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Article

Interaction of Allylic Carbocations with Benzene: a Theoretical Model of Carbocationic Intermediates in Terpene Biosynthesis

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Carbocátions atuam de formas diferentes quando interagem com anéis aromáticos. É interessante como na biosíntese de terpenos, os intermediários carbocatiônicos não alquilam a cadeia lateral aromática de aminoácidos presentes no sítio ativo, como seria esperado para outros carbocátions, como o cátion *terc*-butila. Neste trabalho, a interação entre benzeno e diferentes carbocátions alílicos é analisada, mimetizando carbocátions terpenóides, para melhor compreender como esta interação ocorreria. Cálculos em nível de teoria do funcional da densidade (DFT) mostram que para carbocátions alílicos secundários e terciários (como os encontrados na natureza), a forma não ligada da interação é mais estável energeticamente do que a alquilação do anel aromático, justificando a escolha da natureza por esses carbocátions mais estabilizados.

Carbocations act in different ways when interacting with aromatic rings. It is interesting that in terpene biosynthesis, the carbocationic intermediates do not alkylate the aromatic side chain of the amino acids present in the enzymatic active site, as would be expected by other carbocations such as the *tert*-butyl cation. In this study, the interaction between benzene and different allylic carbocations, mimicking terpenoid cations, is analysed in order to better understand how this interaction would occur. Density-functional-theory (DFT) calculations show that for secondary and tertiary allylic carbocations (as found in nature), the non-covalent interaction is energetically favoured with respect to alkylation of the aromatic ring.

Keywords: density-functional calculations, DFT, electrophilic substitution, cation-π interaction

Introduction

The study of noncovalent interactions has been gaining interest due to their broad applications in diverse fields such as ligand recognition, catalysis[1] and supramolecular chemistry.[2] However, the importance of noncovalent interactions, such as π stacking,[3,4] charge-dipole[5,6] and cation-π interactions,[4,7-10] has only been recognized recently. A cation-π interaction is defined as a strong, attractive, noncovalent and quite specific interaction between a cation and a π-system.[11] The cation-π interaction, which is of the same magnitude or even stronger than a typical hydrogen bond,[9,12] has a key role in protein folding,[13] selectivity of potassium channels[14] and several types of intermolecular recognition.[1,13,15-17]

The nature of the cation in the cation-π interaction can be metallic,[11,18] of ammonium derivatives,[19-22] which are very common in biological systems,[23,24] or carbocationic,[25-30] among others. Most of the available information for cation-π complexes has been obtained from coordinatively saturated cations, such as Na^+ and NH_4^+.[11,18-22] In the case of carbocations, cation-π interactions are found as intermediates in many enzymatic reactions, *e.g.* elongation and cyclization reactions in terpene biosynthesis.[31-33] The study of the interaction of such cations with aromatic side chains of amino acids is essential for better understanding of host-guest recognition and of the stabilization of many reaction intermediates.[34-38] This information facilitates the design of biomimetic catalysts and new drugs as well as a better understanding of protein folding and function.[8,9,19,22,39-41]

Most of the previous studies of cation-π interactions with organic cations have used ammonium derivatives[19-22] and small cations[26,30,42-44] as the probe molecule. It is known that coordinatively saturated cations interact with aromatic rings in a different manner than non-coordinatively saturated carbocations.[26] Until presently, studies of the interaction of an aromatic ring with protons and

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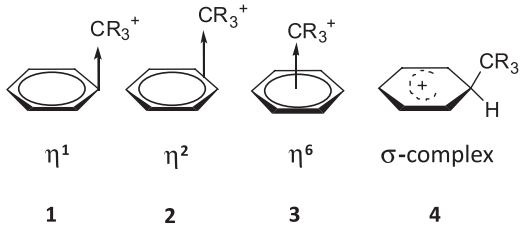
carbocations have focused on the Friedel-Crafts alkylation mechanism,[42,43,45-52] and the formation or characterization of π-[53-56] and σ- complexes (Scheme 1-(**4**)).[57,58] The formation of both complexes is dependent on the nature of the electrophile and on the aromatic ring.[59]



Scheme 1.

