li^+Thr structure are about 20 kJ/mol lower than in the Li^+Ser case, Table S1.)

Relative energetics and critical geometric parameters for the TSs and intermediates are included in Tables S1 and S2, respectively. Briefly, starting from PC_A, the carboxylic acid hydrogen rotates to a trans position enabling the lithium ion to move to the most stable form of $(HCHO)Li^+Cay$, a [COOH] binding mode. The next TS, TS_{IPT}, involves 1,4-hydrogen shift from the ammonium group to the carbonyl oxygen. Similar to the proton transfer process in TS_{DPT}, Figure 5, this proton transfer consumes little energy because the NH···OC hydrogen bond in $(HCHO)Li^+Cay$ is relatively short (2.06 Å). After passing TS_{IPT}, the ion falls into a stable isomer of $(HCHO)Li^+Ade$, 1A-CS[OH,OH], where the lithium cation interacts with two hydroxyl oxygen atoms of Ade. The final rate-limiting step involves a rotation of the C–O bond along with $Li^+(HCHO)$ to bring the ion from a [OH,OH] bidentate binding to [N,OH] binding, the most stable form of $(HCHO)Li^+Ade$. TS_{IR} is calculated to lie 8 – 23 above TS_{APT} for the Ser and between 11 below and 8 kJ/mol above TS_{APT} for Thr system. Thus, this rearrangement can probably take place at the threshold for CH_3CHO loss.

$(XCHO)Li^+Cay$ is calculated to lie 113 – 121 kJ/mol above its stable $(XCHO)Li^+Gly$ isomer (113 – 126 kJ/mol for X = CH_3). Calculations were performed to investigate the rearrangement of $(XCHO)Li^+Cay$ to $(XCHO)Li^+Gly$. The complete PES including all TSs and intermediates along this pathway for the Ser case (X = H) is presented in Figure S8. (Li^+Thr is similar both in energetic and structural information and therefore is not shown.) Relative energetics and critical geometric parameters for the TSs and intermediates are included in Tables S1 and S2, respectively.

Similar to rearrangement of $(CO_2)Li^+May$, the first step is rate-limiting and involves direct transfer of a hydrogen atom either from the carboxylic acid or amino group to the carbon anion. The former four-centered TS, TS_{GPT}, is lower in energy and consumes 151 – 158 kJ/mol of energy. (The latter 1,2-hydrogen shift leads to TS_{GPT2}, which lies 1 – 15 kJ/mol higher than TS_{GPT}.) As noted in the main text, TS_{GPT} lies well above TS_{APT}, indicating that this rearrangement cannot occur at the threshold for reaction 6a. After passing TS_{GPT}, the ion falls to a zwitterionic lithiated glycine solvated by formaldehyde, IM_{GPT1}. However, this is not the most stable form of $(HCHO)Li^+Gly$. Transfer of a hydrogen from the amino group to the carboxylic acid terminus is needed in order to form a charge solvated conformer, IM_{GPT3}. The energy cost is relatively small (0 – 8 kJ/mol with ZPE included and 11 – 19 kJ/mol without ZPE) because the NH···OC hydrogen bond is relatively short (1.75 Å). Further rotation of the carboxylic acid

group along the C-C bond forms the most stable [N,CO] bidentate (HCHO)Li$^+$Gly conformation and requires 46 – 50 kJ/mol of energy to pass TS$_{GR}$, Table S1.

Another reaction pathway found for eliminating XCHO and generating Li$^+$(AA – XCHO) is the transfer of a hydrogen atom from the side-chain hydroxyl group to the carbonyl oxygen of AA, leading to a (XCHO)Li$^+$Ade complex. The complete potential energy surface including all TSs and intermediates along this pathway for the Li$^+$Ser case is presented in Figure S9. (Li$^+$Thr is similar both in energetic and structural information and therefore is not shown.) Relative energetics and critical geometric parameters for the TSs and intermediates are included in Tables S1 and S2, respectively. Starting from the ground structure, M1[N,CO,OH]-cis-OH, the reactant ion passes through four TSs involving only rotations to form an intermediate leading to the rate-limiting proton transfer process. The first rotation (TS$_{R1}$) involves exchanging the positions of the carboxylic oxygen atoms while maintaining tridentate binding of the lithium cation in IM$_{R1}$. The second step (TS$_{R2}$) involves rotation of the hydroxyl side chain away from the metal cation (similar to that in the water elimination pathway) except the lithium cation binds to Ser in a [N,OH] bidentate mode in IM$_{R2}$. In the third step (TS$_{R3}$), the side-chain hydroxyl rotates further in the same direction by ~120°, Table S2, to reach another [N,OH] bidentate intermediate, IM$_{R3}$, lying 103 – 106 kJ/mol above the ground reactant. The fourth step (TS$_{R4}$) rotates the side-chain hydroxyl hydrogen atom from a trans (in IM$_{R3}$) to a cis (in IM$_{R4}$) position relative to the carbonyl oxygen, which forms a long-range hydrogen bond (C$_\beta$OH···O=C distance of 2.44 Å) in IM$_{R4}$. In the rate-limiting step, TS$_{RPT}$, the hydroxyl proton transfers to the carbonyl oxygen, which also induces cleavage of the C$_\beta$–C$_\alpha$ bond (2.43 and 2.56 Å for Ser and Thr, respectively) and formation of the formaldehyde moiety with a C$_\beta$=O double bond (evident by a decrease of ~0.15 Å in the C$_\beta$–O bond for both systems). It is worth noting that the C$_\beta$O···H distance in TS$_{RPT}$(CH$_3$CHO) is ~0.09 Å shorter than that in TS$_{RPT}$(HCHO), whereas the C$_\beta$–C$_\alpha$ bond is ~0.13 longer in TS$_{RPT}$(CH$_3$CHO). In analogy with TS$_{APT}$, the shorter C$_\beta$O···H bond can probably be attributed to the inductive effect of the CH$_3$ group in the Thr system stabilizing the incipient transition state, whereas the longer C$_\beta$–C$_\alpha$ distance appears to be a result of steric repulsion of the CH$_3$ group with the lithiated threonine backbone functional groups (the CH$_3$ group is cis to the C-terminus). Overall, TS$_{RPT}$(CH$_3$CHO) is lower than TS$_{RPT}$(HCHO) by 10 – 15 kJ/mol, which is less than the relative energy difference (23 – 28 kJ/mol, Table S1) between TS$_{APT}$(HCHO) and TS$_{APT}$(CH$_3$CHO), where the CH$_3$ group is trans relative to the C-terminus

