Supplementary Information

A Simpler Method Affords Evaluation of π Stabilization by Phenylalanine of Several Biochemical Carbocations

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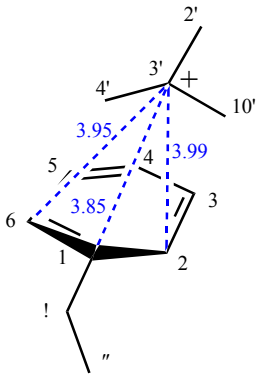
1. Computational Details

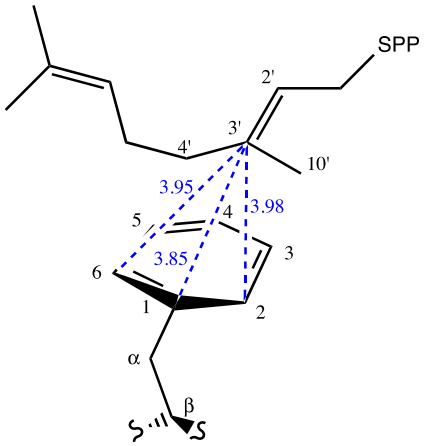
All Density Functional Theory calculations were performed with the M06/cc-pVTZ method[1,2] using the Gaussian 09, revision A.02 software.[3] The ultrafine grid option was employed together with the weighting scheme of Stratman, Scuseria and Frisch.[4] For all fully optimized geometries, vibrational frequency calculations were used to confirm that the structures are local minima. Because structures for many of the model complexes 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. Atomic charges were calculated using the NBO method.[5] Basis set superposition errors were determined using M06/cc-pVTZ counterpoise calculations[6] and were always less than 5% of the calculated binding energies.

2. Table S1. Structural information for model **2** of monomer A, the GSPP-F222 complex shown in Figure 2, based upon X-ray structure with the PDB code 3VC1[7], modifications of model **2**, monomers B-L of GPPMT[7], and models of monomers B-L with their respective stabilization energies.

ChemDraw Version of Model **2**



ChemDraw Version of Figure 2



The values below for model **2** are followed parenthetically by those for the Figure 2 complex.

Distances (Å)[a]

C3'–C1 = 3.85 (3.85)	C3'–C2 = 3.99 (3.98)	C3'–C3 = 4.24 (4.24)
C3'–C4 = 4.35 (4.37)	C3'–C5 = 4.21 (4.19)	C3'–C6 = 3.95 (3.95)

Angles (°)[a]

C4–C1–C3' = 80.0 (80.2)	C5–C2–C3' = 74.7 (74.3)	C3–C6–C3' = 76.0 (75.9)
C1–C3'–C2' = 86.6 (87.3)	C2–C3'–C2' = 76.6 (77.4)	C6–C3'–C2' = 76.6 (77.3)
C4'–C3'–C10' = 119.8 (119.8)	C10'–C3'–C2' = 120.1 (116.0)	C2'–C3'–C4' = 120.1 (124.2)

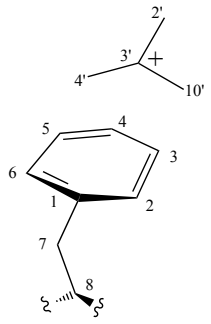
Dihedral angles (°)[a]

C6–C1–Cα–Cβ = 115.9 (115.9)	C4–C1–C3'–C2' = 0.0 (–0.5)
C5–C2–C3'–C2' = –54.4 (–54.1)	C3–C6–C3'–C2' = 54.6 (54.4)
C4–C1–C3'–C10' = –120.1 (–116.4)	C5–C2–C3'–C10' = –174.8 (–171.5)
C3–C6–C3'–C10' = –62.8 (–58.5)	C4–C1–C3'–C4' = 121.3 (124.2)
C5–C2–C3'–C4' = 64.3 (68.3)	C3–C6–C3'–C4' = –176.8 (–175.2)

Modifications of Model **2**

Eight other complexes of the *t*-butyl cation and this ethylbenzene were constructed, principally to try to evaluate the effect of adjustments of the values of the dihedral angles, which cannot be made to correspond precisely to those in the complex shown above as Figure 2 because of the disparity between the values of angles C2'–C3'–C4' and C10'–C3'–C2' in Model **2** vs. Figure 2. The dihedral angle C4–C1–-C3'–C2' of 0.0º in model **2** was changed by rotation of the *t*-butyl group to each of the following eight values: +8,

+6º, +4º, +2º, –2º, –4º, –6º, and –8º. The calculated binding energy of each of these eight complexes was respectively: –12.3, –12.3, –12.3, –12.3, –12.3, –12.3, –12.2, and –12.2 kcal/mol. The version with the dihedral angle C4–C1–C3'–C2' rotated +4º is selected for detailed presentation below because this rotation brings C4' and C10' of the *t*-butyl cation into close correspondence with C4' and C10' of GSPP in the X-ray structure.



Version of model **2** with *t*-Bu^+ rotated by +4º
Calculated stabilization energy = –12.3 kcal/mol

Distances (Å)

C3'–C1 = 3.85	C3'–C2 = 3.99	C3'–C3 = 4.24
C3'–C4 = 4.35	C3'–C5 = 4.21	C3'–C6 = 3.95

Angles (°)[a]

C4–C1–C3' = 80.0	C5–C2–C3' = 74.7	C3–C6–C3' = 76.0
C1–C3'–C2' = 86.6	C2–C3'–C2' = 77.8	C6–C3'–C2' = 75.4
C4'–C3'–C10' = 119.8	C10'–C3'–C2' = 120.1	C2'–C3'–C4' = 120.1

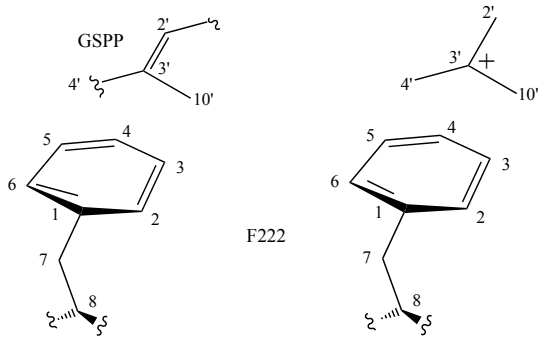
Dihedral angles (°)[a]

C6–C1–C7–C8 = 115.9	C4–C1–C3'–C2' = 4.0
C5–C2–C3'–C2' = –50.5	C3–C6–C3'–C2' = 58.5
C4–C1–C3'–C10' = –116.1	C5–C2–C3'–C10' = –171.0
C3–C6–C3'–C10' = –58.1	C4–C1–C3'–C4' = 125.3
C5–C2–C3'–C4' = 68.3	C3–C6–C3'–C4' = –172.9

Cartesian coordinates of any of the variations of model **2** are available upon request.

Structural information for the twelve monomers in the single crystal in the X-ray structure of the GSPP-F222 complex[7], structural data and calculated stabilization energies for models for each of the twelve monomers.

Numbering systems used in the following two tables



Measurements of monomers A-L from the X-ray structure of the GSPP-F222 complex[7]

monomer	R(3'–1) Å	R(3'–2) Å	R(3'–6) Å	∠3'–1–4°	∠3'–2–5°	∠3'–6–3°	∠2–3'–1°	∠6–3'–1°
A	3.85	3.98	3.95	80.2	74.3	75.9	20.2	20.6
B	3.84	3.96	3.97	81.7	75.9	76.4	20.5	20.4
C	3.85	3.97	4.00	79.9	75.7	74.5	20.3	20.3
D	3.96	4.13	4.06	80.9	75.0	77.2	19.4	20.0
E	3.76	3.77	4.08	80.9	81.0	68.9	21.4	20.2
F	3.91	3.99	4.09	80.5	77.7	73.8	20.2	19.7
G	3.95	4.11	4.13	83.4	77.7	77.5	19.9	19.6
H	3.95	4.11	4.07	81.1	75.8	77.0	19.6	19.9
I	3.94	3.86	4.16	76.4	79.9	67.3	20.4	19.4
J	3.89	4.06	4.03	82.1	74.8	77.3	20.1	20.3
K	3.90	4.11	3.98	81.0	73.1	78.1	20.0	20.1
L	3.84	3.92	3.96	78.5	75.4	73.6	20.4	20.7
Mean	3.89 ± 0.04	4.00 ± 0.07	4.04 ± 0.05	80.5 ± 1.1	76.4 ± 1.4	74.8 ± 2.2	20.2 ± 0.3	20.1 ± 0.2

Measurements and stabilization energies (ΔE (kcal/mol) for the models for monomers

monomer	R(3'–1) Å	R(3'–2) Å	R(3'–6) Å	∠3'–1–4°	∠3'–2–5°	∠3'–6–3°	∠2–3'–1°	∠6–3'–1°	ΔE
A	3.85	3.99	3.95	80.0	74.7	76.0	20.3	20.4	–12.3
B	3.83	3.96	3.99	82.0	76.9	75.8	20.5	20.3	–12.2
C	3.86	3.98	3.99	80.0	75.6	75.0	20.4	20.3	–12.2
D	3.96	4.10	4.07	80.9	75.4	76.7	19.8	19.9	–11.5
E	3.76	3.77	4.02	80.9	80.6	70.7	21.3	20.2	–12.2
F	3.91	3.99	4.07	80.5	77.3	74.2	20.2	19.9	–11.8
G	3.96	4.10	4.13	83.4	76.9	76.8	19.8	19.6	–11.1
H	3.96	4.10	4.07	81.1	75.5	76.8	19.8	19.8	–11.5
I	3.94	3.86	4.16	76.4	79.7	67.6	20.5	19.5	–11.5
J	3.89	4.05	4.02	82.3	76.0	77.3	20.0	20.1	–11.9
K	3.90	4.09	3.97	81.0	73.5	78.5	19.8	20.3	–12.0
L	3.84	3.92	3.97	78.5	75.3	73.6	20.6	20.4	–12.4

The calculated carbocation-π stabilization energies for the models for monomers A-L (model **2** and analogs) ranged from –11.1 to –12.4 kcal/mol (mean –11.9 kcal/mol), roughly correlating with the distances from $C_{3'}$ of GSPP to C_1 of F222 measured for the monomers, which ranged from 3.76Å to 3.96Å (mean 3.89Å).

3. Table S2. M06/cc-pVTZ optimized geometries (Å) and energies (hartrees) for the *t*-butyl cation (*t*-Bu^+), ethylbenzene with the side chain dihedral angle of F222 of geranyl diphosphate C-methyl transferase, model **2**, a modified *t*-Bu^+, and a modified model **2**.

