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Aromatization within the putative bio-medical action mechanism of berberine and related cationic alkaloids with double iso-quinolinoid skeleton. A theoretical study

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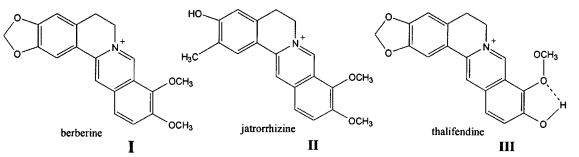
Abstract

In the putative mechanism of action for berberin, to prevent DNA replication the first step is aromatization. The aromatization process, via dehydrogenation has been studied for a series of compounds related to berberine. In contrast to the covalent dehydrogenation, which is endothermic, the aromatization under ionic conditions was found to be exothermic. The availability of the hydride for ionic aromatization was indicated by the effective HOMO of berberine and related compounds. The results indicate that in the aromatization process the ease of hydride ion removal parallels the stabilizations energy of the aromatic compounds to be formed. Comparing the nucleophilic additions to the π-system, the LUMO energy values suggested a greater accessibility of the $N^{(+)}$ heterocycles in comparison to the polycycle aromatic hydrocarbons.

Keywords: Aromatization by dehydrogenation; Hydride transfer and deprotonation; Nucleophilic addition to heteroaromatic cations; HOMO/LUMO study; Ab initio MO; DFT study

1. Introduction

Protoberberines (**I**–**III**) and their relatives exhibit several types of biological activities [1]. However, to date berberine alone was found to be of clinical value and is being used in the treatment of gastrointestinal disorders. These alkaloids are cytotoxic [2], they may act as insect deterrents and insecticides [3,4]. Also, they are toxic to vertebrates (LD_{50} in mice: 23 mg kg^{-1} for berberine).



Sado [5] examined systematically antibacterial activity of berberine (**I**) chloride and iodide against

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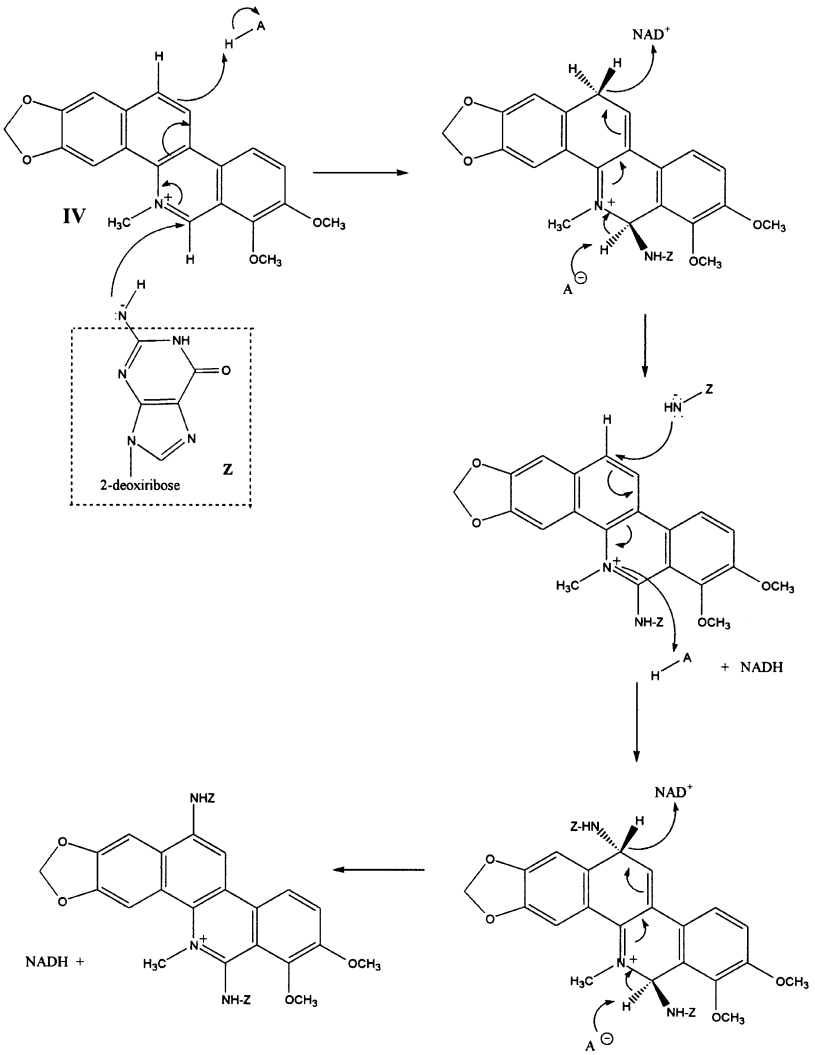
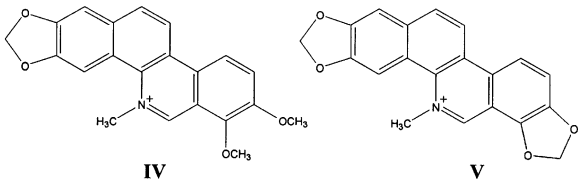


Scheme 1.

Vibrio, *Eberthella*, *Salmonella* and *Escherichia* organisms. Lahiri and Dutta [6] have recommended the use of berberine (**I**) as an adjunct to isotonic saline and electrolyte replacement therapy in acute cholera. Berberine (**I**) is reported to depress intestinal peristalsis and to remove inflammatory congestion of the mucosal surface of the intestine. Berberine (**I**) has also been found effective in the treatment of diarrhea in infancy and childhood [7]. Krey and Hahn [8] have observed that berberine formed a complex with DNA, probably intercalating into supercoiled mitochondrial DNA to produce configurational changes in DNA. Berberine has also been reported as an interesting potential antifungal agent [9]. An exhaustive study about the antifungal effects of berberine against a wide range of pathogenic fungi has been recently carried out by our group [10].