thereby minimizing steric repulsion. Compared to the similar proton transfer process in the lowest energy water elimination pathway (where TS_{NPT} lies 91 – 108 kJ/mol above IM_{NTC}), the proton transfer process from IM_{R4} consumes 147 – 181 kJ/mol. This is because the $C_\beta OH\cdots OC$ distance in IM_{R4} is about 0.8 Å longer than the $OH\cdots OH$ hydrogen bond distance in IM_{NTC}. After passing through TS_{RPT}, the ion falls into a product complex, PC_R, where the carbonyl oxygen of formaldehyde forms a hydrogen bond with one of the hydroxyl hydrogen atoms ($HCHO\cdots HO$ distance of 1.69 Å) in lithiated 2-amino-1,1-dihydroxy-ethene, Li^+Ade. Alternatively, aldehyde elimination can proceed via an intermediate structure, IM_{R5} (not depicted), with the Li^+ bound to the C-terminus of Ser, which is similar to IM_{R4}, Figure S9, except the Li and carboxylic H have their positions exchanged. The TS, TS_{RPT2}, involves shifting the side-chain hydroxyl hydrogen to the carbonyl group of IM_{R5}, which is slightly higher in energy (~5 kJ/mol) than TS_{RPT}, Table S1. Because of the energy release from TS_{RPT} to PC_R, it seems likely that PC_R can rearrange to form the most stable form of $(XCHO)Li^+Ade$, in which Ade is bound to Li^+ in a [N,OH] configuration. In either case, elimination of aldehyde is calculated to be ~100 kJ/mol more favorable than the elimination of the bidentate Ade ligand.

Two possible transformations of $(HCHO)Li^+Ade$ to $(HCHO)Li^+Gly$ were also explored. Both pathways involve 1,3-hydrogen shifts from the hydroxyl group to the alpha carbon forming four-center TSs, TS_{GPT4} and TS_{GPT5}, and are distinguished by the lithium coordination: [N,OH] and [OH,OH], respectively, where the latter $(HCHO)Li^+Ade$ complex $\equiv IM_{IPT}$. Both TSs are situated over 140 and 50 kJ/mol above TS_{APT} and TS_{GPT}, respectively. Thus, rearrangement of the $(HCHO)Li^+Ade$ complexes to $(HCHO)Li^+Gly$ is not feasible.

Another possible pathway for reaction 6 is the direct transfer of a hydrogen atom from the side-chain hydroxyl group to C_α, forming lithiated glycine and the aldehyde. Extensive searches were unable to locate such a rate-limiting TS.

References

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TABLE S1. Relative Energies (kJ/mol) of Transition States and Intermediates for Elimination of H_2O, and CO_2, XCHO from Lithiated Ser and Thr[a]