Coordinates for the *t*-butyl cation

Atom	x	y	z
C	-9.18057191	2.24856231	-0.32629851
C	-9.56033036	2.33763183	1.06868796
H	-10.18044282	3.22248636	1.24283992
H	-10.01174525	1.43685383	1.47393968
H	-8.63573025	2.56246991	1.62499001
C	-9.29470305	0.98829936	-1.03035060
H	-10.37869193	0.83579317	-1.17167873
H	-8.81195327	0.96765141	-2.00341514
H	-8.99662043	0.14796837	-0.39808247
C	-8.67880312	3.41846314	-1.01950079
H	-8.73819074	4.34292249	-0.45331418
H	-7.63118242	3.20698842	-1.28298626
H	-9.16635840	3.51229331	-1.99637891

Energy = –157.4696686

Coordinates for the ethylbenzene representing F222 of geranyl diphosphate C-methyl transferase

Atom	x	y	z
C	-1.57652115	0.50959477	-0.54119333
C	-0.19994465	0.40109062	-0.60689669
C	0.62096708	1.45196632	-0.21087530
C	0.02215312	2.61777053	0.24549003
C	-1.35682616	2.73212793	0.31498947
C	-2.16084699	1.67735356	-0.07710839
H	-2.19813523	-0.31871792	-0.85697419
H	0.25037090	-0.51284462	-0.98009003
H	0.64875317	3.44846935	0.55133421
H	-1.80345424	3.65025048	0.67517428
H	-3.23840098	1.76401547	-0.02542103

C	2.11375247	1.32137328	-0.28342697
H	2.40639294	1.08691473	-1.31210620
H	2.57221008	2.28477027	-0.04727583
C	2.65737153	0.24852423	0.64700835
H	2.24246436	-0.73120633	0.40506887
H	3.74323548	0.17547942	0.57957529

Energy = –310.7225951

Coordinates for model **2**

Atom	x	y	z
C	-0.11379806	0.15382053	4.40298148
C	1.25433201	0.08210172	4.21821740
C	2.07933223	1.15054517	4.55415792
C	1.49261166	2.29606060	5.07329586
C	0.12226950	2.37353981	5.26211753
C	-0.68547142	1.30159587	4.92859936
H	-0.73904712	-0.68764024	4.13238799
H	1.69391344	-0.81629117	3.79750129
H	2.12191548	3.14013116	5.33359542
H	-0.31487235	3.27632522	5.66960377
H	-1.75643922	1.35946134	5.07349891
C	3.56317502	1.05985817	4.35235189
H	3.77207181	0.84246315	3.29978658
H	4.01564088	2.03279180	4.55913096
C	4.21189754	-0.00670702	5.22058435
H	3.80271244	-0.99476880	5.00411815
H	5.28943090	-0.05059755	5.05943513
H	4.03513447	0.19443611	6.27859831
C	1.02740242	2.63414988	1.16080254
C	-0.33232330	2.58249128	1.65720830
H	-0.79253008	3.57483428	1.62626992
H	-0.95717147	1.82742291	1.18932562
H	-0.25582237	2.37132137	2.73646493
C	1.49433447	1.63795396	0.21917749
H	0.99239760	1.88543754	-0.73218407

H	2.56822144	1.63840129	0.05458226
H	1.10933204	0.64443449	0.46295809
C	1.92665942	3.67851122	1.60996951
H	1.46285609	4.44578625	2.22221409
H	2.73306028	3.18490969	2.17339625
H	2.45292568	4.11207271	0.75198303

Energy = –468.2118849

Coordinates for the *t*-butyl cation modified to approximate the geometry of the carbon atoms surrounding the putative carbocationic site in Figure 2.

Atom	x	y	z
C	1.02688000	2.63335000	1.16141000
C	-0.25618000	2.36343000	1.77691000
H	-0.86008000	3.27468000	1.82605000
H	-0.80323000	1.53368000	1.33907000
H	0.16710236	2.16737115	2.81051968
C	1.54501000	1.74290000	0.14369000
H	0.92317000	1.93417000	-0.74792000
H	2.58612000	1.91069000	-0.11763000
H	1.33761000	0.69676000	0.38309000
C	1.79907000	3.79114000	1.56682000
H	1.28668000	4.46386000	2.24768000
H	2.72020000	3.41242000	2.03530000
H	2.17033000	4.32038000	0.68187000

Energy = –157.4662132

Coordinates for the modified model **2**

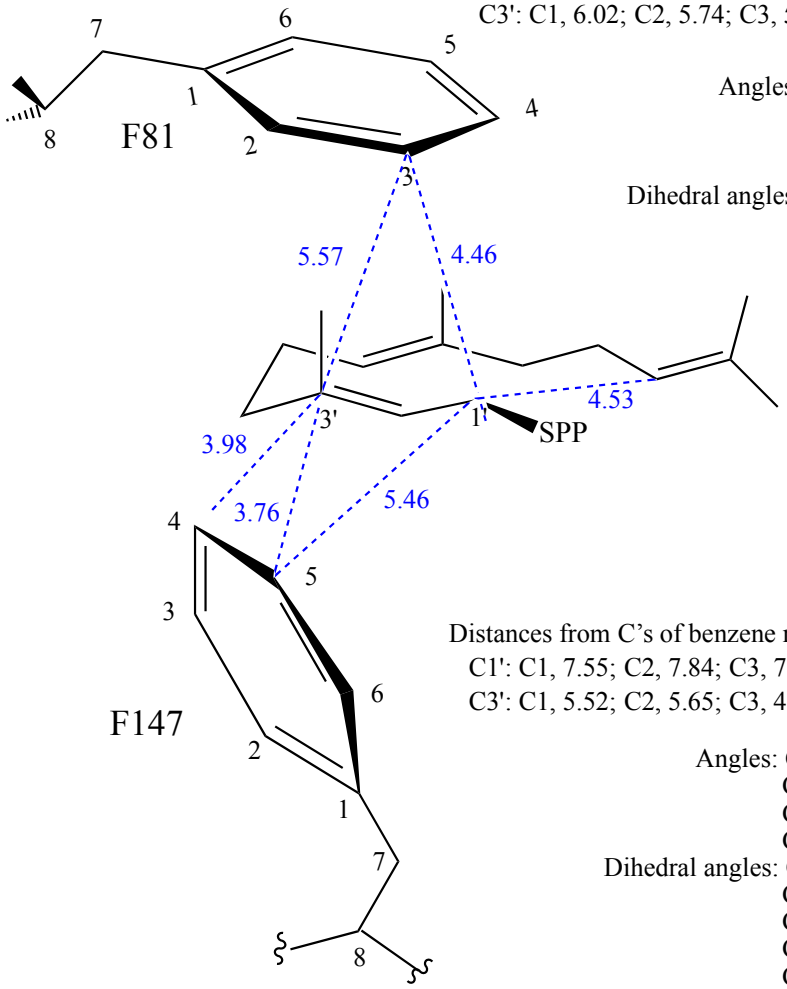
Atom	x	y	z
C	-0.11380000	0.15382000	4.40298000
C	1.25433000	0.08210000	4.21822000
C	2.07933000	1.15055000	4.55416000
C	1.49261000	2.29606000	5.07330000
C	0.12227000	2.37354000	5.26212000
C	-0.68547000	1.30160000	4.92860000

H	-0.73905000	-0.68764000	4.13239000
H	1.69391000	-0.81629000	3.79750000
H	2.12192000	3.14013000	5.33360000
H	-0.31487000	3.27633000	5.66960000
H	-1.75644000	1.35946000	5.07350000
C	3.56318000	1.05986000	4.35235000
H	3.77207000	0.84246000	3.29979000
H	4.01564000	2.03279000	4.55913000
C	4.21190000	-0.00671000	5.22058000
H	3.80271000	-0.99477000	5.00412000
H	5.28943000	-0.05060000	5.05944000
H	4.03513000	0.19444000	6.27860000
C	1.02688000	2.63335000	1.16141000
C	-0.25618000	2.36343000	1.77691000
H	-0.86008000	3.27468000	1.82605000
H	-0.80323000	1.53368000	1.33907000
H	0.16710236	2.16737115	2.81051968
C	1.54501000	1.74290000	0.14369000
H	0.92317000	1.93417000	-0.74792000
H	2.58612000	1.91069000	-0.11763000
H	1.33761000	0.69676000	0.38309000
C	1.79907000	3.79114000	1.56682000
H	1.28668000	4.46386000	2.24768000
H	2.72020000	3.41242000	2.03530000
H	2.17033000	4.32038000	0.68187000

Energy = –468.2077092

4. Table S3. Structural information for the F81-F147-FSPP complex[8] (Figure 6), the complex in which that FSPP has been replaced by an optimized 1,1-dimethylallyl cation (DMA^+), model **3** (Figure 7), model **4** (Figure 8), a modified DMA^+, model **5** (Figure 9), the F81-F147-AI^+ complex[8] (Figure 10) and model **6** (Figure 11).

Structural information for the F81-F147-FSPP complex in the active site of aristolochene synthase[8] as determined from X-ray structure PDB Code 4KUX and shown in Figure 6.



F81

Distances from C's of benzene ring to C1' and C3' of FSPP in Å:
C1': C1, 5.86; C2, 5.05; C3, 4.46; C4, 4.85; C5, 5.68; C6, 6.14
C3': C1, 6.02; C2, 5.74; C3, 5.57; C4, 5.74; C5, 6.04; C6, 6.17

Angles: C6; C3; C1' = 114.0º
C6; C3; C3' = 86.8º
C1; C4; C1' = 96.3º
C1; C4; C3' = 81.9º
Dihedral angles: C6; C3; C1'; C2' = 11.4º
C6; C3; C3'; C2' =141.7º
C1; C4; C1'; C2' = 82.1º
C1; C4; C3'; C2' = -154.4º
C6; C1; C7; C8 = 126.6º

F147

Distances from C's of benzene ring to C1' and C3' of FSPP in Å:
C1': C1, 7.55; C2, 7.84; C3, 7.08; C4, 5.88; C5, 5.46; C6, 6.40
C3': C1, 5.52; C2, 5.65; C3, 4.96; C4, 3.98; C5, 3.76; C6, 4.65

Angles: C2; C5; C1' = 141.7º
C2; C5; C3' = 118.5º
C1; C4; C1' = 116.3º
C1; C4; C3' = 107.5º
Dihedral angles: C2; C5; C1'; C2' = -41.4º
C2; C5; C3'; C2' = -148.8º
C1; C4; C1'; C2' = 38.8º
C1; C4; C3'; C2' = -80.5º
C6; C1; C7; C8 = 79.5º

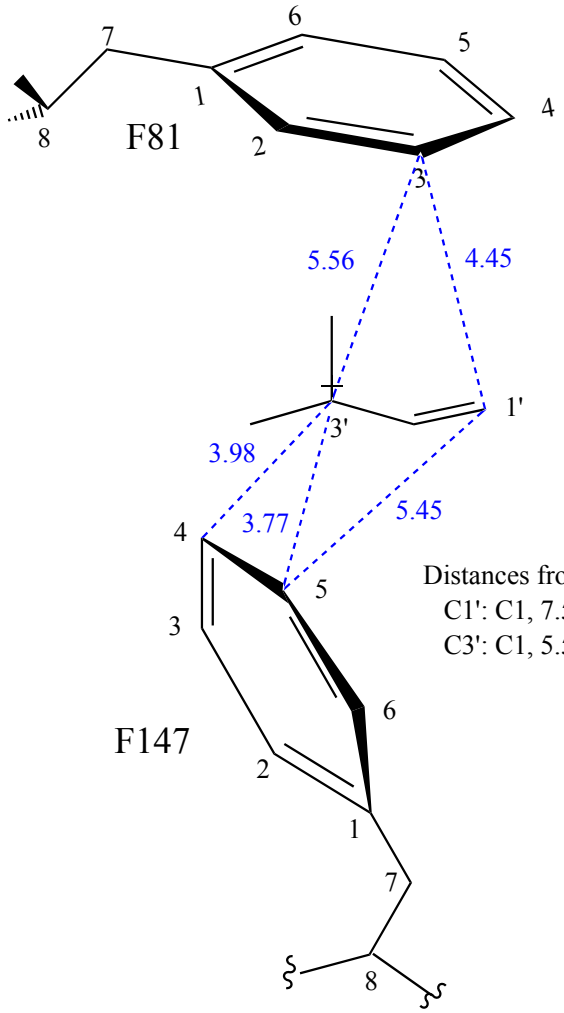
Structural information for the model (designated complex **6A**) in which the X-ray coordinates from Figure 6 were used to convert F81 and F147 to appropriate ethylbenzenes and FSPP has been replaced by an optimized 1,1-dimethylallyl cation (DMA^+). Complex **6A** had a calculated stabilization energy of –9.5 kcal/mol.