It is interesting to note that benzophenathridines (**IV**–**V**), with certain structural similarities, have

also been reported to have significant activity against *C. albicans* [11–13].

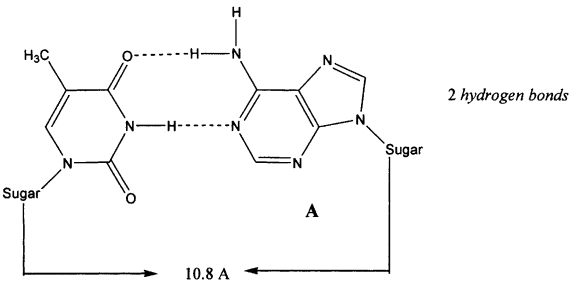


Due to its quaternary nitrogen, within a polycyclic and planar structure, berberine (**I**) can react with nucleophilic and anionic groups of aminoacids in several receptors and enzymes. For example, these alkaloids bind to microtubules [14], inhibit several enzymes [15–18] uncouple oxidative phosphorylation [19] and intercalate in G…C-rich regions of DNA [20–21].

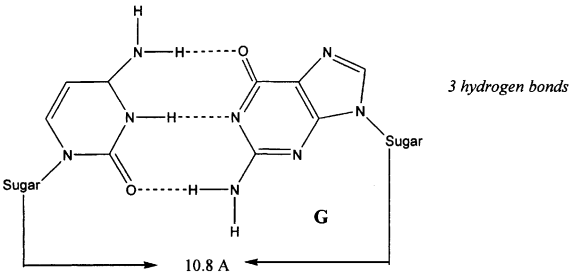
It is clear that a great number of studies have been performed in order to shed some light on the structural aspects and bioactivities of berberine and its congeners. However, compared with these aspects, the action mechanism of these alkaloids, at least at the molecular level, has received relatively little attention. A bio-medical action mechanism of berberine (**I**) and related cationic alkaloids (**II**–**V**) has been recently proposed by us [22].

2. Background

One possible mechanism of action for certain drugs, that prevents DNA replication, is associated with the process of joining together, by covalent bonds, the two helices of DNA. This, of course, requires chemical reaction on both ends of the drug molecule. In most cases, neither the carbohydrate moiety nor the phosphate groups are responsible for the formation of such covalent bonds, but the purine bases, namely adenine (**A**) and guanine (**G**). Since, both **A** and **G** are present in the two helice, (**1**) and (**2**), the proposed drug molecule should therefore carry out similar reaction at both of its end. These two reactive site must be appropriately spaced as suggested by (**1**) and (**2**).

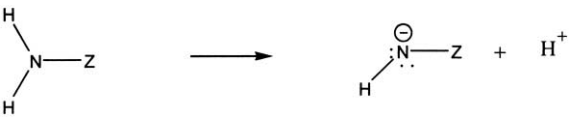


(1)



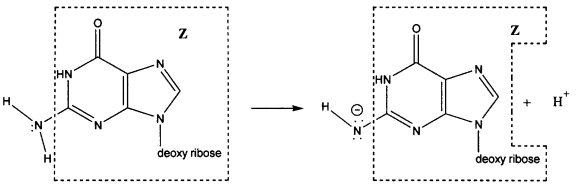
(2)

As both of them (**A** and **G**) have a free N–H bond they can deprotonate (**3**) and act as conjugate bases, with their negatively charged nitrogen, when reacting with the drug molecule.



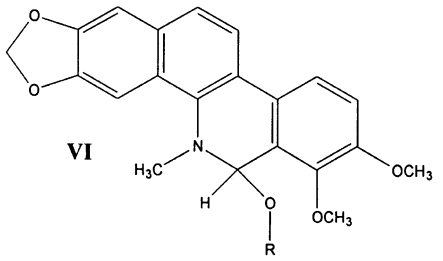
(3)

Since in guanidine three nitrogens atoms are surrounding a carbon while in adenine there are only two nitrogen atoms around one carbon, guanine is expected to be more reactive (4).