Name	Structure	Theory		
		B3LYP	B3P86	MP2(full)
Li$^+$Ser	TS$_{N1}$	23.5	23.9	29.3
(rxn 4)	IM$_{N1}$ = M1[N,CO]	23.8	23.1	29.6
	TS$_{N2}$	53.1	53.0	61.1
	IM$_{N2}$	30.9	30.8	37.8
	TS$_{N3}$	99.7	100.3	110.9
	IM$_{N3}$	24.8	22.1	33.9
	TS$_{NTC}$	76.5	74.4	89.8
	IM$_{NTC}$	77.1	74.2	85.4
	TS$_{NPT}$	168.5	173.9	192.9
	TS$_{NPT2}$	316.0	327.0	363.1
	PC$_N$	105.8	110.4	108.1
	(H_2O)Li$^+$Aca[CS]	14.1	22.5	22.5
	(H_2O)Li$^+$Aca[ZW]	38.3	46.7	47.5
	TS$_Z$	63.8	62.1	68.9
	IM$_Z$	42.2	48.1	56.1
	TS$_{ZR1}$	85.4	93.5	101.4
	IM$_{ZR1}$	35.0	42.8	43.8
	TS$_{ZR2}$	67.7	77.1	77.8
	Li$^+$Aca[CS] + H_2O	109.6	114.3	122.8
	Li$^+$Aca[ZW] + H_2O	131.5	135.5	143.2
	Li$^+$Aca[M6] + H_2O	149.6	151.2	166.1
	Li$^+$$(H_2O)$ + Aca	222.1	222.9	231.4
Li$^+$Ser	TS$_O$	49.7	50.1	60.8
(rxn 4)	IM$_O$	50.6	50.1	60.6
	TS$_{OPT}$	277.5	263.5	280.6
	PC$_O$	121.6	124.6	129.5
	(H_2O)Li$^+$Abl	49.8	57.9	63.6
	Li$^+$Abl + H_2O	150.7	154.6	168.5
	Li$^+$$(H_2O)$ + Abl	211.9	215.3	228.1
Li$^+$Ser	TS$_C$	41.9	41.0	52.2
(rxn 4)	IM$_C$	31.7	31.2	39.1
	TS$_{CPT}$	224.2	218.3	241.2
	PC$_C$	12.6	28.3	29.9
	(H_2O)Li$^+$Apa	-45.6	-25.0	-27.6
	Li$^+$Apa + H_2O	50.0	66.8	73.0
	Li$^+$$(H_2O)$ + Apa	131.3	145.8	151.9
Li$^+$Ser	TS$_{DR1}$	54.0	54.8	55.0
(rxn 5)	IM$_{DR1}$	26.0	25.7	27.1
	TS$_{DR2}$	60.4	63.0	70.9
	IM$_{DR2}$	40.2	39.3	50.0

Name	Structure	Theory		
		B3LYP	B3P86	MP2(full)
Li$^+$Ser	TS$_{DPT}$	66.1	59.5	75.1
(rxn 5)	TS$_{DPT2}$	325.7	319.8	329.5
	IM$_{DPT}$	71.8	68.8	79.6
	TS$_{DCC}$	173.9	188.0	193.8
	PC$_D$ = (CO$_2$)Li$^+$May	137.0	163.6	155.6
	(CO$_2$)Li$^+$Eam	-65.8	-38.6	-55.5
	TS$_{EPT}$	263.4	283.7	285.5
	IM$_{EPT}$	21.0	47.0	36.0
	TS$_{ER1}$	25.4	52.0	42.5
	IM$_{ER1}$	18.5	46.6	34.1
	TS$_{ER2}$	27.6	53.8	45.3
	Li$^+$May + CO$_2$	176.6	197.6	200.0
	Li$^+$Eam + CO$_2$	-21.6	-0.1	-6.2
	Li$^+$CO$_2$ + May	394.5	415.1	416.5
	Li$^+$CO$_2$ + Eam	184.0	202.8	198.2
Li$^+$Ser	TS$_{AR}$	35.6	38.2	43.8
(rxn 6)	IM$_{AR}$	34.6	35.4	40.9
	TS$_{APT}$	164.0	174.9	196.8
	TS$_{APT2}$	171.8	187.2	203.8
	TS$_{APT3}$	220.7	222.1	245.7
	PC$_A$	118.6	145.4	161.7
	TS$_{AR2}$	125.6	151.0	166.7
	(HCHO)Li$^+$Cay	101.6	127.0	140.1
	TS$_{IPT}$	135.3	153.4	170.1
	IM$_{IPT}$	121.6	147.0	156.2
	TS$_{IR}$	172.7	197.8	209.1
	(HCHO)Li$^+$Ade	98.2	126.5	133.8
	TS$_{GPT}$	259.4	278.4	295.6
	TS$_{GPT2}$	260.1	281.8	310.4
	IM$_{GPT1}$	11.5	35.6	41.6
	TS$_{GPT3}$	16.6	36.0	49.2
	IM$_{GPT3}$	2.9	29.2	42.0
	TS$_{GR}$	49.0	78.9	88.5
	(HCHO)Li$^+$Gly	-14.4	13.7	18.9
	Li$^+$Gly + HCHO	84.5	107.3	121.6
	Li$^+$Ade + HCHO	199.3	221.5	238.1
	Li$^+$Cay + HCHO	198.2	218.4	238.6
	Li$^+$HCHO + Gly	179.0	204.6	215.6
	Li$^+$HCHO + Ade	296.2	318.3	339.1
	Li$^+$HCHO + Cay	318.4	336.1	362.0
Li$^+$Ser	TS$_{R1}$	49.0	50.4	50.3
(rxn 6)	IM$_{R1}$ = M5[N,OH,OH]	29.7	30.8	25.4
	TS$_{R2}$	82.6	84.3	86.6