F81

Distances from benzene ring C's to C1' and C3' of DMA^+ in Å:
C1': C1, 5.83; C2, 5.05; C3, 4.45; C4, 4.81; C5, 5.61; C6, 6.08
C3': C1, 6.00; C2, 5.72; C3, 5.56; C4, 5.73; C5, 6.02; C6, 6.14

Angles:
C6; C3; C1' = 112.5º
C6; C3; C3' = 88.3º
C1; C4; C1' = 96.6º
C1; C4; C3' = 81.6º

Dihedral Angles:
C6; C3; C1'; C2' = 8.6º
C6; C3; C3'; C2' = 143.0º
C1; C4; C1'; C2' = 80.9º
C1; C4; C3'; C2' = -153.3º
C6; C1; C7; C8 = 126.6º



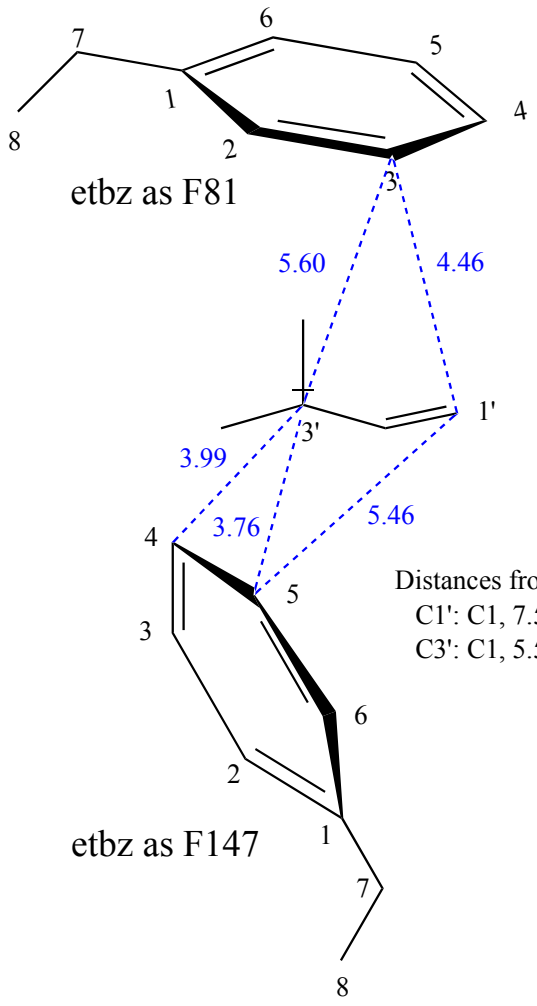
F147

Distances from benzene ring C's to C1' and C3' of DMA^+ in Å:
C1': C1, 7.52; C2, 7.81; C3, 7.05; C4, 5.86; C5, 5.45; C6, 6.38
C3': C1, 5.52; C2, 5.66; C3, 4.94; C4, 3.98; C5, 3.77; C6, 4.64

Angles:
C2; C5; C1' = 140.8º
C2; C5; C3' = 118.5º
C1; C4; C1' = 115.6º
C1; C4; C3' = 107.7º

Dihedral Angles:
C2; C5; C1'; C2' = -43.9º
C2; C5; C3'; C2' = -149.9º
C1; C4; C1'; C2' = 34.3º
C1; C4; C3'; C2' = -81.1º
C6; C1; C7; C8 = 79.5º

Structural information for the complex in which an optimized DMA^+ and appropriate optimized ethylbenzenes representing F81and F147 were separately combined to create Model **3** (Figure 7). This complex had a calculated stabilization energy of –9.5 kcal/mol.



"F81"

Distances from benzene ring C's to C1' and C3' of DMA^+ in Å:

C1': C1, 5.86; C2, 5.03; C3, 4.46; C4, 4.84; C5, 5.68; C6, 6.14

C3': C1, 6.02; C2, 5.74; C3, 5.57; C4, 5.74; C5, 6.04; C6, 6.17

Angles:

C6; C3; C1' = 114.0º
C6; C3; C3' = 86.8º
C1; C4; C1' = 96.3º
C1; C4; C3' = 81.9º

Dihedral Angles:

C6; C3; C1'; C2' = 11.4º
C6; C3; C3'; C2' = 141.7º
C1; C4; C1'; C2' = 82.1º
C1; C4; C3'; C2' = -154.4º
C6; C1; C7; C8 = 126.6º

"F147"

Distances from benzene ring C's to C1' and C3' of DMA^+ in Å:

C1': C1, 7.55; C2, 7.84; C3, 7.08; C4, 5.88; C5, 5.46; C6, 6.40

C3': C1, 5.52; C2, 5.65; C3, 4.96; C4, 3.98; C5, 3.76; C6, 4.65

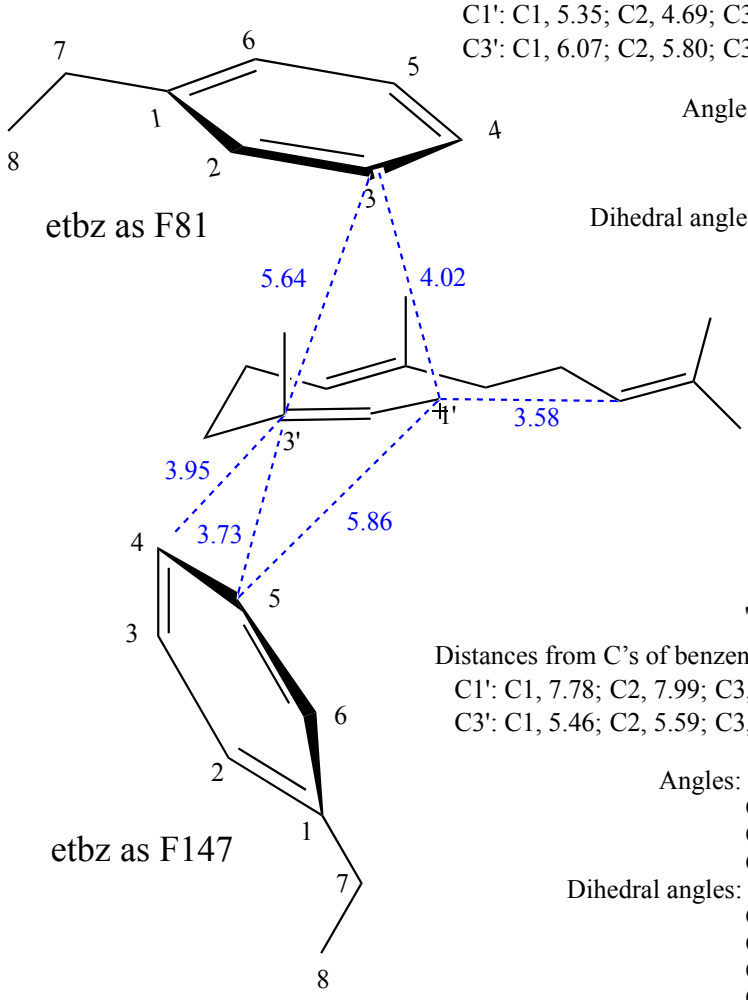
Angles:

C2; C5; C1' = 141.7º
C2; C5; C3' = 118.5º
C1; C4; C1' = 116.3º
C1; C4; C3' = 107.5º

Dihedral Angles:

C2; C5; C1'; C2' = -43.6º
C2; C5; C3'; C2' = -148.8º
C1; C4; C1'; C2' = 38.8º
C1; C4; C3'; C2' = -80.5º
C6; C1; C7; C8 = 79.5º

Structural information for the complex in which F81 and F147 are represented by appropriate ethylbenzenes and the optimized DMA^+ in complex **6A** has been replaced with an appropriately placed farnesyl cation (F^+) in which the segment comprising C_1 to C_4 and the C_3 methyl group has been optimized to create Model **4** (Figure 8). This complex had a calculated stabilization energy of –11.2 kcal/mol.



"F81"

Distances from C's of benzene ring to C1' and C3' of F^+mod in Å:
C1': C1, 5.35; C2, 4.69; C3, 4.02; C4, 4.15; C5, 4.88; C6, 5.43
C3': C1, 6.07; C2, 5.80; C3, 5.64; C4, 5.80; C5, 6.08; C6, 6.21

Angles: C6; C3; C1' = 104.7º
C6; C3; C3' = 88.3º
C1; C4; C1' = 99.0º
C1; C4; C3' = 81.9º
Dihedral angles: C6; C3; C1'; C2' = -26.7º
C6; C3; C3'; C2' =129.7º
C1; C4; C1'; C2' = 65.7º
C1; C4; C3'; C2' = -164.6º
C6; C1; C7; C8 = 126.6º

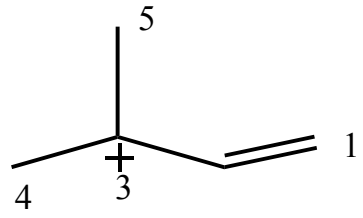
"F147"

Distances from C's of benzene ring to C1' and C3' of F^+mod in Å:
C1': C1, 7.78; C2, 7.99; C3, 7.25; C4, 6.16; C5, 5.86; C6, 6.74
C3': C1, 5.46; C2, 5.59; C3, 4.91; C4, 3.95; C5, 3.73; C6, 4.58

Angles: C2; C5; C1' = 132.6º
C2; C5; C3' = 117.6º
C1; C4; C1' = 115.1º
C1; C4; C3' = 106.6º
Dihedral angles: C2; C5; C1'; C2' = -62.4º
C2; C5; C3'; C2' = -144.1º
C1; C4; C1'; C2' = 7.2º
C1; C4; C3'; C2' = -79.8º
C6; C1; C7; C8 = 79.5º

Structural information for the 1,1-dimethylallyl cation (DMA^+), the DMA^+ modified to approximate the optimized C_1-C_4 segment of the farnesyl cation (F^+) derived from FSPP, and for that optimized C_1–C_4 segment.