The non-bonded interaction of an electrophile with π-electrons can assume several geometries, as illustrated in Scheme 1, and these geometries are used as starting points for this study. The localized complex, with which the cation interacts with a single atom in the aromatic ring, is called η^1 (Scheme 1-(**1**)). When the cation rests over a C-C bond, thus interacting preferentially with two atoms, it is called a η^2 (Scheme 1-(**2**)). On the other hand, if the cation interacts with the aromatic π-system as a whole, located approximately at the center of the ring, it is called a η^6 complex (Scheme 1-(**3**)). The bonded interaction where the electrophile is added to the aromatic ring, disrupting its aromaticity, is called a σ-complex (Scheme 1-(**4**)).

Ishikawa *et al.*[42] studied the energetic profile by quantum molecular dynamics of the alkylation of the benzene ring by methyl cation and found that no π-complex is formed during the reaction. The interaction of the methyl cation and benzene directly affords the σ-complex. This could be anticipated due to the high reactivity of the methyl and primary carbenium ions. However, carbocations in biological media (*e.g.*, tertiary and allylic ones) have greater stability than the methyl cation. Thus it is more likely that these cations would behave similarly to the *tert*-butyl cation, which prefers to form a π-complex before the more stable σ-complex.[48,49] Within this context, the aim of this work is to study the interaction of relatively stable allylic carbocations with an aromatic ring.

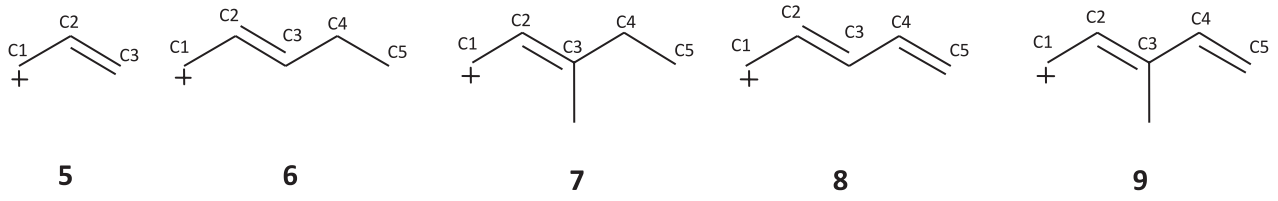
Computational Details

The quantum chemical calculations were carried out using the Gaussian 09 program package.[60] Geometry optimizations were performed with the M06-2X[61-63] functional using the 6-311++G(d,p) basis set. The M06-2X functional was chosen based on the work of Zhao and Thrular[64] that showed that the M06-2X functional describes well the cation-π interaction. The optimized geometries were characterized as minima on the potential energy surface by the absence of imaginary vibrational frequencies, whereas the transition states were characterized by the presence of a single imaginary frequency. Intrinsic reaction coordinate calculations (IRC) were carried out to evaluate whether the transition states connected the reactants to the products. All discussion refers to enthalpy with thermal correction to 298 K. Atomic charges were derived from the fit to the electrostatic potential (ESP) according to the ChelpG scheme[65] and of the atomic polar tensor based (APT) analysis.[66]

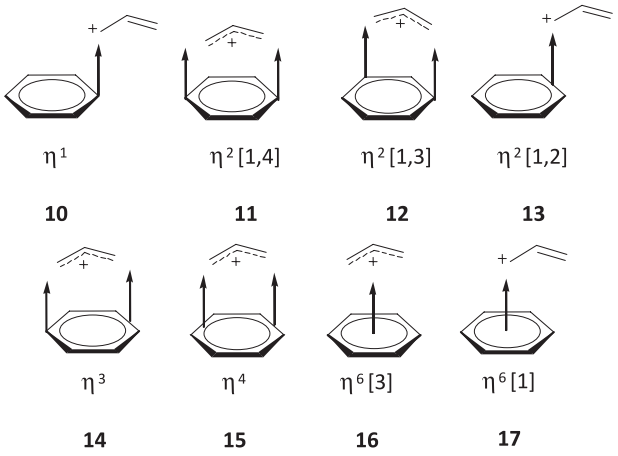
Results and Discussion

In order to study the influence of the carbocation stability on its interaction with an aromatic ring, the interaction of allylic carbocations (Scheme 2) with benzene, as the aromatic model (which can be seen as a model of phenylalanine side chain), is focused in the present study.[35]Allylic carbocations are bidentate electrophiles that can form different types of π-complexes (Scheme 3). All of the π-complex geometries and σ-complex intermediates typical of a Friedel-Crafts alkylation were investigated.