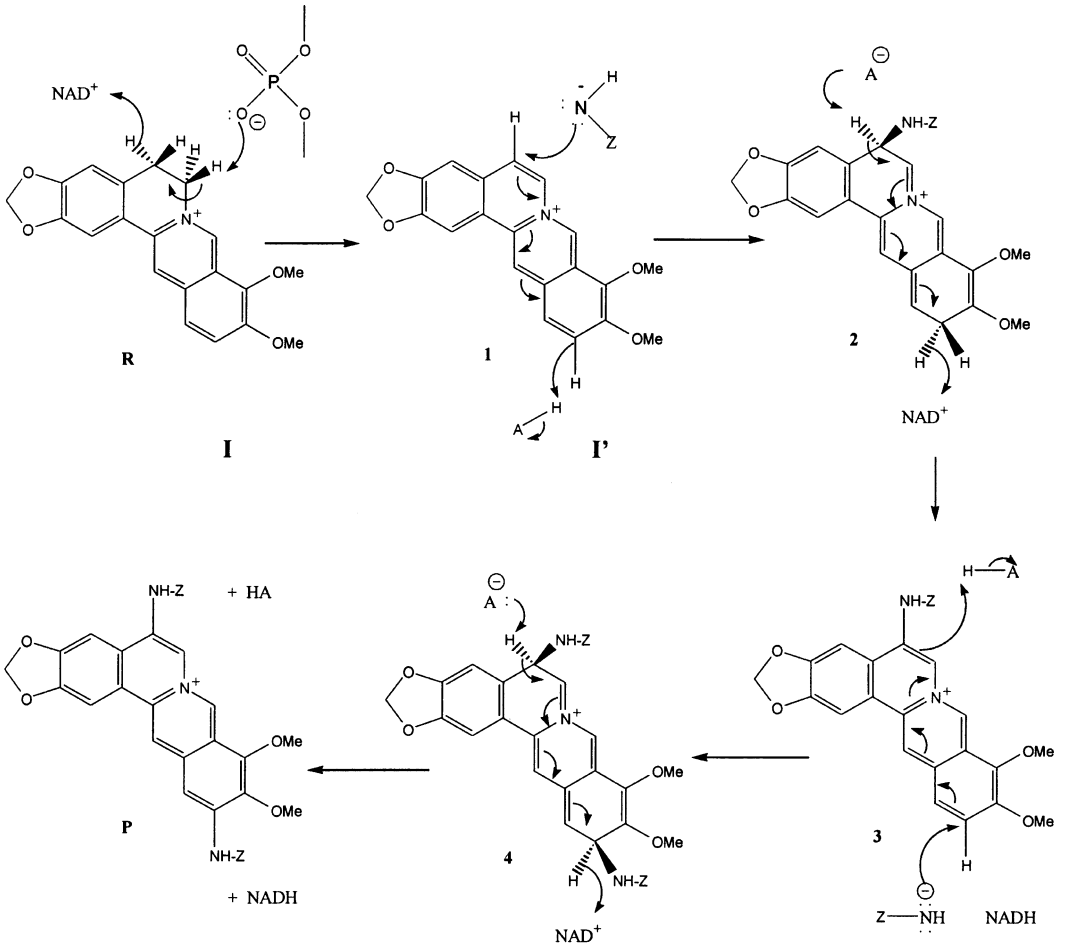


(4)

The above oversimplified deprotonation equation

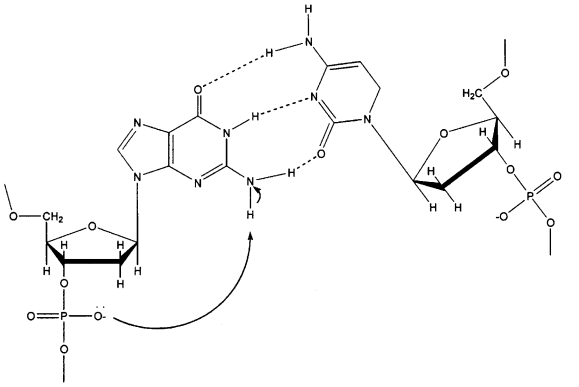


(R= Me or Et)



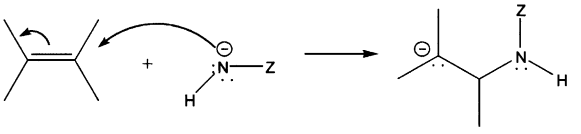
Scheme 2.

may be far more complex as illustrated below (Eq. (5)).



(5)

Such a base, generated by proton transfer, can carry out for example, nucleophilic addition to a double bond (Eq. (6)).



(6)

Nucleophilic addition to an isolated double bond may not be pronounced. However, as may be seen from the structures of certain alkaloids (**I**–**V**), nucleophilic addition to a double bond, near to a positively charged nitrogen in the ring, may be well enhanced.

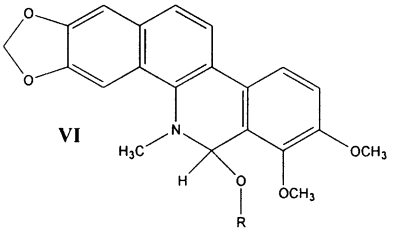
3. Method

Initially, semi-empirical molecular orbital (MO) calculations (AM1 or PM3) have been used for geometry pre-optimizations. Subsequently, ab initio Hartree–Fock calculations were carried out using a 3-21G basis set. These computations were performed using the Gaussian 98 software [23]. Single point, higher level computations (HF/6-31G(d) and B3LYP/6-31G(d)) were performed on selected structures. The visualization of molecular orbitals (HOMO/LUMO) were achieved using Spartan [24].

3.1. Putative mechanism

As a general rule, mechanisms are proposed or postulated. Consequently, they are axiomatic in the sense that they can only be disproved but their validity can never be proven. Thus, one is constantly in search for experimental facts to determine whether the mechanism continues to be acceptable. Consequently, in the first step, one must start with a putative mechanism and see if it is plausible or not. A putative mechanism to prevent DNA replication by heteroaromatic ring systems containing positively charged nitrogen is given below in Scheme 1 (putative mechanism of action of heteroaromatic ring systems of type (**IV**) containing positively charged nitrogen to prevent DNA replication).

Since the molecule carries a positive charge, the attack of the nucleophilic nitrogen may be suggested from first principles. However, oxygen containing derivative of **V**, depicted as **VI**, suggests that such a site is not only acceptable but, in fact, attacks on that site are occurring in nature.