DMA^+



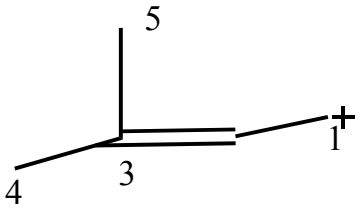
Distances in Å: C1;C2 = 1.35; C2;C3 = 1.41
C3;C4 = 1.46; C3;C5 = 1.46

Angles: C1;C2;C3 = 123.5º; C2;C3;C4 = 118.7º
C4;C3;C5 = 117.5º; C2;C3;C5 = 124.4º

Dihedral Angles: C1;C2;C3;C4 = 178.7º
C1;C2;C3;C5 = -0.6º

NBO Charges: C1, -0.030; C3, +0.468

DMA^+mod



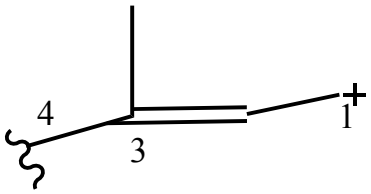
Distances in Å: C1;C2 = 1.35; C2;C3 = 1.41
C3;C4 = 1.48; C3;C5 = 1.49

Angles: C1;C2;C3 = 123.1º; C2;C3;C4 = 117.2º
C4;C3;C5 = 121.1º; C2;C3;C5 = 120.9º

Dihedral Angles: C1;C2;C3;C4 = 150.1º
C1;C2;C3;C5 = -19.8º

NBO Charges: C1, -0.036; C3, +0.474

Comparable segment of F^+ from FSPP



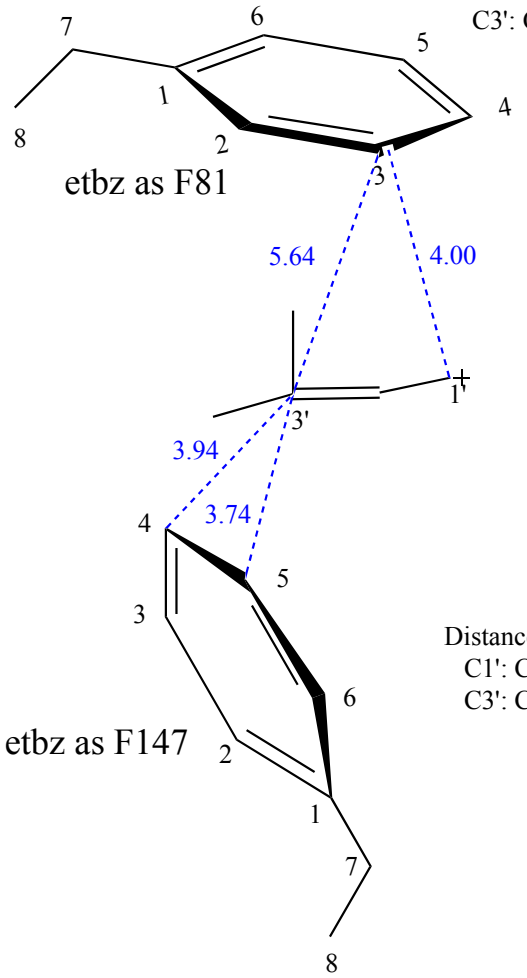
Distances in Å: C1;C2 = 1.35; C2;C3 = 1.41
C3;C4 = 1.48; C3;C5 = 1.49

Angles: C1;C2;C3 = 123.1º; C2;C3;C4 = 116.9º
C4;C3;C5 = 121.8º; C2;C3;C5 = 120.5º

Dihedral Angles: C1;C2;C3;C4 = 150.1º
C1;C2;C3;C5 = -19.6º

NBO Charges: C1, -0.072; C3, +0.452

Structural information for the complex in which F81 and F147 are represented by appropriate ethylbenzenes and the optimized DMA^+ in Structure **6A** has been replaced with the DMA^+ modified to approximate the optimized segment of F^+ comprising C_1 to C_4 and the C_3 methyl group, to create model **5**, shown in Figure 9. This complex had a calculated stabilization energy of –10.3 kcal/mol.



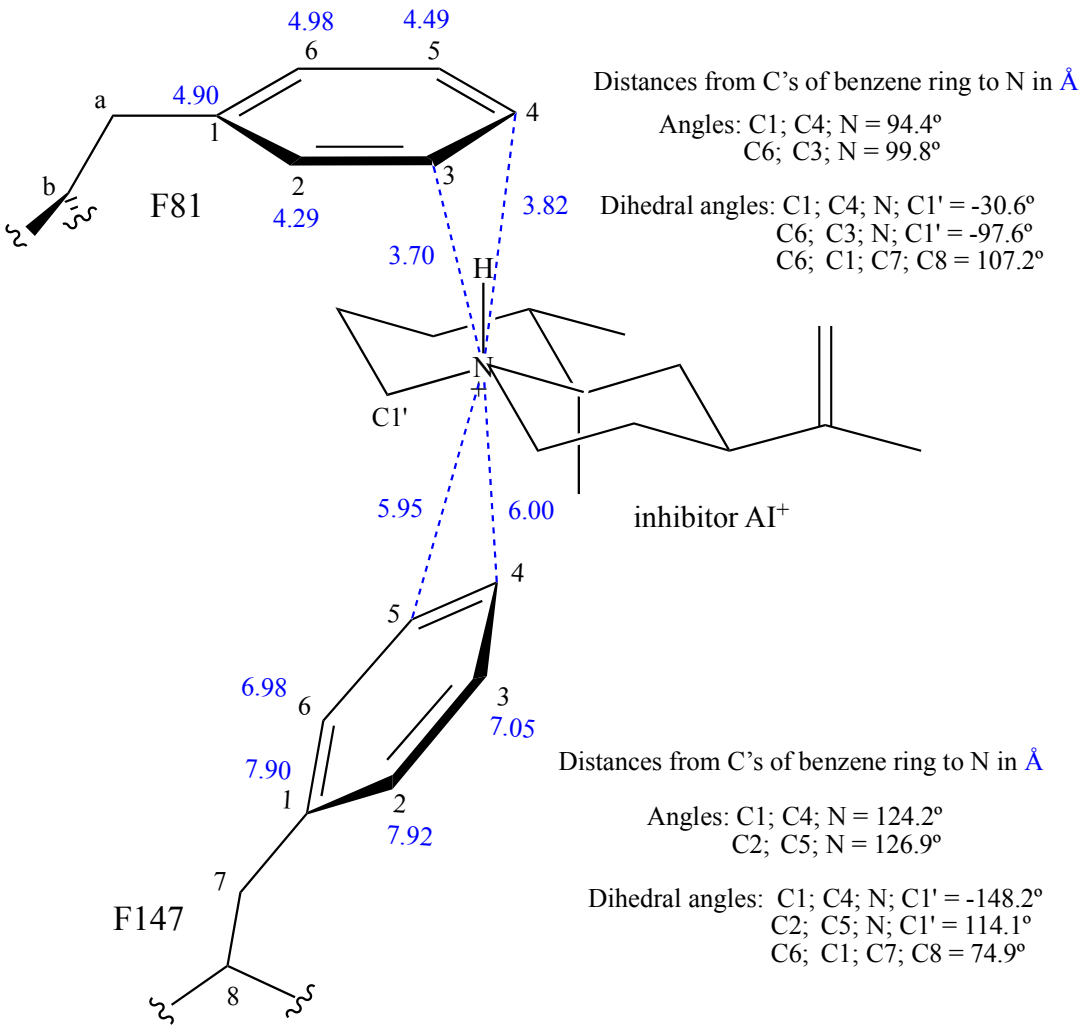
Distances from benzene C's to C1' and C3' of DMA^+mod in Å:
C1': C1, 5.32; C2, 4.67; C3, 4.00; C4, 4.14; C5, 4.87; C6, 5.40
C3': C1, 6.05; C2, 5.79; C3, 5.64; C4, 5.79; C5, 6.06; C6, 6.18

Angles: C6; C3; C1' = 104.4º
C6; C3; C3' = 87.7º
C1; C4; C1' = 85.8º
C1; C4; C3' = 81.6º
Dihedral angles: C6; C3; C1'; C2' = -26.9º
C6; C3; C3'; C2' = 132.4º
C1; C4; C1'; C2' = 66.1º
C1; C4; C3'; C2' = -162.9º
C6; C1; C7; C8 = 126.6º

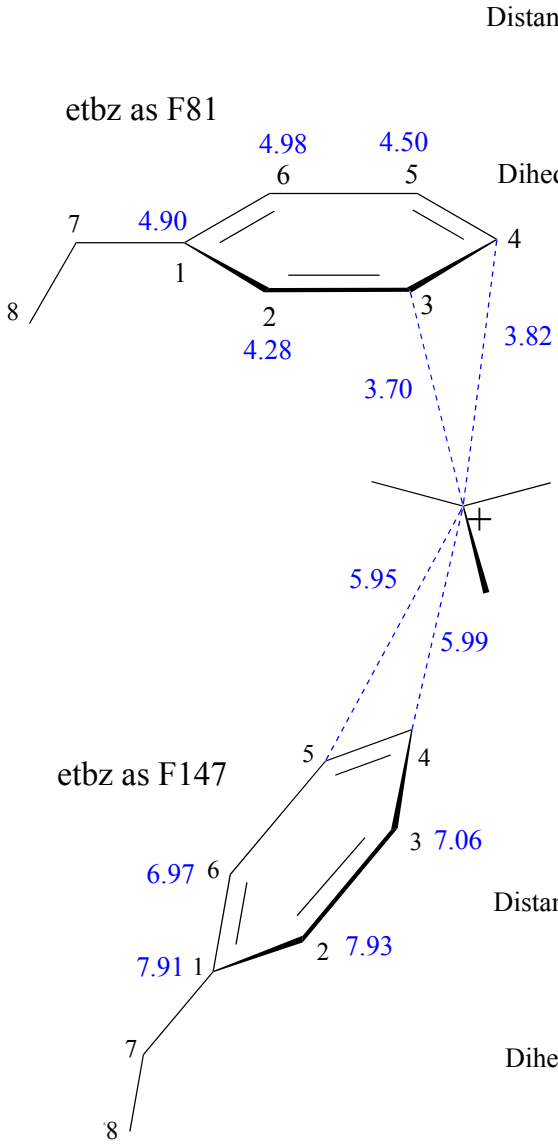
Distances from benzene C's to C1' and C3' of DMA^+mod in Å:
C1': C1, 7.76; C2, 7.97; C3, 7.22; C4, 6.13; C5, 5.83; C6, 6.72
C3': C1, 5.45; C2, 5.58; C3, 4.89; C4, 3.94; C5, 3.74; C6, 4.58

Angles: C2; C5; C1' = 131.9º
C2; C5; C3' = 116.7º
C1; C4; C1' = 115.3º
C1; C4; C3' = 106.7º
Dihedral angles: C2; C5; C1'; C2' = -63.4º
C2; C5; C3'; C2' = -146.7º
C1; C4; C1'; C2' = -82.4º
C1; C4; C3'; C2' = -82.4º
C6; C1; C7; C8 = 79.5º

Structural information for the F81-F147-inhibitor AI^+ complex in the active site of aristolochene synthase[8] as determined from X-ray structure PDB Code 4KVY and shown in Figure 10.



Structural information for the complex of the ethylbenzenes constructed from F81 and F147, as shown in Figure 10, with the *t*-butyl cation placed so as to approximate the geometry of the inhibitor AI^+ in Figure 10, to create model **6** (Figure 11). This complex had a calculated stabilization energy of –10.1 kcal/mol.



Distances from C's of benzene ring to N in Å

Angles: C1; C4; N = 94.4º
C6; C3; N = 100.0º

Dihedral angles: C1; C4; N; C1' = -31.4º
C6; C3; N; C1' = -95.7º
C6; C1; Cα; Cβ = 107.2º

Distances from C's of benzene ring to N in Å

Angles: C1; C4; N = 124.3º
C2; C5; N = 127.5º

Dihedral angles: C1; C4; N; C1' = -117.0º
C2; C5; N; C1' = 153.2º
C6; C1; Cα; Cβ = 74.9º

5. Table S4. M06/cc-pVTZ optimized geometries (Å) and energies (hartrees) for the 1,1-dimethylallyl cation, ethylbenzenes with the side chain dihedral angles of F81 and F147 of aristolochene synthase, the original model with the 1,1-dimethylallyl cation positioned between F81 and F147 with their X-ray locations coordinates, model **3**, the farnesyl cation, model **4**, the modified 1.1-dimethylallyl cation, model **5**, and model **6**.