Our results show that, the η^1, η^2 [1, 2] and η^6 geometries were not found as minima in the potential energy surface, regardless of the starting geometry used. In the first two cases, all the attempts lead to σ-complexes, while the η^6 geometry lead to η^3 or η^4 type π–complexes (Scheme 3). The π-complexes are formed for all secondary (**6**, **8**) and tertiary (**7**, **9**) allylic carbocations, but not for the primary one (**5**), the latter directly forms the σ-complex. Their structures are given in Figure 1. The distances between the benzene and the electrophile in the π-complex range



Scheme 2.



Scheme 3.

from 2.7 to 3.2 Å are shown in Table 1. In the case of 2-pentenylium (**6**) and 3-methyl-pentenylium (**7**), the π-complexes revealed a η^3 geometry, while for the two other electrophiles the geometries were η^4 (Figure 1).

Table 2 shows that, when the π-complex was formed, the distance between the electrophile and benzene increases with the stability of the carbocation. In the case of charge transfer, all the three most stable cations among the studied species have the same order of total charges. In the case of the 2-pentenylium (**6**), one can verify that the C_1-C_2 and C_2-C_3 distances are basically the same, showing the same sp^2 character and charge delocalization between these carbon atoms. The presence of a methyl group attached to C_3, as in the case of 3-methyl-2-pentenylium (**7**) and 3-methyl-pentadienylium (**9**), causes an increase of the C_2-C_3 distance, showing the preference of the charge to be located at C_3. For the 3-methyl-pentadienylium (**9**), the difference between C_1-C_2 and C_2-C_3 distances is the largest in the series, indicating the larger charge over C_3.

For 2-pentenylium (**6**), the complex formed from the separated carbocation and benzene is exothermic by 18.5 kcal mol^{-1}. In the three other cases, for pentadienylium (**8**), 3-methyl-pentenylium (**7**) and 3-methyl-pentadienylium (**9**), the difference in enthalpy is *ca.* 14 kcal mol^{-1} (Figure 1). This difference in enthalpy from 2-pentenylium(**6**) to the other electrophiles is because of the formation of a more stabilized electrophile due to the attachment of a

