Supplementary Information

Carbocation-\(\pi\) Interaction: Evaluation of the Stabilization by Phenylalanine of a Biochemical Carbocation Intermediate

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**Computational Details**

All Density Functional Theory calculations were performed with the M06/cc-pVTZ method\(^1\)\(^2\) using the Gaussian 09, revision A.02 software.\(^3\) The ultrafine grid option was employed together with the weighting scheme of Stratman, Scuseria and Frisch.\(^4\) Vibrational frequency calculations confirmed that \(\pi\) complex 1 is a local minima. Because the structures for complexes 2, and 3 are not fully optimized, vibrational frequency calculations were not performed on these systems, and thus all reported energies do not include zero-point vibrational corrections. All atomic charges were calculated using the NBO method.\(^5\)

To determine a representative magnitude of the basis set superposition error (BSSE), M06/cc-pVTZ counterpoise calculations\(^6\) were conducted on Model 2 resulting in a correction of 0.0006699 hartrees (0.4 kcal/mol).

CCSD(T)\(^7\) calculations were performed with the cc-pVTZ basis set\(^2\) using the CFOUR v1.0 suite of programs\(^8\).

**Table S1.** M06/cc-pVTZ optimized geometries (Å) and energies (hartrees) for \(t\)-butyl cation, ethylbenzene, and \(\pi\) complex 1.

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Table S1. (continued)

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Comparison of the conformation of the hydrocarbon backbone of isolated GSPPMg$^{2+}$ with that found for GSPPMg$^{2+}$ bound to GPPMT in monomer A of the X-ray structure 3VC1.

Figure S1. a) The minimum energy conformation of GSPP complexed to Mg$^{2+}$ (calculated at M06/cc-pVTZ). b) Comparison of the M06/cc-pVTZ optimized conformation (shown in blue) of the –S–C1–C2–C3–C4–C5–C6–C7– backbone with the corresponding backbone conformation (shown in green) for GSPPMg$^{2+}$ bound to GPPMT in monomer A of the X-ray structure.\textsuperscript{9,10}

To determine if the hydrocarbon backbone of isolated GSPPMg$^{2+}$ differs from that found for GSPPMg$^{2+}$ when it is bound to GPPMT, we have optimized the geometry of the GSPP–Mg$^{2+}$ complex, and the minimum energy conformation calculated at M06/cc-pVTZ is shown in Figure S1(a). To show the difference between this minimum energy conformation and that found in monomer A of the X-ray structure 3VC1, we have superimposed the two backbones so that the positions of C2, C3 and C4 correspond as closely as possible. As shown in Figure S1(b), although the positions of S and C1 in the two structures are also very similar, those of C6, C7, C8 and C9 are very different. These results show that the C1-C7 backbone of GSPPMg$^{2+}$ bound to GPPMT is much more extended than that calculated for isolated GSPPMg$^{2+}$.
Table S2. Bond lengths and angles defining the position of C3 of GSPP with respect to the aromatic ring of F222. The correspondences between the atom designations shown in the Figure and those in the X-ray structure are 3 ≡ C3/303 GST; C1 ≡ CG/222 PHE; C2 ≡ CD1/222 PHE; C3 ≡ CE1/222 PHE; C4 ≡ CZ/222 PHE; C5 ≡ CE2/222 PHE; and C6 ≡ CD2/222 PHE.

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Table S3. Cartesian coordinates (Å) and M06/cc-pVTZ energies (hartrees) for model complex 2, the F222 mimic, and its binding partner (Figure 6).

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Energy (complex 2) = –3354.4890721; Energy (F222 mimic) = –726.5906212

Energy (binding partner) = –2627.8751000

S9
Table S4. Calculated NBO<sup>5</sup> charges on the tertiary carbon atom

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Estimate of the carbocation-π binding contribution to the stabilization energy of complex 2

In addition to a contribution from carbocation-π binding, the total stabilization energy calculated for complex 2 may contain components from other attractive interactions, such as that between the F222 mimic and the (–diphosphate–Mg<sup>2+</sup>) moiety. To estimate the contribution that carbocation-π binding *alone* makes to the stabilization energy of complex 2, calculations were performed on complex 3, shown in Figure S2, in which the (–diphosphate–Mg<sup>2+</sup>) fragment has been replaced by a methyl group. The calculated binding energy for this complex is −13.6 kcal/mol.

Figure S2. Complex 3 constructed from model structure 2 by replacing the (–diphosphate–Mg<sup>2+</sup>) fragment with a methyl group. The fragment labeled A is the F222 mimic, that labeled B is a model of the carbocation species, and the separation of these two binding partners is identical to that in model structure 2.

Because the NBO<sup>5</sup> charge (0.651) on C3 in complex 3 is larger than the value of 0.590 calculated for model structure 2, we have rescaled the binding energy for complex 3 by the ratio of these charges, producing an estimate of −12.3 kcal/mol for the carbocation-π binding contribution to the stabilization energy for complex 3. Although approximate, this analysis suggests that the contribution from the attractive interaction between the (–diphosphate–Mg<sup>2+</sup>) fragment and F222 is approximately 2 kcal/mol.
Table S5. Cartesian coordinates (Å) and M06/cc-pvtz energies (hartrees) for complex 3 and binding partners A and B

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Energy (fragment A) = \(-726.5906212\); Energy (fragment B) = \(-1333.2338595\);

Energy (complex 3) = \(-2059.8462203\).
**Figure S3.** Bond angles in the C2 – C3 – C4 fragment of model structure 2 (X – C3 – X is the pyramidal axis – it is equivalent to the three-fold axis if C3 were trigonal planar)

\[ \angle X – C3 – C10 = 94.1^\circ \quad \angle X – C3 – C4 = 91.5^\circ \quad \angle X – C3 – C2 = 92.7^\circ \]

\[ \angle H – C2 – C3 = 95.7^\circ \quad \angle H – C2 – C3 – X = -160.4^\circ \]
Notes and References

(10) The structure of monomer A is from Protein Data bank entry 3VC1.