	Structure	Theory		
		B3LYP	B3P86	MP2(full)
Li⁺Ser	IM_R2	71.9	73.7	73.8
(rxn 6)	TS_R3	99.7	102.7	105.8
	IM_R3	90.5	93.3	90.5
	TS_R4	93.9	96.7	98.2
	IM_R4	86.1	87.3	89.5
	TS_RPT	233.2	238.0	270.3
	IM_R5	85.1	79.9	94.7
	TS_RPT2	238.2	242.7	275.4
	PC_R	145.2	165.7	178.1
	TS_GPT4	315.3	334.0	353.6
	TS_GPT5	312.8	330.2	358.3
Li⁺Thr	TS_N1	25.3	25.7	30.5
(rxn 4)	IM_N1 = M1[N,CO]	27.2	24.6	30.9
	TS_N2	64.7	65.3	71.4
	IM_N2	52.5	52.7	56.9
	TS_N3	104.0	105.3	113.5
	IM_N3	38.8	36.3	45.2
	TS_NTC	80.3	78.2	90.7
	IM_NTC	77.6	74.2	83.5
	TS_NPT	160.7	168.8	190.4
	TS_NPT2	292.0	304.6	342.7
	PC_N	98.0	102.5	102.2
	$(H_2O)Li^+Amca[CS]$	13.5	22.3	22.9
	$(H_2O)Li^+Amca[ZW]$	32.2	41.3	44.4
	TS_Z	61.2	61.3	69.0
	IM_Z	43.0	49.5	58.8
	TS_ZR1	87.2	96.8	105.3
	IM_ZR1	33.6	42.2	43.4
	TS_ZR2	66.2	76.0	77.1
	$Li^+Amca[CS] + H_2O$	107.5	111.5	122.4
	$Li^+Amca[ZW] + H_2O$	123.7	128.1	139.3
	$Li^+Amca[M6] + H_2O$	149.5	151.1	168.2
	$Li^+(H_2O) + Amca$	226.4	227.1	237.0
Li⁺Thr	TS_O	55.9	56.4	64.4
(rxn 4)	IM_O	54.4	53.8	61.4
	TS_OPT	272.9	259.4	275.0
	PC_O	110.3	115.2	120.4
	$(H_2O)Li^+Ambl$	39.4	48.6	54.2
	$Li^+Ambl + H_2O$	138.7	142.8	157.9
	$Li^+(H_2O) + Ambl$	211.2	214.6	227.4
Li⁺Thr	TS_C	41.0	39.6	50.3
(rxn 4)	IM_C	36.1	34.3	41.5
	TS_CPT	231.6	225.2	250.2

	Structure	Theory		
		B3LYP	B3P86	MP2(full)
Li^+Thr	TS_{CPT2}	228.7	237.4	261.7
(rxn 4)	PC_C	14.8	29.4	40.6
	$(H_2O)Li^+(trans\text{-}Aba)$	-56.3 (0.0)[b]	-36.7 (0.0)[b]	-30.0 (0.0)[b]
	$(H_2O)Li^+(cis\text{-}Aba)$	-43.4 (12.9)[b]	-22.7 (13.0)[b]	-16.7 (13.3)[b]
	$(H_2O)Li^+(3\text{-}Aba)$	-11.0 (45.3)[b]	9.8 (46.5)[b]	4.2 (34.2)[b]
	$Li^+(trans\text{-}Aba) + H_2O$	36.9 (0.0)[b]	52.7 (0.0)[b]	68.5 (0.0)[b]
	$Li^+(cis\text{-}Aba) + H_2O$	49.7 (12.8)[b]	65.8 (13.1)[b]	82.1 (13.6)[b]
	$Li^+(3\text{-}Aba) + H_2O$	83.5 (46.6)[b]	100.5 (47.9)[b]	103.8 (35.3)[b]
	$Li^+(H_2O) + trans\text{-}Aba$	136.9	150.7	161.5
Li^+Thr	TS_{DCC}	180.2	194.5	197.6
(rxn 5)	$PC_D = (CO_2)Li^+Eay$	144.9	170.6	162.5
	TS_{EPT}	266.1	287.6	287.8
	$(CO_2)Li^+Pam$	-63.3	-38.3	-52.7
	$Li^+Pam + CO_2$	-20.5	0.5	-3.9
	$Li^+Eay + CO_2$	183.4	203.6	206.2
	$Li^+CO_2 + Pam$	162.2	180.8	176.7
	$Li^+CO_2 + Eay$	409.3	429.2	429.9
Li^+Thr	TS_{AR}	35.3	38.4	42.8
(rxn 6)	IM_{AR}	34.4	34.9	40.1
	TS_{APT}	138.6	146.5	173.4
	PC_A	76.8	104.9	136.2
	TS_{AR2}	83.5	109.8	141.4
	$(CH_3CHO)Li^+Cay$	61.1	87.5	115.7
	TS_{IPT}	92.9	111.1	144.2
	IM_{IPT}	78.1	104.3	129.6
	TS_{IR}	127.8	153.3	181.2
	TS_{GPT}	217.9	238.9	270.7
	TS_{RPT}	215.8	223.5	260.3
	$(CH_3CHO)Li^+Gly$	-55.5	-24.7	-6.4
	$(CH_3CHO)Li^+Ade$	56.4	86.1	108.3
	$Li^+Gly + CH_3CHO$	61.6	85.1	113.0
	$Li^+Ade + CH_3CHO$	176.5	199.3	229.6
	$Li^+Cay + CH_3CHO$	175.4	196.2	230.0
	$Li^+CH_3CHO + Gly$	129.0	154.2	183.9
	$Li^+CH_3CHO + Ade$	220.0	240.2	279.7
	$Li^+CH_3CHO + Cay$	268.3	285.8	330.4