Coordinates for the1,1-dimethylallyl cation

Atom	x	y	z
C	0.08794449	0.26304771	0.24966428
C	1.03471012	-0.78599361	0.19485269
H	0.70425645	-1.76573589	0.52031138
C	-1.26539346	-0.05522584	0.69769824
H	-1.28693264	-0.85903968	1.43306648
H	-1.82314395	0.81580090	1.03466473
C	0.36566924	1.64495274	-0.12668612
H	-0.45217857	2.02725261	-0.74468188
H	0.31163125	2.24628664	0.79092169
H	1.31868886	1.82509514	-0.61118266
C	2.30333198	-0.62043910	-0.22546319
H	2.69106196	0.33412148	-0.55828562
H	2.99630596	-1.45234370	-0.24188528
H	-1.79222226	-0.44819027	-0.18706888

Energy = –195.5434670

Coordinates for the ethylbenzene representing F81 of aristolochene synthase

Atom	x	y	z
C	-1.65948260	0.45270164	-0.34433776
C	-0.29179476	0.28204918	-0.45505036
C	0.58491503	1.32755712	-0.18405702
C	0.04853946	2.55105084	0.19367089
C	-1.32047236	2.72789219	0.30757045
C	-2.17994341	1.67781360	0.03986380
H	-2.32417662	-0.37394095	-0.56143045
H	0.10316558	-0.67927204	-0.76480875
H	0.71815379	3.37775789	0.40445901
H	-1.71582601	3.69035173	0.60679759

H	-3.25022863	1.81205011	0.12804057
C	2.06878549	1.14643411	-0.32461543
H	2.31352520	1.00335427	-1.38269231
H	2.56961268	2.06970803	-0.02302872
C	2.61932246	-0.02273991	0.47489207
H	2.18743353	-0.96987461	0.14907203
H	3.70128730	-0.10119541	0.36561088
H	2.39358386	0.09097123	1.53649852

Energy = –310.7221889

Coordinates for the ethylbenzene representing F147 of aristolochene synthase

Atom	x	y	z
	-1.61530167	0.46763443	-0.42070803
C	-0.24450109	0.31203976	-0.54036544
C	0.61796408	1.37084138	-0.29070073
C	0.07353251	2.59209887	0.08877703
C	-1.29478173	2.75389295	0.20922338
C	-2.14465669	1.69000008	-0.04566748
H	-2.27250452	-0.36846636	-0.62367146
H	0.16805603	-0.64678846	-0.83618618
H	0.73777485	3.42753744	0.28623942
H	-1.70105849	3.71434704	0.50016014
H	-3.21582279	1.81503869	0.04536471
C	2.10390104	1.19089242	-0.36406736
H	2.33947487	0.34668899	-1.01725113
H	2.55875215	2.07503482	-0.82024765
C	2.71002670	0.96172029	1.01235036
H	2.28140933	0.07220500	1.47820601
H	3.79131669	0.83037245	0.95971458
H	2.50340973	1.80685321	1.67180281

Energy = –310.7230323

Coordinates for the original model with the optimized 1,1-dimethylallyl cation positioned between F81 and F147 in their X-ray locations

C	-70.85200000	21.37500000	9.88000000
C	-69.83500000	19.29500000	10.48400000
C	-70.08700000	20.63500000	10.74000000
C	-59.62100000	20.71600000	2.13600000
C	-60.81000000	21.54800000	2.63100000
C	-61.97100000	20.72500000	3.13200000
C	-61.95200000	20.16600000	4.40400000
C	-63.07398000	20.50339800	2.31535300
C	-63.02100000	19.37000000	4.86000000
C	-64.16600000	19.75200000	2.78200000
C	-64.12000000	19.16700000	4.03800000
H	-72.43980200	18.04295500	7.62064000
H	-72.22004500	19.62106900	6.67408800
H	-71.98557200	21.37463200	8.07569600
H	-70.22489700	17.65597600	9.13959400
H	-71.03866500	22.40833900	10.08559100
H	-69.22533200	18.72225900	11.15121300
H	-69.67992700	21.09350900	11.61690400
H	-69.87451200	17.97019500	6.76409200
H	-60.45130200	22.09218400	3.47958700
H	-61.17453300	22.07376200	1.77333500
H	-63.10323600	20.93043000	1.33469700
H	-61.11416800	20.34254200	5.04569400
H	-65.02651600	19.61614100	2.16074700
H	-62.98566200	18.92545700	5.83264200
H	-64.93321000	18.55809400	4.37389100
H	-58.94049800	20.60886400	2.95474200
H	-70.68959700	18.71931400	5.42391800
H	-71.21545100	17.14739700	6.03639800
H	-59.89523100	19.72208600	1.84993700
H	-59.13799600	21.22706800	1.32951600
C	-65.37539100	20.71804400	7.47773200
C	-65.01236900	20.68447600	8.84409500

H	-64.31868500	21.44285200	9.18860400
C	-64.82660800	21.78668400	6.64682900
H	-63.83044700	22.09552700	6.96246600
H	-64.86285900	21.56579400	5.58230400
C	-66.27656800	19.76411900	6.84028600
H	-66.98950600	20.30097400	6.20747200
H	-65.67677100	19.17835200	6.13060400
H	-66.80017800	19.08554400	7.50421700
C	-65.47384100	19.76486000	9.71290200
H	-66.16462600	18.98192500	9.42633600
H	-65.16072900	19.77331100	10.74945300
H	-65.47528800	22.66215000	6.81283000

Energy = -816.9788185

Coordinates for model **3**

Atom	x	y	z
C	-3.42846000	6.00074000	-4.68523000
C	-3.72591000	7.05903000	-3.84650000
C	-5.02336000	7.26944000	-3.39100000
C	-6.01454000	6.39139000	-3.80804000
C	-5.72265000	5.32874000	-4.64709000
C	-4.42701000	5.12893000	-5.08798000
H	-2.41211000	5.85609000	-5.02931000
H	-2.93722000	7.73958000	-3.54495000
H	-7.03218000	6.54383000	-3.46540000
H	-6.51154000	4.65498000	-4.95677000
H	-4.19498000	4.29953000	-5.74343000
C	-5.34844000	8.43100000	-2.49681000
H	-5.22422000	9.36229000	-3.05996000
H	-6.40554000	8.38425000	-2.22374000
C	-4.49456000	8.49228000	-1.24124000
H	-3.43685000	8.60833000	-1.48111000
H	-4.78142000	9.33320000	-0.60935000
H	-4.59797000	7.57756000	-0.65514000

C	-2.33243107	2.88612549	-0.16193121
C	-1.66715107	2.33548549	-1.28176121
H	-1.62025107	1.25433549	-1.34477121
C	-2.93800107	1.96695549	0.79824879
H	-2.39001107	1.02923549	0.88610879
H	-3.12253107	2.41974549	1.76996879
C	-2.47024107	4.31568549	0.09456879
H	-3.49910107	4.53610549	0.39429879
H	-1.87610107	4.54147549	0.99042879
H	-2.16310107	4.97620549	-0.70845121
C	-1.09386107	3.08085549	-2.24575121
H	-1.10512107	4.16347549	-2.23467121
H	-0.58712107	2.61439549	-3.08130121
H	-3.92168107	1.69784549	0.38018879
C	-2.30834000	4.17145000	4.62464000
C	-2.26791000	3.04753000	5.43260000
C	-1.42899000	1.98302000	5.13222000
C	-0.62418000	2.07342000	4.00261000
C	-0.66069000	3.19298000	3.19133000
C	-1.50453000	4.24719000	3.50072000
H	-2.97212000	4.99003000	4.87260000
H	-2.90028000	2.98974000	6.31229000
H	0.03560000	1.24722000	3.75716000
H	-0.03088000	3.24307000	2.31213000
H	-1.53671000	5.12312000	2.86586000
C	-1.34102000	0.78994000	6.03480000
H	-2.26162000	0.70201000	6.61752000
H	-1.26403000	-0.12058000	5.43336000
C	-0.14565000	0.88175000	6.97131000
H	-0.21249000	1.77613000	7.59390000
H	-0.08115000	0.01403000	7.62867000
H	0.78544000	6.40512000	6.40512000

Energy = –817.0037781

Coordinates for the farnesyl cation with the positions of the first five carbon atoms optimized

Atom	x	y	z
C	-66.06508285	20.46138220	9.74102193
C	-65.19368720	20.96881275	8.84181014
C	-65.31460103	20.76536484	7.45003878
C	-66.13707583	19.64442196	6.91803631
C	-64.79412187	21.83240076	6.57231163
C	-66.06196811	22.61600224	6.13698037
C	-66.54401789	23.37199434	7.33900385
C	-67.75000967	23.12000172	7.82700275
C	-68.61901079	22.03600340	7.19800108
C	-68.13801037	23.94600369	9.03500137
C	-66.80601038	24.24900371	9.76500149
C	-67.15001051	23.61200358	11.03800171
C	-66.60901039	22.98500352	12.05300183
C	-65.16900955	22.65500345	12.35200190
C	-67.77101060	22.63000348	12.92200200
H	-64.45976016	21.69397423	9.17609236
H	-66.44801773	18.89400771	7.64899345
H	-65.63100934	19.11201292	6.10999916
H	-67.06700377	20.01999117	6.46801276
H	-64.29101771	21.52101730	5.68403185
H	-64.10602158	22.55098901	7.02297422
H	-66.80201562	21.91700551	5.80800913
H	-65.87501667	23.28301091	5.32100535
H	-65.94101142	24.08300609	7.78299917
H	-68.10801025	21.61000327	6.36000096
H	-69.55801042	22.44600342	6.89000108
H	-68.80501077	21.27100328	7.92200117
H	-68.80901029	23.40600360	9.67000148
H	-68.65101067	24.84300379	8.75500136
H	-66.62201015	25.29800388	9.86700152
H	-65.91101025	23.91000366	9.28700140
H	-68.16901063	23.68100363	11.18700168
H	-64.54700985	23.02500350	11.56400178

H	-65.04500956	21.59700329	12.45600190
H	-64.88500965	23.12000352	13.27300204
H	-68.67501044	22.98400348	12.47200189
H	-67.65001052	23.05700348	13.89500211
H	-67.82201058	21.56600330	13.02400202
H	-66.01472264	20.74787691	10.78341390
H	-66.87795414	19.80067800	9.46201455

Energy = –585.9343551

Coordinates for model **4**

Atom	x	y	z
C	-70.82501051	18.11000278	6.29300098
C	-71.80301103	18.81300285	7.23800111
C	-71.15701049	19.45000298	8.45000127
C	-71.38701051	20.78700316	8.74000135
C	-70.39201070	18.69500288	9.33300140
C	-70.85201072	21.37500328	9.88000150
C	-69.83501037	19.29500294	10.48400161
C	-70.08701039	20.63500319	10.74000168
C	-59.62100944	20.71600319	2.13600032
C	-60.81000933	21.54800328	2.63100040
C	-61.97100940	20.72500317	3.13200048
C	-61.95200929	20.16600308	4.40400068
C	-63.08600968	20.52200316	2.32400036
C	-63.02100978	19.37000296	4.86000074
C	-64.16600964	19.75200300	2.78200042
C	-64.12001038	19.16700322	4.03800039
C	-66.06508285	20.46138220	9.74102193
C	-65.19368720	20.96881275	8.84181014
C	-65.31460103	20.76536484	7.45003878
C	-66.13707583	19.64442196	6.91803631
C	-64.79412187	21.83240076	6.57231163
C	-66.06196811	22.61600224	6.13698037
C	-66.54401789	23.37199434	7.33900385
C	-67.75000967	23.12000172	7.82700275