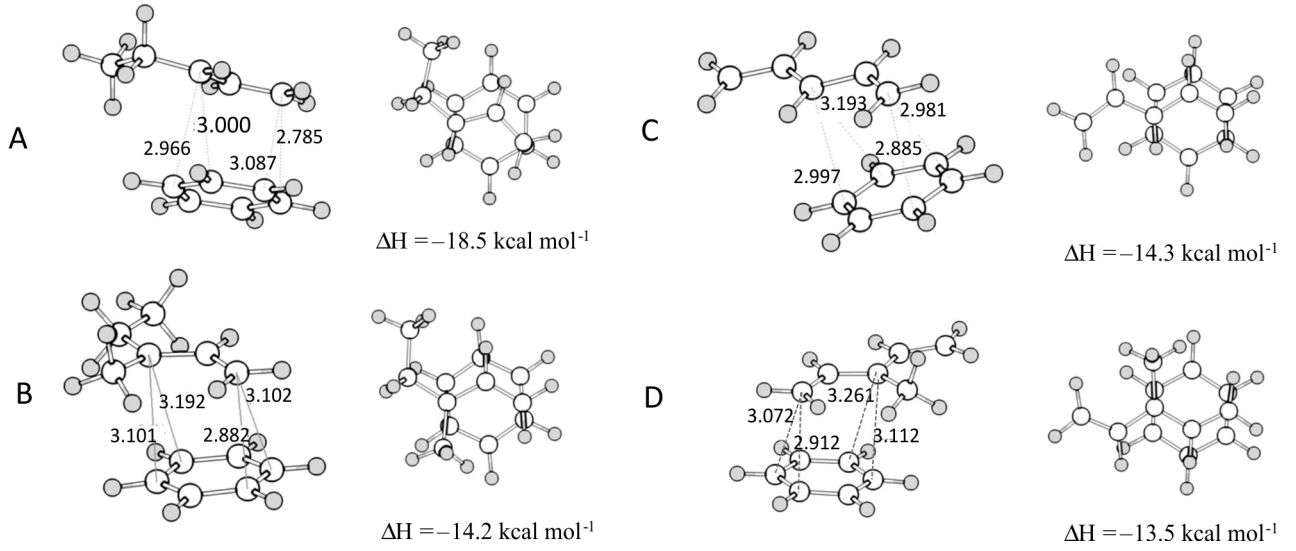


Figure 1. Computed π-complex geometries at M06-2x/6-311++G(d,p) level and selected distances in Å for the interaction between benzene and (A) 2-pentenylium, (B) 3-methyl-2-pentenylium, (C) pentadienylium and (D) 3-methyl-pentadienylium; the enthalpy difference is relative to the difference between enthalpies of the π-complex and the reagents.

Table 1. Distances (Å) between the carbon C_1 and C_3 of the allylic electrophiles to the two closest carbons of the aromatic ring

Compound	C_1		Diference[a]	C_3		Diference[a]
	C_{B1}	C_{B2}		C_{B1}	C_{B2}	
2-Pentenylium	2.785	3.087	0.302	2.966	3.000	0.034
3-Methyl-2-pentenylium	2.882	3.102	0.220	3.101	3.192	0.091
Pentadienylium	2.885	2.981	0.096	2.997	3.193	0.196
3-Methyl-pentadienylium	2.912	3.072	0.160	3.112	3.261	0.149

[a](distance C-C_{B2}) – (distance C-C_{B1}).

Table 2. Charges and distances (Å) in each electrophile in π-complex

	Pentenylium		3-Methyl-pentenylium		Pentadienylium		3-Methyl-pentadienylium	
	ESP	APT	ESP	APT	ESP	APT	ESP	APT
Total charge in the electrophile	+0.700	+0.949	+0.750	+0.976	+0.740	+1.061	+0.784	+1.020
Charge in C_1	−0.005	+0.494	+0.045	+0.432	−0.020	+0.975	+0.020	+0.478
Charge in C_3	+0.156	+0.737	+0.345	+0.888	+0.206	+0.513	+0.415	+1.112
Charge in C_6	−0.207	+0.010	−0.206	−0.001	−0.054	+0.235	−0.020	+0.210
Distance C_B-C_1[a]	2.785		2.882		2.885		2.912	
Distance C_1-C_2	1.368		1.360		1.363		1.357	
Distance C_2-C_3	1.390		1.408		1.398		1.416	
Distance C_3-C_4	1.472		1.485		1.423		1.442	
Distance C_4-C_5	1.522		1.521		1.348		1.344	
Distance C_1-H_{1A}[b]	1.085		1.084		1.084		1.083	
Distance C_1-H_{1B}[b]	1.085		1.083		1.085		1.084	

[a]C_B: benzene carbon closest to the C_1; [b]H_{1A} and H_{1B}: hydrogen atoms bound to C_1.

second double bond to the structure (delocalization of the charge) or a methyl group (forming a tertiary carbocation). The complexes between benzene and more stabilized carbocations present lower dissociation energies in relation to the respective complex involving less stable carbocations. This decrease in the binding energy is not additive, as can be seen in the case of the 3-methyl-pentadienylium (**9**). This complex is only 0.5 kcal mol^{-1} more stable than the complex involving pentadienylium (**8**). The binding energy for the complex involving the most stable carbocation investigated in this work is still larger, or of the same magnitude as the stabilization that occurs with a typical