VI

(R= Me or Et)

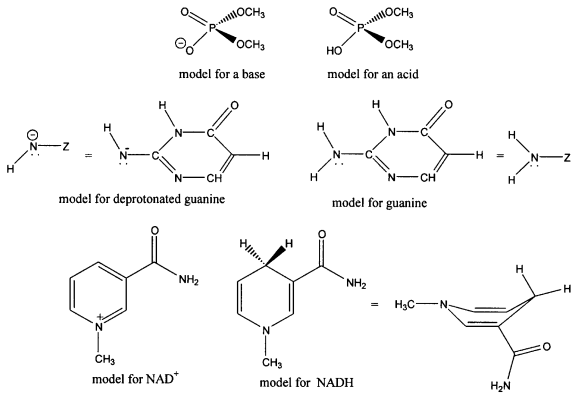
Analogously to Scheme 1 a putative mechanism of action for berberine (**I**) may be proposed as shown by Scheme 2 (putative mechanism of action for berberine (**I**) to prevent DNA replication).

Note that in Scheme 2 the first step is aromatization. The actual bio-medical mechanism will start with the fully aromatic compound (**IV** and **I′**) as shown in both Schemes 1 and 2, respectively.

4. Scope

For an investigation, concerned with the thermodynamic aspect of a putative mechanism, only reactants, reaction intermediates and products need to be studied. Since these are, by definition, minima on the potential energy hypersurface (PEHS) therefore they can be located by geometry optimization using, for example, the Gaussian 98 software. It is clear from

Schemes 1 and 2 that a number of molecules are involved in the general mechanism. Some of these are fairly large so it may be necessary to mimic them. The following mimetics could be considered for the overall study.



We have reason to believe that the hydride abstraction ability of the above model for NAD^+ is substantially different from that of the whole NAD^+. Consequently a weak hydride abstractor (Li^+) and a strong hydride abstractor (CH_3^+) may be used initially to bracket the hydride affinity of NAD^+.

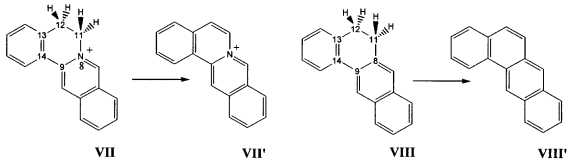
$$Li^+ + H^- \rightarrow Li–H \text{ (relatively small hydride affinity)}$$

$$H_3C^+ + H^- \rightarrow H_3C–H \text{ (relatively large hydride affinity)}$$

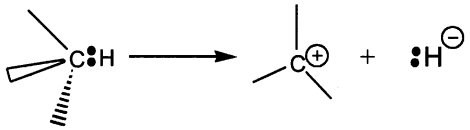
A hetero-aromatic ring structure, to model berberine (**I**), must, however, be studied in full but without the substituents. This is prudent because all three alkaloids (**I**–**III**) have the same skeleton (**VII**). The dehydrogenation process can be studied with (**VII** → **VII′**) and without (**VII** → **VIII′**) positively charged nitrogen.

Before a detailed study could begin we can look for signs of reactivity in the MOs of the first hetero aromatic compound (structures **R** and **1**, in Scheme 1).

As a general rule, for electrophilic attack, including protonation, the effective HOMO (E-HOMO) need to be considered. The E-HOMO may not be the actual HOMO; it could be HOMO − 1, HOMO − 2, etc. Similarly, for nucleophilic addition the E-LUMO is to be investigated (again it could be LUMO + 1, LUMO + 2, etc). For both of these (E-HOMO and E-LUMO) a lobe (i.e. a large coefficient square; c^2) is required to be present where those reagents attack. The location of such lobes can be taken to be diagnostic for the *possibility* for the reaction to occur. Of course the possibility is not yet the *probability*. For the probability we need to study the energetics of the reaction.



In the present case, however, these orbitals (i.e. the proton acceptor and the hydride acceptor) are the HOMO of the anionic base and the LUMO of the cationic Lewis acid, respectively. For the compounds to be aromatized it is the hydride transfer that may be energetically the most significant step as in that case a heterolytic bond cleavage is required where the least electronegative atom (i.e. the hydrogen) will take away the bonding electron pair. This removal of electron density from the carbon looks like the ionization of the organic compound that is related to the orbital energy in terms of Koopmans' theorem.


(7)

Thus, for the aromatization process, perhaps the HOMO may be the most relevant orbital to be considered.

5. Results and discussion

On the basis of some accumulated experience, a putative mechanism (Scheme 2) has been suggested for the biomedical mechanism of action of berberine (**I**) involving a reaction with DNA. The first step of the reaction involved the aromatization (**I** → **I′**) of the ring which contained a $–CH_2–CH_2–$ moiety. The mechanism was conceived as a base catalyzed reduction in which one of the hydrogen atoms of the $–CH_2–CH_2–$ bridge was transferred, as a proton, to the