[a] Structures are optimized at the B3LYP/6-311+G(d,p) level and zero point energies calculated at this level are included in all values. Single point energies are calculated using the indicated level of theory and the 6-311+G(2d,2p) basis set. [b] Value in parenthesis is the energy relative to the trans-Aba form.

Table S2. Geometric Parameters of Transition State and Intermediate Structures Optimized at B3LYP/6-311+G(d,p) Level of Theory

	Species	r(Li$^+$–OC) (Å)	r(Li$^+$–N) (Å)	r(Li$^+$–OH) (Å)	∠Li$^+$OC (°)	∠Li$^+$OCC$_\alpha$ (°)	∠NC$_\alpha$CO(°)
Li$^+$Ser	Li$^+$Ser	1.968	2.091	1.975	103.8	11.6	32.8
(rxn 4)	TS$_{N1}$	1.856	2.039	-	112.7	3.1	5.7
	IM$_{N1}$	1.857	2.033	-	113.6	0.7	7.9
	TS$_{N2}$	1.855	2.065	-	113.1	6.5	25.0
	IM$_{N2}$	1.856	2.061	-	112.8	13.5	29.0
	TS$_{N3}$	1.867	2.051	-	114.4	9.9	26.1
	IM$_{N3}$	1.828	2.079	-	116.5	1.4	16.3
	TS$_{NTC}$	1.726	3.828	-	180.0	127.2	17.4
	IM$_{NTC}$	1.919	-	2.061[a]	94.1	176.7	19.1
	TS$_{NPT}$	1.940	-	1.955[a]	84.1	175.8	24.8
	TS$_{NPT2}$	1.905	1.944	-	110.4	5.1	9.0
	PC$_N$	1.952	-	1.949[a]	82.9	179.2	7.5
	(H$_2$O)Li$^+$Aca[CS]	1.930	2.069	1.894[b]	113.6	9.5	5.8
	(H$_2$O)Li$^+$Aca[ZW]	1.977	-	2.022[a], 1.896[b]	84.4	179.2	169.0
	TS$_Z$	1.962	-	2.113[a], 1.884[b]	81.3	179.3	176.3
	IM$_Z$	1.794	-	1.883[b]	153.3	178.7	176.5
	TS$_{ZR1}$	1.789	-	1.882[b]	163.6	153.2	73.5
	IM$_{ZR1}$	1.909	2.087	1.892[b]	115.8	8.1	3.9
	TS$_{ZR2}$	1.938	2.068	1.892[b]	114.8	6.2	3.0
	Li$^+$Aca[CS]	1.887	2.028	-	113.1	9.0	5.2
	Li$^+$Aca[ZW]	1.940	-	1.975[a]	83.9	179.0	168.8
	Li$^+$Aca[M6]	1.755	-	-	156.7	178.8	176.5
Li$^+$Ser	TS$_O$	1.858	2.046	-	113.9	2.7	18.2
(rxn 4)	IM$_O$	1.864	2.047	-	113.6	1.2	15.3
	TS$_{OPT}$	1.838	2.103	-	110.8	5.6	9.3
	PC$_O$	1.915	2.168	-	100.8	14.9	38.1
	(H$_2$O)Li$^+$Abl	1.968	2.249	1.882[b]	102.4	15.0	38.6
	Li$^+$Abl	1.920	2.189	-	101.9	15.1	37.6