C	-68.61901079	22.03600340	7.19800108
C	-68.13801037	23.94600369	9.03500137
C	-66.80601038	24.24900371	9.76500149
C	-67.15001051	23.61200358	11.03800171
C	-66.60901039	22.98500352	12.05300183
C	-65.16900955	22.65500345	12.35200190
C	-67.77101060	22.63000348	12.92200200
H	-69.87501087	17.97000274	6.76400107
H	-72.55001086	18.11700273	7.55800115
H	-72.23201079	19.61600297	6.67500102
H	-71.96401056	21.35400325	8.09900128
H	-70.23101063	17.69300274	9.14600138
H	-71.03201089	22.37200338	10.07800158
H	-69.24701083	18.74300286	11.12800169
H	-69.69401056	21.07700320	11.58600180
H	-58.94000912	20.60900318	2.95500045
H	-61.14400961	22.19500338	1.84600028
H	-60.45500919	22.10900340	3.47000052
H	-61.14400961	20.33600307	5.02300077
H	-63.11900970	20.94100316	1.38100022
H	-62.98700961	18.94100288	5.79800086
H	-64.99600987	19.62100300	2.18300034
H	-64.90401081	18.58000002	4.36200108
H	-64.45976016	21.69397423	9.17609236
H	-66.44801773	18.89400771	7.64899345
H	-65.63100934	19.11201292	6.10999916
H	-67.06700377	20.01999117	6.46801276
H	-64.29101771	21.52101730	5.68403185
H	-64.10602158	22.55098901	7.02297422
H	-66.80201562	21.91700551	5.80800913
H	-65.87501667	23.28301091	5.32100535
H	-65.94101142	24.08300609	7.78299917
H	-68.10801025	21.61000327	6.36000096
H	-69.55801042	22.44600342	6.89000108
H	-68.80501077	21.27100328	7.92200117
H	-68.80901029	23.40600360	9.67000148

H	-68.65101067	24.84300379	8.75500136
H	-66.62201015	25.29800388	9.86700152
H	-65.91101025	23.91000366	9.28700140
H	-68.16901063	23.68100363	11.18700168
H	-64.54700985	23.02500350	11.56400178
H	-65.04500956	21.59700329	12.45600190
H	-64.88500965	23.12000352	13.27300204
H	-68.67501044	22.98400348	12.47200189
H	-67.65001052	23.05700348	13.89500211
H	-67.82201058	21.56600330	13.02400202
H	-59.89524073	19.72208904	1.84993681
H	-59.13800502	21.22707172	1.32951641
H	-71.21546130	17.14739989	6.03639933
H	-70.68960781	18.71931662	5.42391927

Energy = –1207.3626666

Coordinates for the modified 1,1-dimethylallyl cation

Atom	x	y	z
C	0.12128500	0.27737000	0.32912700
C	1.03205700	-0.79617600	0.19551200
H	0.73278287	-1.75159865	0.61246675
C	-1.29027697	-0.06424775	0.59495627
H	-1.49262496	-1.07251670	0.95448734
H	-1.81729589	0.56218229	1.28314426
C	0.52287052	1.66905235	-0.01594064
H	0.04033334	1.99440332	-0.94851444
H	0.19362600	2.38921000	0.73572900
H	1.59212660	1.83173212	-0.16657506
C	2.13713789	-0.73533528	-0.57939753
H	2.44761570	0.16406428	-1.09884597
H	2.73401126	-1.62112441	-0.75735789
H	-1.76625883	0.03723032	-0.35896412

Energy = –195.5352548

Coordinates for model **5**

Atom	x	y	z
C	-70.82501100	18.11000300	6.29300100
C	-71.80301100	18.81300300	7.23800100
C	-71.15701000	19.45000300	8.45000100
C	-71.38701100	20.78700300	8.74000100
C	-70.39201100	18.69500300	9.33300100
C	-70.85201100	21.37500300	9.88000200
C	-69.83501000	19.29500300	10.48400200
C	-70.08701000	20.63500300	10.74000200
C	-59.62100900	20.71600300	2.13600000
C	-60.81000900	21.54800300	2.63100000
C	-61.97100900	20.72500300	3.13200000
C	-61.95200900	20.16600300	4.40400100
C	-63.08601000	20.52200300	2.32400000
C	-63.02101000	19.37000300	4.86000100
C	-64.16601000	19.75200300	2.78200000
C	-64.12001000	19.16700300	4.03800000
H	-69.87501100	17.97000300	6.76400100
H	-72.55001100	18.11700300	7.55800100
H	-72.23201100	19.61600300	6.67500100
H	-71.96401100	21.35400300	8.09900100
H	-70.23101100	17.69300300	9.14600100
H	-71.03201100	22.37200300	10.07800200
H	-69.24701100	18.74300300	11.12800200
H	-69.69401100	21.07700300	11.58600200
H	-58.94000900	20.60900300	2.95500000
H	-61.14401000	22.19500300	1.84600000
H	-60.45500900	22.10900300	3.47000100
H	-61.14401000	20.33600300	5.02300100
H	-63.11901000	20.94100300	1.38100000
H	-62.98701000	18.94100300	5.79800100
H	-64.99601000	19.62100300	2.18300000
H	-64.90401100	18.58000000	4.36200100
H	-59.89524100	19.72208900	1.84993700

H	-59.13800500	21.22707200	1.32951600
H	-71.21546100	17.14740000	6.03639900
H	-70.68960800	18.71931700	5.42391900
C	-65.35168269	20.78884332	7.41094321
C	-65.19975191	20.96855331	8.80538958
H	-64.43161994	21.66075481	9.13262207
C	-64.80717266	21.84233076	6.53142749
H	-64.08500874	22.52742309	6.97407760
H	-64.33258008	21.52013657	5.62880921
C	-66.22396923	19.71069810	6.86886840
H	-67.14340772	20.13229282	6.43842592
H	-65.74919942	19.17456734	6.04473641
H	-66.55478937	18.95967065	7.58926955
C	-66.07495265	20.48234737	9.71259246
H	-66.91889812	19.85667995	9.44531564
H	-65.99295510	20.75480965	10.75738538
H	-65.66613737	22.41816925	6.25319707

Energy = –816.9620788

Coordinates for model **6**

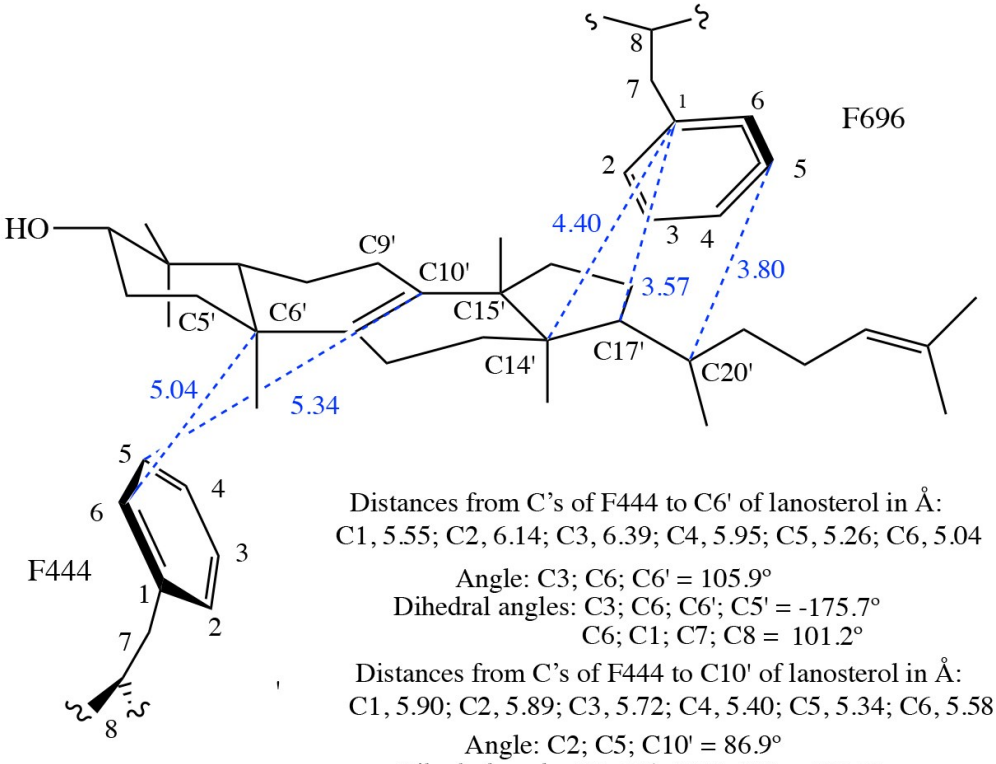
Atom	x	y	z
C	-5.01749000	2.87369000	0.79443000
C	-3.64847000	2.71286000	0.67158000
C	-2.79328000	3.80567000	0.73335000
C	-3.34339000	5.06631000	0.92669000
C	-4.71168000	5.23350000	1.05027000
C	-5.55354000	4.13622000	0.98398000
C	-1.30837000	3.62072000	0.65789000
C	-0.76631000	2.95561000	1.91425000
C	-5.74916000	2.40487000	4.38684000
C	-5.47384000	3.81690000	4.55533000
C	-4.65886000	1.47063000	4.19844000
C	-7.11641000	1.92376000	4.39914000
C	-4.39455520	4.26812642	11.05651631
C	-5.18324647	3.95166326	12.14877933
C	-5.72624847	2.68131613	12.29267620

C	-5.45546453	1.73142889	11.31613148
C	-4.66742430	2.04189025	10.22158252
C	-4.13450095	3.31286762	10.08845744
C	-6.53144528	2.32597725	13.50522580
C	-5.71870942	1.49785509	14.48926640
H	-5.66925000	2.01096000	0.73883000
H	-3.22973000	1.72299000	0.52125000
H	-2.68476000	5.92739000	0.97694000
H	-5.12311000	6.22434000	1.19559000
H	-6.62411000	4.26494000	1.07680000
H	-1.05716000	3.01451000	-0.21677000
H	-0.82346000	4.59048000	0.51652000
H	-1.22747000	1.97683000	2.06078000
H	0.31433000	2.81795000	1.86451000
H	-0.99225000	3.55802000	2.79641000
H	-6.05442000	4.22647000	5.38766000
H	-4.41971000	4.06724000	4.63026000
H	-5.90404000	4.31988000	3.67381000
H	-4.16920000	1.39865000	5.18502000
H	-4.96387000	0.47474000	3.88942000
H	-3.88056000	1.88800000	3.55437000
H	-7.85912000	2.67087000	4.66164000
H	-7.32334000	1.52593000	3.39394000
H	-7.19451000	1.03675000	5.03793000
H	-3.98371949	5.26500050	10.95835709
H	-5.38779726	4.70181605	12.90591729
H	-5.87412765	0.73541996	11.41834543
H	-4.47101674	1.29010010	9.46766448
H	-3.52090682	3.55898799	9.23158305
H	-6.88205437	3.23885018	13.99443785
H	-7.42329636	1.76941302	13.20461232
H	-4.83256051	2.04685081	14.81402344
H	-6.29985182	1.23676982	15.37433540
H	-5.37608552	0.57238359	14.02210424

Energy = – 778.9314976

Table S5. Structural information for the product lanosterol in the active site of oxidosqualene cyclase[9] (Figure 13), model **7** (Figure 14A), model **8** (Figure 14B), and the complexes showing the relationships of ethylbenzenes representing F696 with the *t*-butyl cation representing C_{14} and F444 with the *t*-butyl cation representing the carbocations at C_6 and C_{10} during the formation of lanosterol.

Structural information on the geometrical relationship of F444 and F696 to product lanosterol in the active site of oxidosqualene cyclase[9] as determined from X-ray structure PDB Code 1WGK and shown in Figure 13.