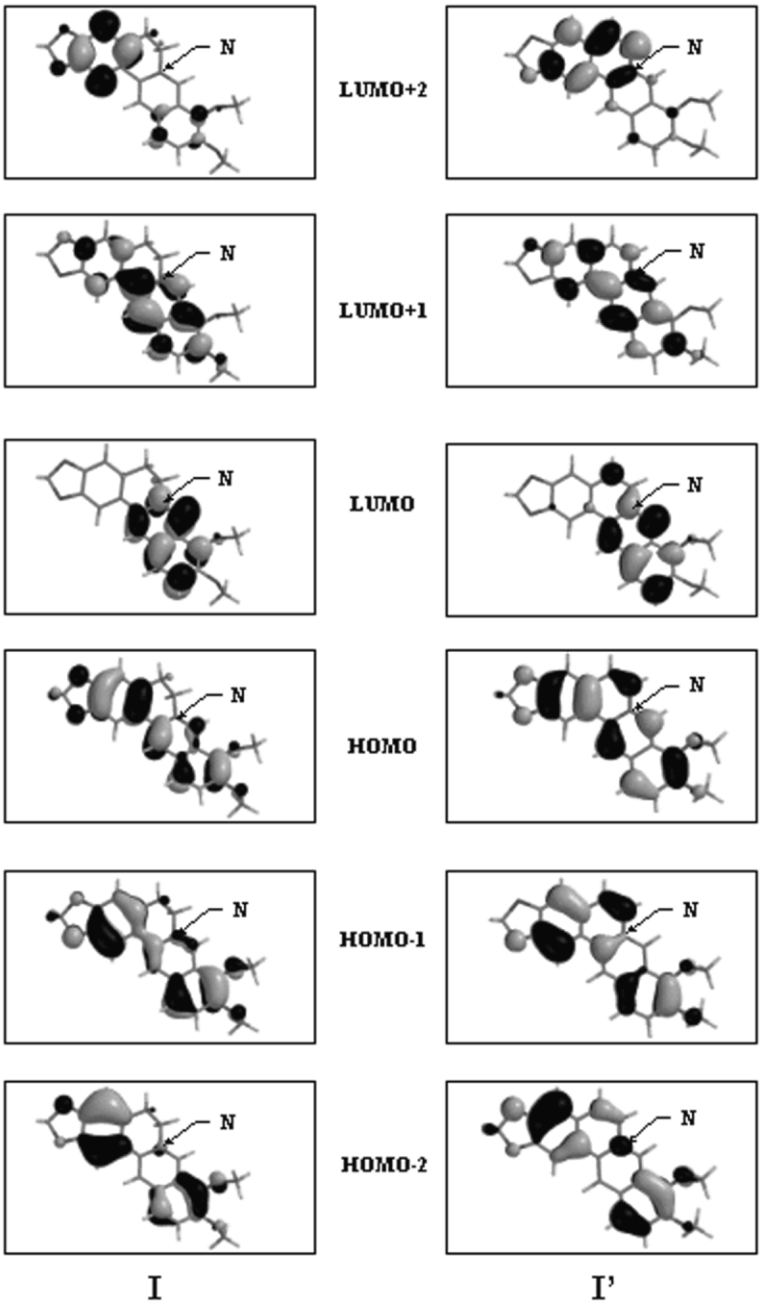


Fig. 1. Effective HOMO and LUMO for berberine (**I**) and its aromatized form (**I**′).

negatively charged oxygen of the phosphate linkage of the DNA. This was coupled (either in a concerted or stepwise fashion) with the redox step, namely the hydride (i.e.: $H^{(-)}$) transfer.

This aromatization process (i.e.**I** → **I**′) was compared with the analogous step of the berberine skeleton (**VII** → **VII**′) as well as to the analogous hydrocarbon analog (**VIII** → **VIII**′). The frontier

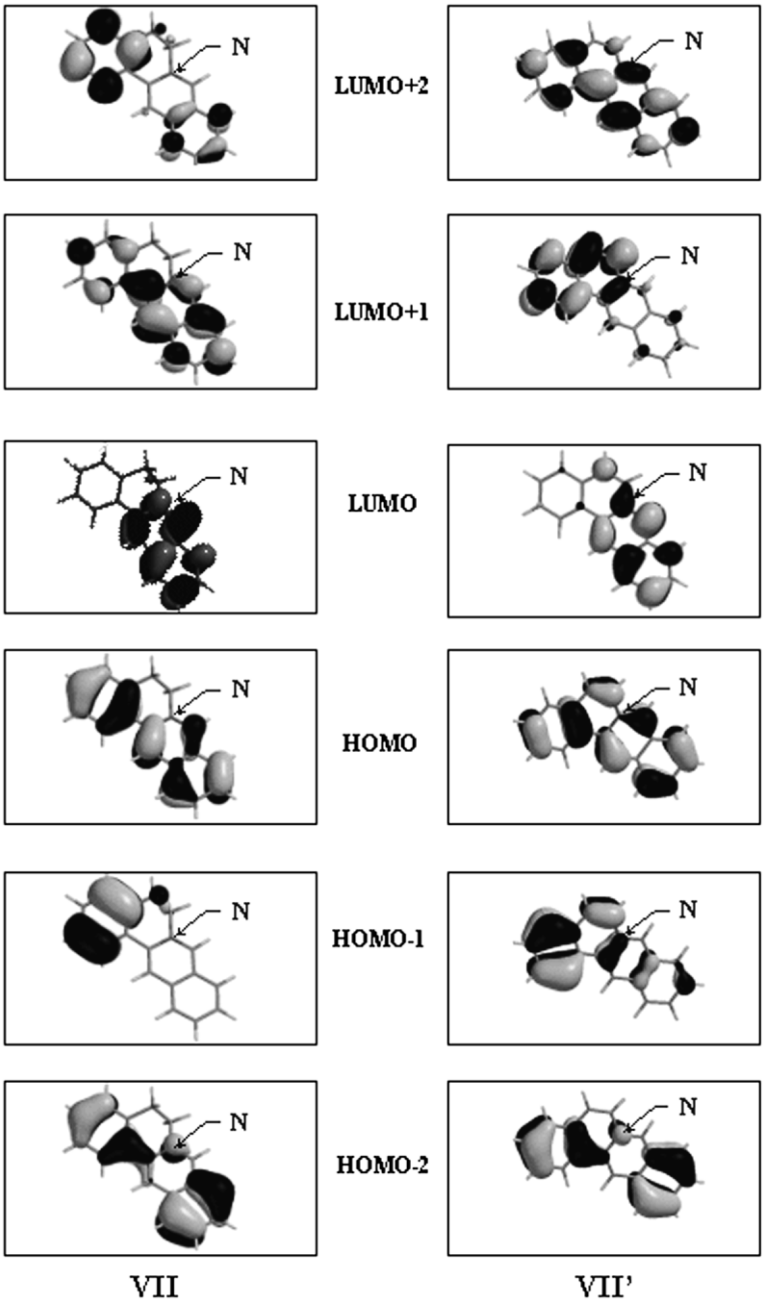


Fig. 2. Effective HOMO and LUMO for berberine skeleton (**VII**) and its aromatized form (**VII**′).

molecular orbitals (HOMO − 2, HOMO − 1, HOMO, LUMO, LUMO + 1, LUMO + 2) are depicted for the three aromatization process **I** → **I**′, **VII** → **VII**′, **VIII** → **VIII**′ in Figs. 1–3, respectively.