	Species	$r(\text{Li}^+\text{–OC})$ (Å)	$r(\text{Li}^+\text{–N})$ (Å)	$r(\text{Li}^+\text{–OH})$ (Å)	$\angle\text{Li}^+\text{OC}$ (°)	$\angle\text{Li}^+\text{OCC}_\alpha$ (°)	$\angle\text{NC}_\alpha\text{CO}$(°)
Li$^+$Ser	TS$_C$	1.869	2.027	-	112.7	3.1	9.3, 5.2[f]
(rxn 4)	IM$_C$	1.873	2.030	-	112.9	1.5	12.8, 51.6[f]
	TS$_{CPT}$	1.828	2.058	-	111.1	3.2	14.0, 105.9[f]
	PC$_C$	1.860	2.035	-	112.2	4.2	10.7
	(H$_2$O)Li$^+$Apa	1.900	2.110	1.894[b]	114.1	6.4	10.7
	Li$^+$Apa	1.845	2.060	-	113.8	3.8	8.4
Li$^+$Thr	Li$^+$Thr	1.968	2.083	1.961	103.3	11.9	32.6
(rxn 4)	TS$_{N1}$	1.854	2.034	-	112.5	2.5	6.3
	IM$_{N1}$	1.853	2.030	-	113.6	0.2	6.7
	TS$_{N2}$	1.853	2.053	-	112.5	9.9	28.7
	IM$_{N2}$	1.856	2.050	-	112.6	9.6	27.0
	TS$_{N3}$	1.861	2.042	-	115.0	5.4	19.6
	IM$_{N3}$	1.828	2.071	-	116.1	1.8	12.8
	TS$_{NTC}$	1.725	3.817	-	180.0	133.2	12.7
	IM$_{NTC}$	1.921	-	2.049[a]	93.6	176.2	14.2
	TS$_{NPT}$	1.947	-	1.937[a]	84.0	175.0	15.5
	TS$_{NPT2}$	1.905	1.926	-	109.7	6.0	10.5
	PC$_N$	1.912	-	1.958[a]	83.9	179.4	178.3
	(H$_2$O)Li$^+$Amca[CS]	1.930	2.069	1.896[b]	113.6	9.5	5.8
	(H$_2$O)Li$^+$Amca[ZW]	1.970	-	2.014,[a] 1.896[b]	84.4	178.8	174.1
	TS$_Z$	1.959	-	2.104,[a] 1.885[b]	89.9	177.7	177.6
	IM$_Z$	1.791	-	1.884[b]	152.9	177.5	178.5
	TS$_{ZR1}$	1.787	-	1.883[b]	162.0	163.1	79.8
	IM$_{ZR1}$	1.909	2.082	1.893[b]	114.9	4.6	0.5
	TS$_{ZR2}$	1.937	2.063	1.894[b]	113.9	3.5	0.6
	Li$^+$Amca[CS]	1.886	2.022	-	112.3	4.9	2.1
	Li$^+$Amca[ZW]	1.932	-	1.970[a]	83.9	178.3	174.1
	Li$^+$Amca[M6]	1.751	-	-	155.8	177.3	178.1

	Species	r(Li$^+$–OC) (Å)	r(Li$^+$–N) (Å)	r(Li$^+$–OH) (Å)	∠Li$^+$OC (°)	∠Li$^+$OCC$_\alpha$ (°)	∠NC$_\alpha$CO(°)
Li$^+$Thr	TS$_O$	1.856	2.040	-	113.9	4.7	22.2
(rxn 4)	IM$_O$	1.864	2.047	-	113.6	1.2	15.3
	TS$_{OPT}$	1.832	2.095	-	110.5	1.9	8.9
	PC$_O$	1.908	2.159	-	100.6	14.7	38.1
	(H$_2$O)Li$^+$Ambl	1.959	2.243	1.884[b]	102.3	14.9	38.6
	Li$^+$Ambl	1.913	2.180	-	101.7	15.1	37.8
Li$^+$Thr	TS$_C$	1.867	2.024	-	112.6	3.9	10.7, 3.2[c]
(rxn 4)	IM$_C$	1.874	2.023	-	112.6	7.1	21.5, 45.8[c]
	TS$_{CPT}$	1.821	2.146	-	111.6	1.6	11.2, 112.0[c]
	TS$_{CPT2}$	2.032	2.049	1.856	103.1	24.3	19.9, 57.7[c]
	PC$_C$	1.846	2.018	-	112.9	2.0	10.7
	(H$_2$O)Li$^+$(trans-Aba)	1.879	2.094	1.898[b]	114.5	0.0	0.0
	Li$^+$(trans-Aba)	1.838	2.057	-	113.8	0.0	0.0
	(H$_2$O)Li$^+$(cis-Aba)	1.884	2.088	1.898[b]	114.8	3.7	10.9
	Li$^+$(cis-Aba)	1.840	2.046	-	114.4	1.7	7.9
	(H$_2$O)Li$^+$(3-Aba)	1.910	2.087	1.896[b]	113.3	1.2	19.6
	Li$^+$(3-Aba)	1.838	2.057	-	112.6	2.1	20.0
Li$^+$Ser	TS$_{DR1}$	1.984	2.082	1.977	104.1	15.3	28.9
(rxn 5)	IM$_{DR1}$	1.940	2.101	1.965	105.7	10.6	34.3
	TS$_{DR2}$	1.819	-	1.905	127.2	1.6	79.5
	IM$_{DR2}$	1.823	-	1.922	122.3	52.6	151.9
	TS$_{DPT}$	1.788	-	1.974	117.5	66.5	164.7
	TS$_{DPT2}$	1.994	2.100	1.930	111.3	9.2	36.6
	IM$_{DPT}$	1.774	-	1.993	118.2	68.6	161.0
	TS$_{DCC}$	1.883	2.491[d]	1.855	105.0	17.1	145.3
	PC$_D$ = (CO$_2$)Li$^+$May	1.955	2.148[d]	1.909	178.7	93.5[e]	102.4[f]
	(CO$_2$)Li$^+$Eam	1.944	2.039	1.891	179.4	30.9[e]	30.9[f]