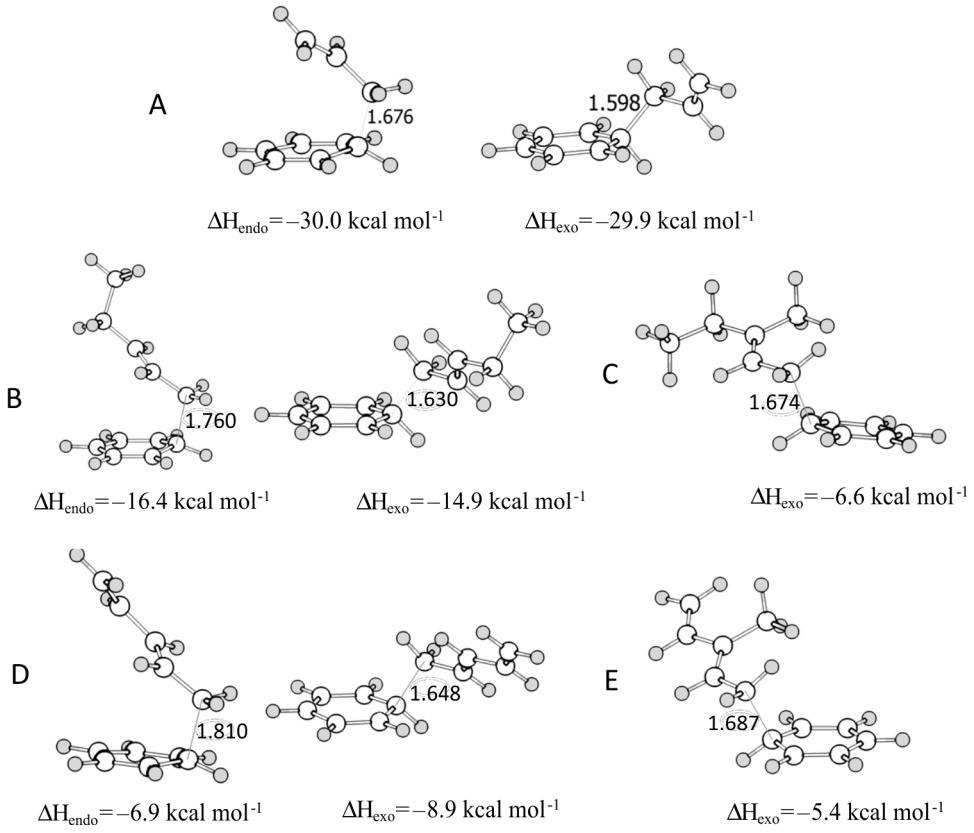


Figure 2. Computed σ-complex geometries at M06-2x/6-311++G(d,p) level and selected distances in Å for the interaction between benzene and (A) propenylium, (B) 2-pentenylium, (C) 3-methyl-2-pentenylium, (D) pentadienylium and (E) 3-methyl-pentadienylium; the enthalpy difference is relative to the difference between enthalpies of the π/σ-complex and the reagents.

hydrogen bond interaction.[9] This makes the aromatic ring a really smart choice for nature to incorporate in the active site of enzymes with carbocationic intermediates, since they avoid the presence of water, which could react with the just formed carbocation and also improves the latter stabilization in relation to polar side chains.

From several geometries used as starting points, including the interaction of the two most important cationic sites of the electrophile, only two types of σ-complex were found: a complex with the side chain pointing into the molecule (endo) and another one with this group pointing away from the aromatic ring (exo). These complexes are illustrated in Figure 2. The endo complexes are more hindered and at higher or similar energy to the corresponding exo ones. For the most hindered 3-methyl-pentenylium (**7**) and 3-methyl-pentadienylium (**9**), the respective endo σ-complexes were not found, despite all attempts to localize them, all geometry optimizations converged to the respective π-complexes. The endo σ-complex for pentadienylium (**8**) has a longer bond with the aromatic ring, indicating that this interaction is less stabilizing and the conformation is less stable when compared to 2-pentenylium (**6**).

As shown in Figure 3, the π-complexes for all secondary and tertiary allylic carbocations are more stable than the respective σ-complexes. This result suggests that, in biological reactions, the amino acid aromatic side chains in the enzyme active site will not be alkylated by allylic tertiary or secondary intermediates in terpene biosynthesis and that they provide a stabilizing influence on the intermediates.