Distances from C's of F444 to C6' of lanosterol in Å:
C1, 5.55; C2, 6.14; C3, 6.39; C4, 5.95; C5, 5.26; C6, 5.04

Angle: C3; C6; C6' = 105.9°
Dihedral angles: C3; C6; C6'; C5' = -175.7°
C6; C1; C7; C8 = 101.2°

Distances from C's of F444 to C10' of lanosterol in Å:
C1, 5.90; C2, 5.89; C3, 5.72; C4, 5.40; C5, 5.34; C6, 5.58

Angle: C2; C5; C10' = 86.9°
Dihedral angle: C2; C5; C10'; C9' = 130.0°

Distances from C's of F696 to C14' of lanosterol in Å:
C1, 4.40; C2, 4.61; C3, 5.13; C4, 5.53; C5, 5.37; C6, 4.84

Angles: C4; C1; C14' = 97.5°; C3; C6; C14' = 79.3°
Dihedral Angles: C6; C1; C7; C8 = 93.9°
C1; C4; C17'; C14 = –172.9°'

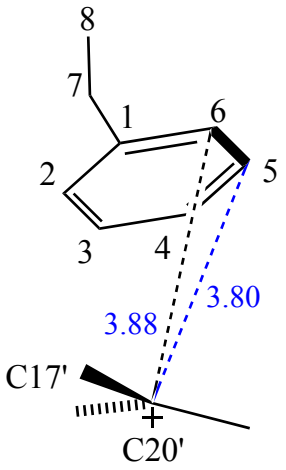
Distances from C's of F696 to C17' of lanosterol in Å:
C1, 3.57; C2, 3.65; C3, 3.87; C4, 4.10; C5, 4.03; C6, 3.80

Angles: C3; C6; C17' = 69.8°; C2; C5; C17' = 61.4°
Dihedral angle: C2; C5; C17'; C20' = 174.2°

Distances from C's of F696 to C20' of lanosterol in Å:
C1, 4.20; C2, 4.50; C3, 4.41; C4, 4.11; C5, 3.80; C6, 3.88

Angles: C3; C6; C20' = 80.7°; C2; C5; C20' = 84.3°
Dihedral angle: C2; C5; C20'; C19' = -60.2°

Structural information on the complex in which an optimized ethylbenzene with the geometry of F696 of oxidosqualene cyclase is positioned relative to a *t*-butyl cation so as to approximate the relationship between C_{20} and F696 shown in the X-ray structure depicted in Figure 13. This complex is Model **7** (Figure 14A) and had a calculated stabilization energy of –10.0 kcal/mol.



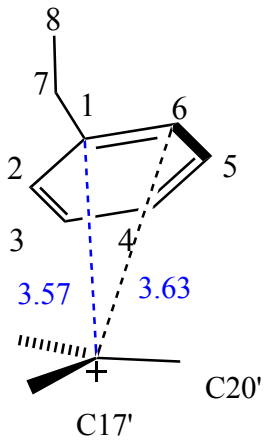
etbz as F696

Distances from C's of "F696" to C20' of "lanosterol" in Å:
C1, 4.22; C2, 4.47; C3, 4.41; C4, 4.09; C5, 3.80; C6, 3.88

Angles: C3; C6; C20' = 81.4°; C2; C5; C20' = 84.2°

Dihedral angles: C2; C5; C20'; C17' = -60.2°
C6; C1; C7; C8 = 93.9°

Structural information on the complex in which an optimized ethylbenzene with the geometry of F696 of oxidosqualene cyclase is positioned relative to a *t*-butyl cation so as to approximate the relationship between C_{17} and F696 shown in the X-ray structure depicted in Figure 13. This complex is Model **8** (Figure 14B) and had a calculated stabilization energy of –11.8 kcal/mol.



etbz as F696

Distances from C's of "F696" to C17' of "lanosterol" in Å

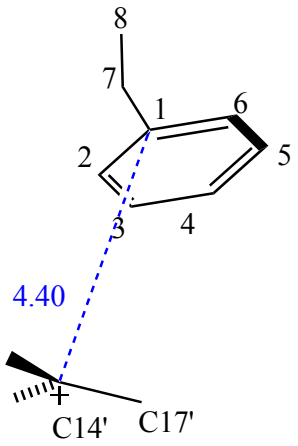
C1; 3.57; C2, 3.78; C3, 4.03; C4, 4.08; C5, 3.89; C6, 3.63

Angles: C4; C1; C17' = 78.8°; C5; C2; C17' = 76.7°

Dihedral angles: C4; C1; C17'; C20' = 58.0°

C6; C1; C7; C8 = 93.9°

Structural information on the complex in which an optimized ethylbenzene with the geometry of F696 of oxidosqualene cyclase is positioned relative to a *t*-butyl cation so as to approximate the relationship between C_{14} and F696 shown in the X-ray structure depicted in Figure 13. This complex is had a calculated stabilization energy of –5.8 kcal/mol.



etbz as F696

Distances from C's of "F696" to C14 of "lanosterol" in Å:
C1, 4.40; C2, 4.59; C3, 5.16; C4, 5.52; C5, 5.16; C6, 4.83

Angles: C4; C1; C14' = 97.9º; C3; C6; C14= 80.6º

Dihedral angle: C6; C1; C7; C8 = 93.9°

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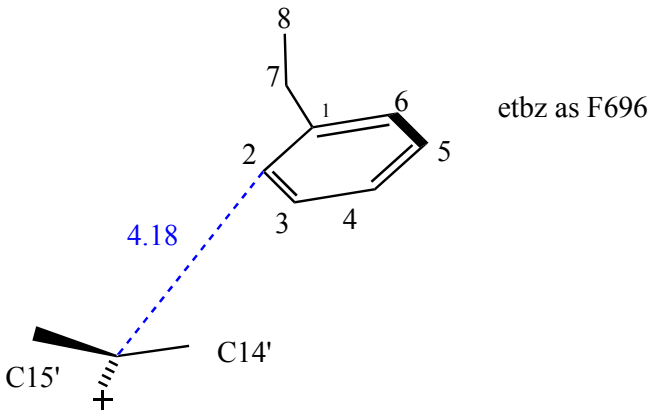
Structural information on the complex in which an optimized ethylbenzene with the geometry of F696 of oxidosqualene cyclase is positioned relative to a *t*-butyl cation so as to approximate the relationship between C_{15} and F696 shown in the X-ray structure depicted in Figure 13. This complex is had a calculated stabilization energy of –7.4 kcal/mol.

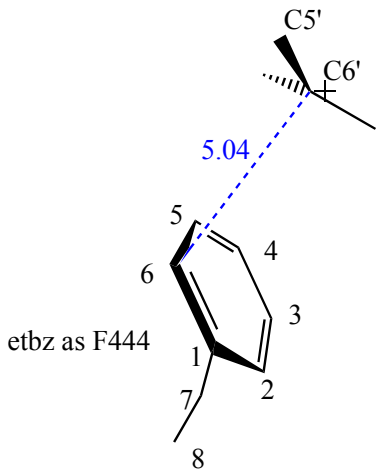


etbz as F696

Distances from C's of "F696" to C15 of "lanosterol" in Å:
C1, 4.29; C2, 4.18; C3, 4.88; C4, 5.59; C5, 4.88; C6, 5.09

Angles: C4; C1; C15' = 102.0º; C5; C2; C15'= 108.2º
Dihedral angle: C6; C1; C7; C8 = 93.9º

Structural information on the complex in which an optimized ethylbenzene with the geometry of F444 of oxidosqualene cyclase is positioned relative to a *t*-butyl cation so as to approximate the relationship between C_6 and F444 shown in the X-ray structure depicted in Figure 13. This complex had a calculated stabilization energy of –4.0 kcal/mol.

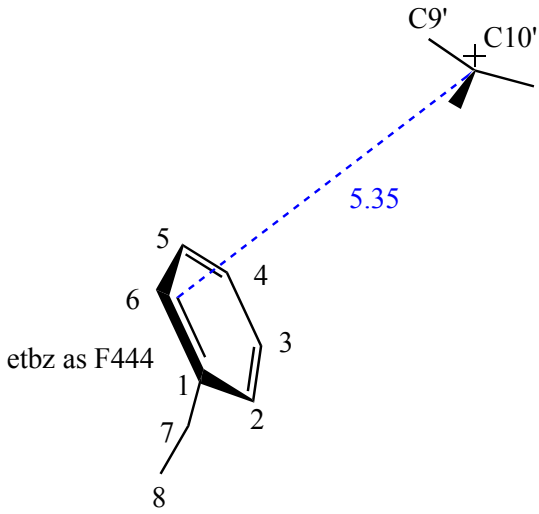


Distances from C's of "F444 to C6' of lanosterol" in Å:
C1, 5.54; C2, 6.17; C3, 6.35; C4, 5.93; C5, 5.26; C6, 5.04

Angle: C3; C6; C6' = 105.1º

Dihedral angles: C3; C6; C6'; C5' = -171.5º
C6; C1; C7; C8 = 101.2º

Structural information on the complex in which an optimized ethylbenzene with the geometry of F444 of oxidosqualene cyclase is positioned relative to a *t*-butyl cation so as to approximate the relationship between C_{10} and F444 shown in the X-ray structure depicted in Figure 13. This complex had a calculated stabilization energy of –4.5 kcal/mol.



Distances from C's of "F444 to C10" of lanosterol" in Å:
C1, 5.88; C2, 5.92; C3, 5.70; C4, 5.41; C5, 5.35; C6, 5.59

Angle: C2; C5; C10' = 87.7º

Dihedral angles: C2; C5; C10'; C9' = 133.9º
C6; C1; C7; C8 = 101.2º

7. Table S6. M06/cc-pVTZ optimized geometries (Å) and energies (hartrees) for the ethylbenzenes representing F444 and F696 of oxidosqualene cyclase[9], model **7**, model **8**, and the complexes of the *t*-butyl cation representing carbocations at C_{14} and C_{15} with an ethylbenzene representing F696, and at C_6 and C_{10} with an ethylbenzene representing F444 of oxidosqualene cyclase.

Coordinates for the ethylbenzene representing F444 of oxidosqualene cyclase

Atom	x	y	z
C	-1.61417739	0.46997725	-0.42620122
C	-0.24437359	0.31663467	-0.53741673
C	0.61708402	1.37627680	-0.27727512
C	0.06962540	2.59568341	0.09689620
C	-1.30146814	2.75519051	0.21090921
C	-2.14770134	1.69210077	-0.05017170
H	-2.26968545	-0.36544990	-0.63730522
H	0.17117141	-0.64037568	-0.83669533
H	0.73058871	3.43184053	0.29894519
H	-1.70997832	3.71476346	0.50159658
H	-3.21957506	1.81515985	0.03505061
C	2.10130684	1.18550591	-0.36199765
H	2.34645583	0.61830606	-1.26486570
H	2.59029549	2.15777336	-0.46284038
C	2.64802857	0.45729430	0.85664260
H	2.18690522	-0.52678723	0.95965002
H	3.72774298	0.31869362	0.79189063
H	2.43086781	1.01610630	1.76894801

Energy = –310.7229789

Coordinates for the ethylbenzene representing F696 of oxidosqualene cyclase

Atom	x	y	z
C	-1.61143621	0.46780582	-0.42142175
C	-0.24144799	0.31582285	-0.53928885
C	0.61905066	1.37717335	-0.28673778
C	0.07230955	2.59642986	0.09072266

C	-1.29784578	2.75455828	0.21085474
C	-2.14425723	1.68972318	-0.04540332
H	-2.26694953	-0.36897176	-0.62706028
H	0.17472587	-0.64151369	-0.83650918
H	0.73421953	3.43291144	0.28966350
H	-1.70640830	3.71385726	0.50237443
H	-3.21585856	1.81196424	0.04429912
C	2.10357254	1.18948202	-0.36523392
H	2.34581309	0.51964287	-1.19516438
H	2.58399878	2.14650207	-0.58524415
C	2.66304257	0.61920598	0.92951175
H	2.20689091	-0.34704149	1.15397755
H	3.74327570	0.47981817	0.87585439
H	2.44688340	1.28452255	1.76780547