	Species	r(Li$^+$−OC) (Å)	r(Li$^+$−N) (Å)	r(Li$^+$−OH) (Å)	∠Li$^+$OC (°)	∠Li$^+$OCC$_\alpha$ (°)	∠NC$_\alpha$CO(°)
	TS$_{EPT}$	1.934	2.282[d]	1.873	178.7	95.1[e]	102.9[f]
	IM$_{EPT}$	1.900	2.950[d]	1.840	179.7	1.4[e]	179.3[f]
	TS$_{ER1}$	1.902	2.988[d]	1.834	179.7	0.1[e]	180.0[f]
	IM$_{ER1}$	1.902	2.976[d]	1.834	179.3	13.7[e]	173.9[f]
	TS$_{ER2}$	1.900	-	1.833	179.6	102.6[e]	127.9[f]
	Li$^+$May	-	2.118[d]	1.871	-	17.7[e]	106.5[f]
	Li$^+$Eam	-	2.011	1.863	-	30.5[e]	50.3[f]
Li$^+$Ser (rxn 6)	TS$_{AR}$	1.848	3.528	1.877	124.9	6.8	85.5
	IM$_{AR}$	1.869	-	1.887	125.7	19.4	105.6
	TS$_{APT}$	1.871	-	1.830	121.0	77.1	23.7
	TS$_{APT2}$	1.811	-	1.904	124.6	88.9	14.9
	TS$_{APT3}$	1.873	-	2.054[a]	94.7	174.3	154.6
	PC$_A$	1.741	-	1.853[g]	157.1	179.5	0.0
	TS$_{AR2}$	1.784	-	1.857[g]	127.7	162.6	0.7
	(HCHO)Li$^+$Cay	1.874	-	2.124,[a] 1.863[g]	97.9	179.7	0.0
	TS$_{IPT}$	1.888	-	2.184,[a] 1.850[g]	98.9	180.0	180.0
	IM$_{IPT}$	1.951[k]	-	2.041,[k] 1.842[g]	98.9[h]	180.0[i]	0.0[j]
	TS$_{IR}$	1.900[k]	3.224	3.429,[k] 1.833[g]	107.9[h]	74.1[i]	0.2[j]
	(HCHO)Li$^+$Ade	-	2.049	1.943,[k] 1.861[g]	110.3[h]	0.0[i]	180.0[j]
	TS$_{GPT}$	2.006	-	2.045,[a] 1.853[g]	86.8	176.6	24.7
	TS$_{GPT2}$	1.803	-	3.086,[a] 1.849[g]	133.1	175.8	4.5
	IM$_{GPT1}$	1.964, 2.052	-	1.861[g]	81.5	180.0	0.0
	TS$_{GPT3}$	1.948, 2.158	-	1.850[g]	91.3	180.0	180.0
	IM$_{GPT3}$	1.793	-	1.843[g]	153.4	180.0	180.0
	TS$_{GR}$	1.806	-	1.840[g]	151.4	171.4	65.9
	(HCHO)Li$^+$Gly	1.905	-	2.104,[a] 1.862[g]	114.6	0.2	6.8
	Li$^+$Gly	1.860	2.063	-	113.9	0.2	5.1
	Li$^+$Ade	-	2.009	1.896[a]	109.3[h]	0.0[i]	180.0[j]
	Li$^+$Cay	1.843	-	2.033	95.8	180.0	0.0
	Li$^+$(HCHO)	1.793			180.0		

	Species	r(Li$^+$–OC) (Å)	r(Li$^+$–N) (Å)	r(Li$^+$–OH) (Å)	∠Li$^+$OC (°)	∠Li$^+$OCC$_\alpha$ (°)	∠NC$_\alpha$CO(°)
Li$^+$Ser	TS$_{R1}$	3.211	2.034	1.857	113.2[h]	15.3[i]	100.6, 43.7[c]
(rxn 6)	IM$_{R1}$	2.018a	2.051	1.941	106.3[h]	14.6[i]	150.4, 52.0[c]
	TS$_{R2}$	-	1.987	1.901[a]	114.7[h]	10.0[i]	156.1, 5.9[c]
	IM$_{R2}$	-	1.987	1.900[a]	115.6[h]	5.1[i]	162.6, 50.9[c]
	TS$_{R3}$	-	2.003	1.887[a]	115.8[h]	10.6[i]	156.0, 127.3[c]
	IM$_{R3}$	-	2.016	1.886[a]	113.7[h]	22.2[i]	141.0, 168.5[c]
	TS$_{R4}$	-	2.004	1.881[a]	115.8[h]	12.3[i]	156.8, 164.9[c]
	IM$_{R4}$	-	2.008	1.898[a]	114.8[h]	13.4[i]	149.9, 164.1[c]
	TS$_{RPT}$	-	2.001	1.877[a]	112.0[h]	6.1[i]	178.2, 179.5[c]
	IM$_{R5}$	1.915	-	2.133[a]	94.9	178.1	170.7
	TS$_{RPT2}$	1.901	-	1.972[a]	92.3	174.5	178.3
	PC$_R$	-	1.998	1.876	109.2[h]	0.0[i]	180.0[j]
Li$^+$Thr	TS$_{AR}$	1.848	3.422	1.876	123.9	0.3	77.8
(rxn 6)	IM$_{AR}$	1.870		1.876	125.1	17.7	103.5
	TS$_{APT}$	1.853	-	1.867[c]	122.0	59.5	22.0
	PC$_A$	1.748	-	1.828[c]	157.0	179.7	0.0
	TS$_{AR2}$	1.791	-	3.053,[a] 1.833[g]	127.4	162.9	0.6
	(CH$_3$CHO)Li$^+$Cay	1.878	-	2.617,[a] 1.838[g]	98.5	180.0	0.0
	TS$_{IPT}$	1.891	-	2.220,[k] 1.824[g]	99.9	180.0	0.0
	IM$_{IPT}$	1.963[k]	-	2.049,[k] 1.818[g]	99.9[h]	180.0[i]	0.0[j]
	TS$_{IR}$	1.908[a]	3.202	3.447,[a] 1.807[g]	107.8[h]	73.1[i]	0.3[j]
	TS$_{GPT}$	2.015		2.057,[a] 1.827[g]	87.0	176.6	150.4
	(CH$_3$CHO)Li$^+$Ade	1.950[a]	2.057	1.836[g]	110.6	0.2	0.0
	(CH$_3$CHO)Li$^+$Gly	1.914	2.110	1.837[g]	114.7	0.4	6.5
	Li$^+$(CH$_3$CHO)	1.766			175.0	172.1	