Considering the three effective HOMOs, in agreement with (**7**), we see that **I** has a lobe at the hydride like hydrogen in HOMO, HOMO − 1, and HOMO − 2. Compound **VII** has a lobe in

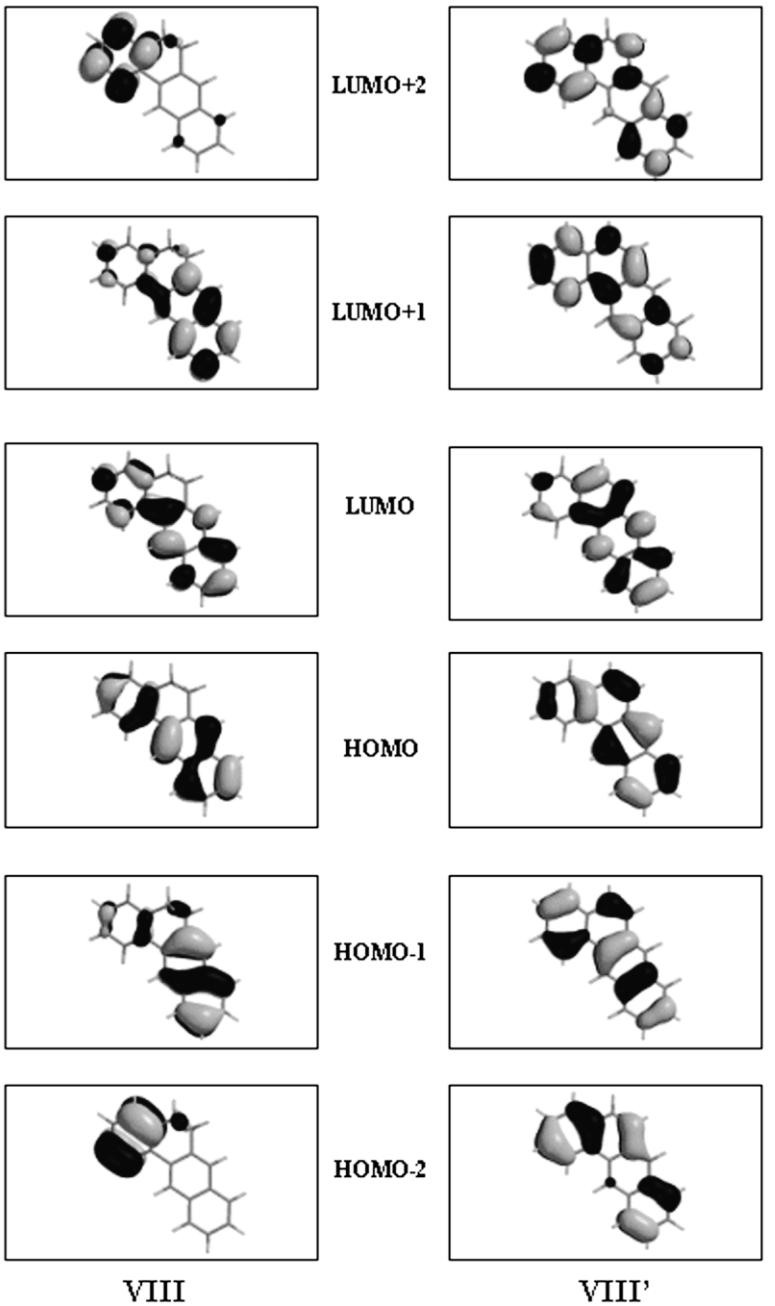


Fig. 3. Effective HOMO and LUMO for dihydrobenzphenantrene (**VIII**) and benzphenantrene (**VIII**$^{\prime}$).

HOMO − 1 and compound **VIII** has a lobe in HOMO − 2. The frontier molecular orbital energies for all species involved are listed in Table 1.

The total energy values computed at three levels of theory for the various species under considerations are listed in Table 2.

The energy of aromatization is expected to be related to the aromatic character. The more exothermic the