The potential energy surface (Figure 3) shows that in the case of secondary and tertiary carbocations, the difference in enthalpy from the σ-complex to the transition

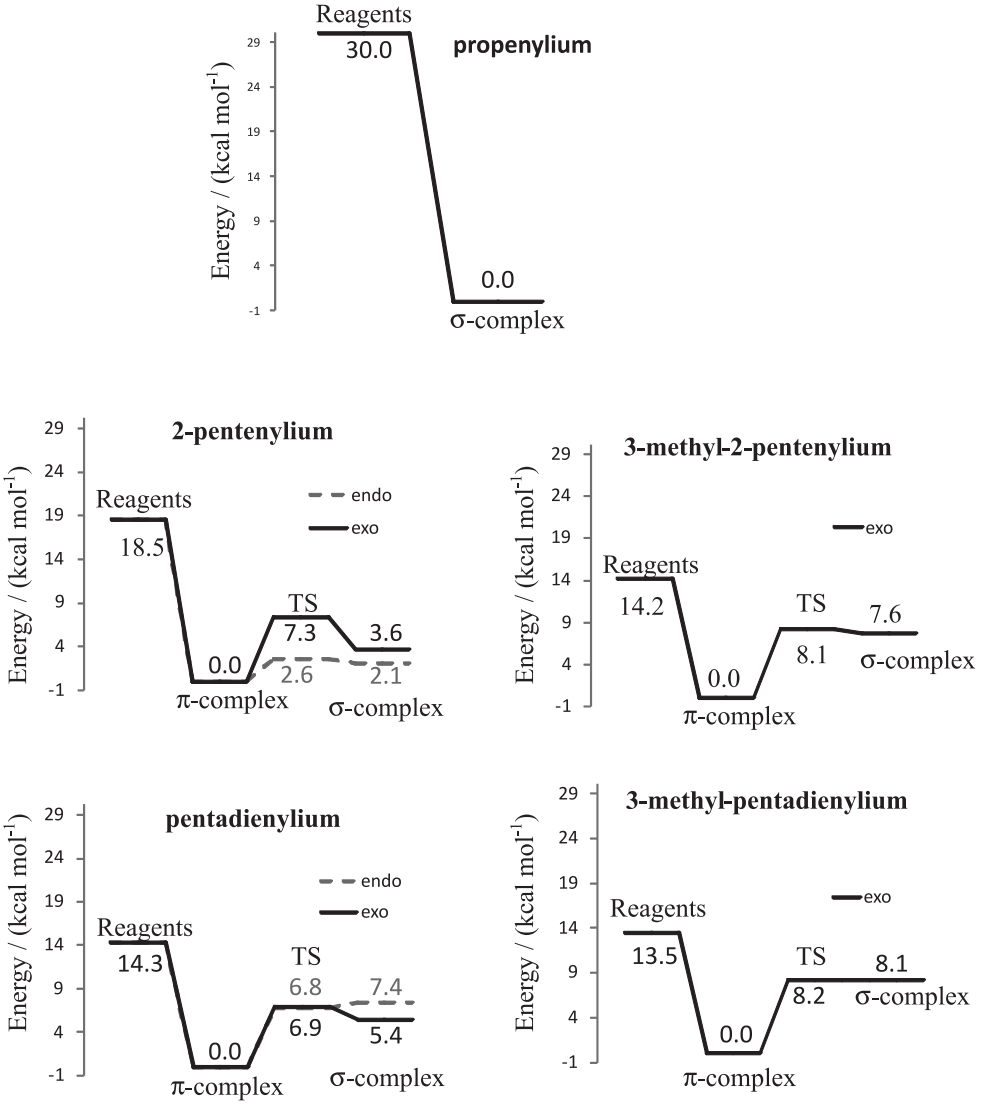


Figure 3. Potential energy surface for the interaction of benzene with different allylic cations, showing the relative enthalpy for reagents, transition state (TS), π- and σ-complexes.