Energy = –310.7230772

Coordinates for model **7**

Atom	x	y	z
C	-1.15275000	0.52264000	1.27111000
C	0.21724000	0.37066000	1.15325000
C	1.07774000	1.43201000	1.40580000
C	0.53100000	2.65127000	1.78326000
C	-0.83916000	2.80939000	1.90339000
C	-1.68557000	1.74456000	1.64713000
H	-1.80826000	-0.31414000	1.06547000
H	0.63342000	-0.58668000	0.85603000
H	1.19291000	3.48775000	1.98220000
H	-1.24772000	3.76869000	2.19491000
H	-2.75717000	1.86680000	1.73683000
C	2.56226000	1.24432000	1.32730000
H	2.80450000	0.57448000	0.49737000
H	3.04269000	2.20134000	1.10729000
C	3.12173000	0.67404000	2.62205000
H	2.66558000	-0.29221000	2.84651000
H	4.20197000	0.53465000	2.56839000

H	2.90557000	1.33936000	3.46034000
C	-0.56770354C	3.62807367	-1.80224975
C	-1.13340472	4.92568253	-1.49512809
H	-0.78176185	5.67746847	-2.20854363
H	-2.21438472	4.93575705	-1.39126135
H	-0.67434845	5.24355205	-0.54476911
C	-1.41423546	2.45332925	-1.82041261
H	-2.02761120	2.55595100	-2.73229586
H	-0.87831952	1.50945781	-1.86763393
H	-2.14911806	2.47664600	-1.01160192
C	0.84813510	3.50051977	-2.08529686
H	1.38225572	4.44218971	-2.16705051
H	1.28084797	2.89327085	-1.27555872
H	0.99746923	2.87435046	-2.97210761

Energy = –468.2086411

Coordinates for model **8**

Atom	x	y	z
C	-1.218843000	0.701799000	0.907031000
C	0.154263000	0.537146000	0.870556000
C	1.007269000	1.568921000	1.242747000
C	0.449597000	2.771393000	1.656342000
C	-0.923765000	2.942041000	1.695438000
C	-1.762503000	1.906806000	1.320268000
H	-1.868062000	-0.111611000	0.608598000
H	0.579113000	-0.406770000	0.544104000
H	1.105644000	3.584808000	1.948505000
H	-1.340612000	3.888141000	2.016832000
H	-2.836339000	2.039101000	1.346522000
C	2.491649000	1.364614000	1.250850000
H	2.781436000	0.741903000	0.399730000
H	2.995773000	2.325926000	1.121077000
C	2.957679000	0.710177000	2.542799000
H	2.477386000	-0.260968000	2.678045000

H	4.037557000	0.558493000	2.551975000
H	2.693308000	1.327498000	3.403688000
C	0.392325000	3.018126000	-1.966043000
C	-0.157659270	4.308401360	-1.604332110
H	0.302983080	5.103488700	-2.198842060
H	-1.242243060	4.360373950	-1.623905190
H	0.197494020	4.517839310	-0.582100180
C	-0.488677560	1.891174270	-2.191396480
H	-1.312441760	1.876838100	-1.473081600
C	1.826023330	2.849436040	-2.096585020
H	2.400237330	3.768260680	-2.027664380
H	2.137680270	2.152341560	-1.303742620
H	2.055802830	2.298754610	-3.015701380
H	-0.986081870	2.103938460	-3.153485520
H	0.014083140	0.930974080	-2.266080520

Energy = –468.2115330

Coordinates for the model of the *t*-butyl cation positioned relative to an ethylbenzene representing F696 of oxidosqualene cyclase so as to replicate the geometry of the carbocation intermediate at C_{14} during the cyclization of squalene oxide, using measurements on the X-ray structure[9] of lanosterol bound in the active site of oxidosqualene cyclase.

Atom	x	y	z
C	-1.16341000	0.45986300	1.50058900
C	0.20969600	0.29521000	1.46411400
C	1.06270200	1.32698500	1.83630500
C	0.50503000	2.52945700	2.24990000
C	-0.86833200	2.70010500	2.28899600
C	-1.70707000	1.66487000	1.91382600
H	-1.81262900	-0.35354700	1.20215600
H	0.63454600	-0.64870600	1.13766200
H	1.16107700	3.34287200	2.54206300
H	-1.28517900	3.64620500	2.61039000
H	-2.78090600	1.79716500	1.94008000
C	2.54708200	1.12267800	1.84440800
H	2.83686900	0.49996700	0.99328800
H	3.05120600	2.08399000	1.71463500

C	3.01311200	0.46824100	3.13635700
H	2.53281900	-0.50290400	3.27160300
H	4.09299000	0.31655700	3.14553300
H	2.74874100	1.08556200	3.99724600
C	1.66053605	2.23721660	-2.42910258
C	2.64674435	3.18967984	-1.96184135
H	3.51633371	3.20057034	-2.62629180
H	2.26105492	4.18811399	-1.77804069
H	3.05040055	2.77775644	-1.02251284
C	0.26333281	2.61218269	-2.49386360
H	0.19337487	3.31201561	-3.34453274
H	-0.41992120	1.78563949	-2.66799406
H	-0.02814335	3.22138377	-1.63439815
C	2.06810412	0.90417336	-2.82643226
H	3.14196000	0.74780161	-2.85949546
H	1.60938614	0.20484623	-2.11075869
H	1.59236045	0.63498000	-3.77618273

Energy = –468.2019226

Coordinates for the model of the *t*-butyl cation positioned relative to an ethylbenzene representing F696 of oxidosqualene cyclase so as to replicate the geometry of the carbocation intermediate at C_{15} during the cyclization of squalene oxide, using measurements on the X-ray structure[9] of lanosterol bound in the active site of oxidosqualene cyclase.

Atom	x	y	z
C	-1.16484528	0.47469242	1.48555262
C	0.207751	0.30455594	1.45563504
C	1.06281428	1.32859845	1.84410596
C	0.50770571	2.52892904	2.26726032
C	-0.86513727	2.705033	2.29986185
C	-1.70592934	1.67750162	1.90846139
H	-1.81565615	-0.33266735	1.17442668
H	0.63060005	-0.63760448	1.12160094
H	1.16538274	3.33633203	2.57215822
H	-1.27994341	3.64939742	2.62891045
H	-2.77933792	1.81410917	1.92962541
C	2.54624159	1.11785373	1.85901026

H	2.83859482	0.50310341	1.00299453
H	3.05520358	2.07833689	1.74267841
C	3.00159786	0.44755586	3.14662684
H	2.51639123	-0.52292075	3.26846977
H	4.08074983	0.29115332	3.16071757
H	2.73457744	1.05670239	4.01250688
C	1.80978507	0.86428148	-2.35921253
C	0.68011371	0.37798168	-3.12438058
H	0.4974504	-0.67980485	-2.91102415
H	-0.22207542	0.97508442	-3.02986371
H	1.00288071	0.37211115	-4.17829938
C	1.71964215	2.12608036	-1.65443647
H	1.04838351	1.93020885	-0.80041951
H	2.66550615	2.50049937	-1.27301369
H	1.17963465	2.87439116	-2.24025945
C	3.03577702	0.09310788	-2.30244267
H	2.97593779	-0.8904508	-2.75823198
H	3.81158893	0.69189326	-2.8036829
H	3.39489366	0.03689333	-1.26866379

Energy = –468.20446516

Coordinates for the model of the *t*-butyl cation positioned relative to an ethylbenzene representing F444 of oxidosqualene cyclase so as to replicate the geometry of the carbocation intermediate at C_6 during the cyclization of squalene oxide, using measurements on the X-ray structure[9] of lanosterol bound in the active site of oxidosqualene cyclase.

Atom	x	y	z
C	-2.38917000	-2.53454000	-1.48589000
C	-1.04864000	-2.66573000	-1.79895000
C	-0.17423000	-1.59372000	-1.66177000
C	-0.67870000	-0.38474000	-1.20293000
C	-2.02018000	-0.24742000	-0.88687000
C	-2.87963000	-1.32263000	-1.02724000
H	-3.05605000	-3.37932000	-1.60347000
H	-0.66751000	-3.61476000	-2.16254000
H	-0.00777000	0.46089000	-1.09510000

H	-2.39567000	0.70431000	-0.53280000
H	-3.92891000	-1.21690000	-0.78403000
C	1.28393000	-1.76064000	-1.96577000
H	1.40162000	-2.32001000	-2.89863000
H	1.73803000	-0.78034000	-2.13124000
C	2.01540000	-2.48533000	-0.84592000
H	1.58935000	-3.47701000	-0.68249000
H	3.07569000	-2.60656000	-1.07014000
H	1.92691000	-1.93394000	0.09209000
C	-1.28295191	2.33875004	-5.40452079
C	-1.50151191	2.45630004	-3.97745079
H	-2.02118191	3.39060004	-3.74334079
H	-1.98203191	1.59640004	-3.52018079
H	-0.50652191	2.59930004	-3.52526079
C	-1.57861191	1.09451004	-6.08382079
H	-2.68054191	1.03555004	-6.10751079
H	-1.20639191	1.03514004	-7.10277079
H	-1.28724191	0.23023004	-5.48142079
C	-0.76123191	3.46345004	-6.15542079
H	-0.68086191	4.38823004	-5.59236079
H	0.23028809	3.16434004	-6.52834079
H	-1.34123191	3.60075004	-7.07496079

Energy = –468.1990960

Coordinates for the model of the *t*-butyl cation positioned relative to an ethylbenzene representing F444 of oxidosqualene cyclase so as to replicate the geometry of the carbocation intermediate at C_{10} during the cyclization of squalene oxide, using measurements on the X-ray structure of lanosterol bound in the active site of oxidosqualene cyclase

Atom	x	y	z
C	-2.56396000	-2.17601000	-1.37835000
C	-1.22343000	-2.30720000	-1.69141000
C	-0.34902000	-1.23519000	-1.55423000
C	-0.85349000	-0.02621000	-1.09539000
C	-2.19497000	0.11111000	-0.77933000
C	-3.05442000	-0.96410000	-0.91970000
H	-3.23084000	-3.02079000	-1.49593000

H	-0.84230000	-3.25623000	-2.05500000
H	-0.18256000	0.81942000	-0.98756000
H	-2.57046000	1.06284000	-0.42526000
H	-4.10370000	-0.85837000	-0.67649000
C	1.10914000	-1.40211000	-1.85823000
H	1.22683000	-1.96148000	-2.79109000
H	1.56324000	-0.42181000	-2.02370000
C	1.84061000	-2.12680000	-0.73838000
H	1.41456000	-3.11848000	-0.57495000
H	2.90090000	-2.24803000	-0.96260000
H	1.75212000	-1.57541000	0.19963000
C	-3.52827260	1.24224660	-5.83599484
C	-4.06642199	1.28996267	-4.49204131
H	-4.25050914	2.32498205	-4.18768120
H	-4.93288727	0.65610041	-4.32799200
H	-3.25076637	0.97014093	-3.82320468
C	-4.06292747	0.30190395	-6.79875901
H	-5.05912725	0.69706128	-7.06279674
H	-3.47723578	0.20259215	-7.70838217
H	-4.28310807	-0.66355621	-6.33595871
C	-2.44866869	2.13033836	-6.21902395
H	-2.19111801	2.87967683	-5.47681919
H	-1.57438504	1.49561033	-6.42981253
H	-2.66564232	2.58507063	-7.19213366

Energy = –468.1998718

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