Table 1
Frontier orbital energies of selected compounds

Compounds	Orbital energies (hartree)																	
	HF/3-21G						HF/6-31G(d)						B3LYP/6-31G(d)					
	HOMO −2	HOMO −1	HOMO	LUMO	LUMO + 1	LUMO + 2	HOMO −2	HOMO −1	HOMO	LUMO	LUMO + 1	LUMO + 2	HOMO −2	HOMO −1	HOMO	LUMO	LUM + 1O	LUMO + 2
I	−0.47	−0.44	−0.40	−0.08	−0.05	0.03	−0.46	−0.43	−0.39	−0.08	−0.05	0.03	−0.36	−0.34	−0.31	−0.20	−0.17	−0.11
I′	−0.47	−0.45	−0.40	−0.10	−0.06	−0.02	−0.46	−0.44	−0.39	−0.08	−0.06	−0.007	−0.36	−0.35	−0.32	−0.20	−0.18	−0.15
VII	−0.49	−0.46	−0.43	−0.09	−0.06	0.02	−0.48	−0.45	−0.42	−0.09	−0.06	0.02	−0.39	−0.37	−0.36	−0.21	−0.19	−0.12
VII′	−0.50	−0.45	−0.43	−0.10	−0.07	−0.02	−0.49	−0.44	−0.42	−0.09	−0.07	−0.02	−0.40	−0.37	−0.36	−0.22	−0.19	−0.16
VIII	−0.33	−0.30	−0.28	0.08	0.12	0.15	−0.33	−0.29	−0.27	0.09	0.12	0.15	−0.24	−0.22	−0.21	−0.04	−0.01	0.006
VIII′	−0.34	−0.30	−0.27	0.07	0.10	0.14	−0.33	−0.29	−0.26	0.07	0.10	0.14	−0.25	−0.22	−0.20	−0.05	−0.03	0.001
IX	−0.34	−0.32	−0.28	0.10	0.13	0.16	−0.32	−0.32	−0.28	0.11	0.14	0.16	−0.24	−0.24	−0.21	−0.02	0.001	0.01
IX′	−0.35	−0.30	−0.29	0.10	0.10	0.16	−0.34	−0.29	−0.28	0.10	0.10	0.15	−0.26	−0.22	−0.21	−0.03	−0.03	0.01
X	−0.44	−0.42	−0.30	0.14	0.26	0.27	−0.45	−0.42	−0.30	0.14	0.24	0.25	−0.31	−0.30	−0.21	−0.01	0.09	0.10
X′	−0.46	−0.35	−0.29	0.05	0.14	0.27	−0.49	−0.33	−0.33	0.15	0.15	0.24	−0.34	−0.25	−0.25	0.007	0.007	0.09
$^{(-)}OPO(OMe)_2$	−0.23	−0.20	−0.19	0.42	0.44	0.45	−0.25	−0.23	−0.21	0.38	0.41	0.42	−0.08	−0.06	−0.05	0.24	0.26	0.27
$HOPO(OMe)_2$	−0.47	−0.43	−0.43	0.21	0.25	0.26	−0.49	−0.44	−0.44	0.19	0.23	0.24	−0.32	−0.28	−0.27	0.03	0.07	0.08
$Li^{(+)}$	–	–	−2.77	−0.19	−0.13	−0.13	–	–	−2.79	−0.20	−0.12	−0.12	–	–	−2.35	−0.225	−0.17	−0.17
LiH	–	−2.43	−0.30	0.002	0.05	0.05	–	−2.45	−0.30	0.007	0.06	0.06	–	−2.01	−0.19	−0.05	0.00	0.00
$H_3C^{(+)}$	−1.25	−0.96	−0.96	−0.29	−0.001	0.05	−1.28	−0.95	−0.95	−0.28	−0.02	0.04	−1.06	−0.79	−0.79	−0.49	−0.17	−0.12
H_4C	−0.55	−0.55	−0.55	0.29	0.35	0.35	−0.55	−0.55	−0.55	0.26	0.33	0.33	−0.39	−0.39	−0.39	0.12	0.18	0.18

Table 2
Computed total energy values for selected compounds

Compound	Total energy (hartree)		
	HF/3-21G	HF/6-31G(d)[a]	B3LYP/6-31G(d)[a]
I	−1115.3057533	−1121.5267060	−1128.3745675
I′	−1114.1306427	−1120.3512617	−1127.1622109
VII	−702.2691104	−706.2079365	−710.8079979
VII′	−701.0625448	−705.0305158	−709.5928735
VIII	−685.9735651	−689.8228158	−694.3792180
VIII′	−684.8069456	−688.6566712	−693.1735825
IX	−534.1767550	−537.1706076	−540.7362622
IX′	−533.0157243	−536.0095904	−539.5346613
X	−230.5432311	−231.8316006	−233.4168030
X′	−229.4194455	−230.6243802	−232.1964519
$^{(-)}$O–PO(OMe)$_2$	−715.6159542	−719.5025760	−722.1902158
HO–PO(OMe)$_2$	−716.1858643	−720.0515089	−722.7333588
Li$^{(+)}$	−7.1870942	−7.2355361	−7.2845444
LiH	−7.9298426	−7.9808664	−8.0818830
$H_3C^{(+)}$	−39.0091261	−39.2306340	−39.4797803
H_4C	−39.9768768	−40.1951671	−40.5181113
H_2	−1.1229598	−1.1268096	−1.1754427

[a] Single point calculations at the geometry optimized at the HF/3-21G level of theory.

Table 3
Energy (ΔE) and relative energy ($\Delta\Delta E$) of aromatization via dehydrogenation of compounds **I**, **VII** and **VIII**

Level of theory	Process	ΔE (kcal/mole)	$\Delta\Delta E$ (kcal/mole)
HF/3-21G	**VII** → **VII′** + H_2	33.638	9.748
	I → **I′** + $\mathbf{H_2}$	32.725	8.835
	VIII → **VIII′** + H_2	27.397	3.507
	IX → **IX′** + H_2	23.890	0.000
	X → **X′** + H_2	0.518	−23.372
HF/6-31G(d)	**VII** → **VII′** + H_2	31.759	10.293
	I → **I′** + $\mathbf{H_2}$	30.519	9.053
	VIII → **VIII′** + H_2	24.683	3.217
	IX → **IX′** + H_2	21.466	0.000
	X → **X′** + H_2	50.459	28.993
B3LYP/6-31G(d)	**VII** → **VII′** + H_2	24.900	8.485
	I → **I′** + $\mathbf{H_2}$	23.164	6.749
	VIII → **VIII′** + H_2	18.946	2.531
	IX → **IX′** + H_2	16.415	0.000
	X → **X′** + H_2	28.180	11.765