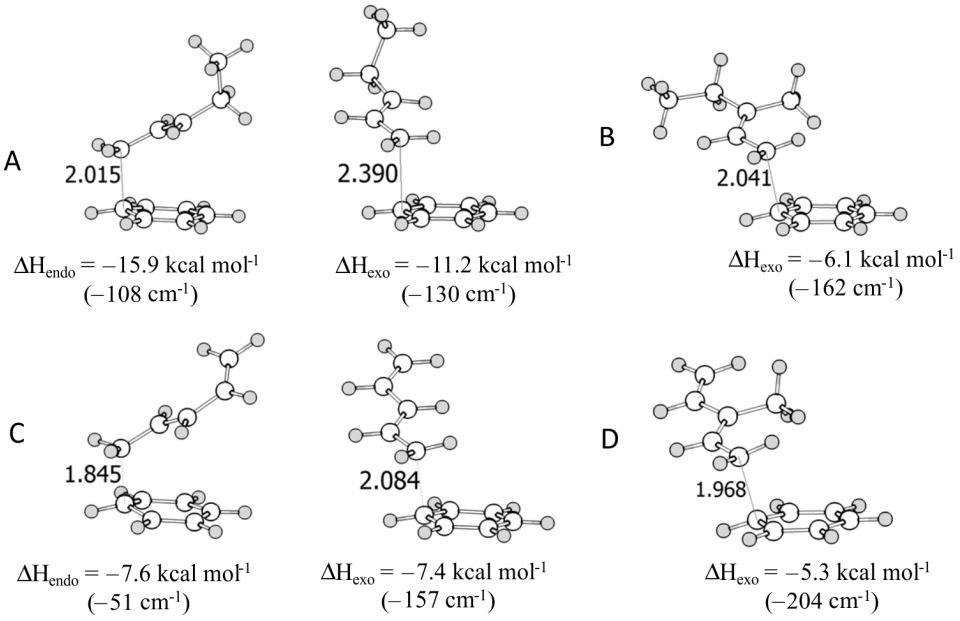


Figure 4. Computed transition state geometries at M06-2x/6-311++G(d,p) level and selected distances in Å for the interaction between benzene and (A) 2-pentenylium, (B) 3-methyl-2-pentenylium, (C) pentadienylium and (D) 3-methyl-pentadienylium; the enthalpy difference is relative to the difference between enthapies of the TS and the reagents. Brackets indicate the characteristic imaginary frequency of the transition state.

state (geometries in Figure 4) is so small, that even if the σ-complex is formed, it could easily overcome the transition state barrier to form the π-complex. The enthalpy difference between π- and σ-complexes become larger for the substrates methylated at carbon 3, showing that not only the stabilization of the carbocationic center is important, but also that steric hindrance has an important role in avoiding the alkylation of the side chain of residues in enzymes with carbocationic intermediates. Pentadienylium (**8**), which has a closer structural similarity to secondary intermediates in terpene biosynthesis, also shows a prominent preferential formation for the non-bonded complex. This shows that secondary delocalized carbocations can also exist as stable intermediates for terpene biosynthesis. Primary allylic carbocations would directly alkylate aromatic rings, as the π-complex does not exist as a minimum on the potential energy surface.

Conclusion

The interaction between allylic carbocations and benzene was analyzed in this study as a model for understanding how carbocationic intermediates of enzymatic reactions interact with amino acid aromatic side chains. We have seen that the alkylation of benzene is not favored for stabilized carbocations, such as those involved in terpene biosynthesis. The formation of a non-bonded π-complex is interesting because there is enough stabilization of the carbocation, but there is no loss of aromaticity as in σ-complex. The π-complexes have η^3 or η^4 geometry, and the η^6 geometry, usually found in coordinatively saturated cations, was not found as a minimum on the potential energy surface.

As the carbocation is less delocalized, the more it is stabilized by the interaction with benzene. However, the more stable carbocations, when interacting with benzene, reach a stabilization plateau. It seems that there is, in this case, a minimum boundary of *ca*. 14 kcal mol^{-1}. From a biological context, one can see that nature prefers the formation of more stabilized carbocations, allylic secondary or tertiary, that can be further stabilized by the formation of a π-complex. The presence of only stabilized carbocations prevents the alkylation of the amino acid aromatic side chain. An interesting fact (even for secondary carbocations), the formation of the non-bonded π-complex is more stable. The gain in energy generated by this interaction turns possible its existence in biological medium.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

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