[a] The Li$^+$–OH(CO) distance. [b] The Li$^+$–OH$_2$ distance. [c] ∠NC$_\alpha$C$_\beta$O(°). [d] The Li$^+$–C$_\alpha$ distance. [e] ∠Li$^+$O(H)C$_\beta$C$_\alpha$(°). [f] ∠NC$_\alpha$C$_\beta$O(H)(°). [g] The Li$^+$–OCHX distance. [h] ∠Li$^+$O(H)C(°). [i] ∠Li$^+$O(H)CC$_\alpha$(°). [j] ∠NC$_\alpha$CO(H)(°). [k] The Li$^+$–OH(COH) distance.

Figure Captions

Figure S1. Optimized structures of (AA – M) and (M)Li$^+$(AA – M) where X = H for (Ser – H$_2$O) = Apa, Abl, and Aca, (Ser – CO$_2$) = Eam and May, and (Ser – XCHO) = Cay and Ade; and X = CH$_3$ for (Thr – H$_2$O) = Aba, Ambl, and Amca, (Thr – CO$_2$) = Pam and Eay, and (Thr – XCHO) = Cay and Ade calculated at the B3LYP/6-311+G(d,p) level of theory. Relative energies in kJ/mol calculated at the MP2(full)/6-311+G(2d,2p) with zero point energy corrections included are shown for Ser, with values in parentheses corresponding to species derived from Thr. Dashed lines show hydrogen bonds with bond lengths indicated in Å for X = H (values for X = CH$_3$ in parentheses).

Figure S2. Calculated potential energy surface for rearrangement of (H$_2$O)Li$^+$Aca conformers at the MP2(full)/6-311+G(2d,2p)//B3LYP/6-311+G(d,p) level of theory.

Figure S3. Calculated potential energy surface for loss of H$_2$O from Li$^+$Ser by transfer of hydrogen from the carboxylic acid group to the side-chain hydroxyl oxygen at the MP2(full)/6-311+G(2d,2p)//B3LYP/6-311+G(d,p) level of theory. The notation describing each transition state and intermediate is described in the text. See Figure 4 for the steps between Li$^+$Ser and IM$_{N2}$.

Figure S4. Calculated potential energy surface for loss of H$_2$O from Li$^+$Ser by transfer of hydrogen from C$_\alpha$ at the MP2(full)/6-311+G(2d,2p)//B3LYP/6-311+G(d,p) level of theory. The notation describing each transition state and intermediate is described in the text.

Figure S5. Calculated potential energy surface for rearrangement of (CO$_2$)Li$^+$May conformers at the MP2(full)/6-311+G(2d,2p)//B3LYP/6-311+G(d,p) level of theory.

Figure S6. Calculated potential energy surface for loss of CO$_2$ from Li$^+$Ser by transfer of the carboxylic acid hydrogen to C$_\alpha$ at the MP2(full)/6-311+G(2d,2p)//B3LYP/6-311+G(d,p) level of theory. The notation describing each transition state and intermediate is described in the text.

Figure S7. Calculated potential energy surface for rearrangement of (HCHO)Li$^+$Cay conformers at the MP2(full)/6-311+G(2d,2p)//B3LYP/6-311+G(d,p) level of theory.

Figure S8. Calculated potential energy surface for loss of HCHO from Li$^+$Ser by transfer of the hydroxyl hydrogen to the carbonyl oxygen to form Li$^+$Ade at the MP2(full)/6-311+G(2d,2p)//B3LYP/6-311+G(d,p) level of theory. The notation describing each transition state and intermediate is described in the text.

Figure S9. Calculated potential energy surface for rearrangement of (HCHO)Li$^+$Cay conformers at the MP2(full)/6-311+G(2d,2p)//B3LYP/6-311+G(d,p) level of theory.