Table 4
Dihedral angles computed at the HF/3-21G level of thoery indicating the extend of rotations about the CH_2–CH_2 bond of selected dihydro aromatic compounds

Compound	Dihedral angle	Degrees	Dihedral angle	Degrees
I	C^{13}–C^{14}–C^9–N^8	− 24.155	C^{13}–C^{12}–C^{11}–N^8	− 58.990
VII	C^{13}–C^{14}–C^9–N^8	− 24.755	C^{13}–C^{12}–C^{11}–N^8	− 59.315
VIII	C^{13}–C^{14}–C^9–C^8	− 24.215	C^{13}–C^{12}–C^{11}–C^8	–58.603
IX	C^3–C^{12}–C^{11}–C^6	− 23.203	C^3–C^4–C^5–C^6	− 56.887
X	C^2–C^3–C^4–C^5	− 15.246	C^2–C^1–C^6–C^5	− 44.180

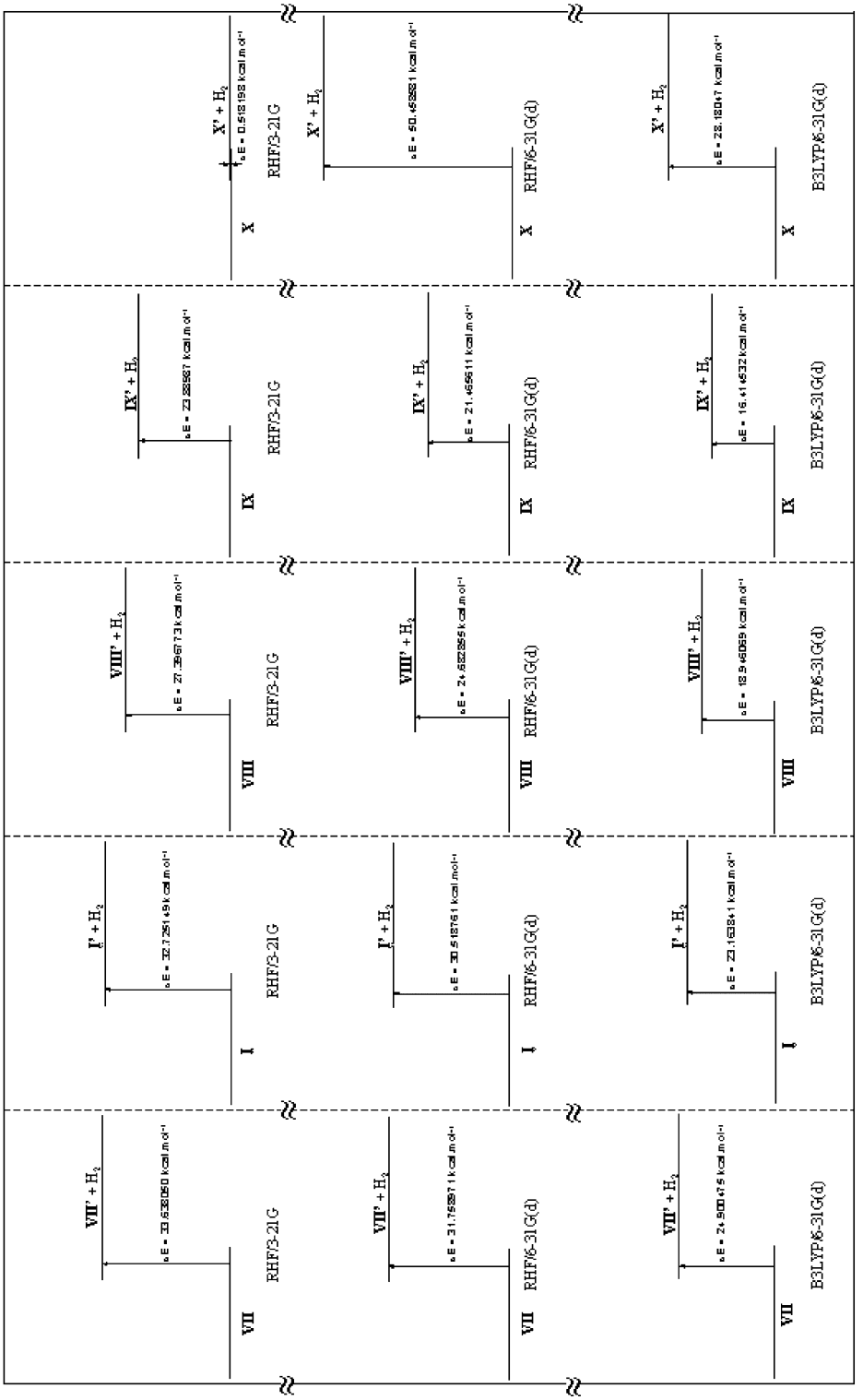


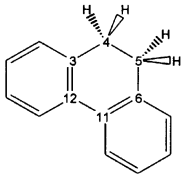
Fig. 4. Covalents aromatizations energies of five selected compounds (**I**, **VII**, **VIII**, **IX** and**X**).

process, the stronger aromatic character has evolved. In view of that, it is prudent to include the formation of phenantrene (**IX**) and benzene (**X**) into the realms of consideration. The following sequence of reactions was considered.

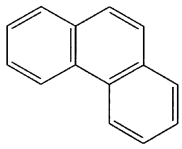
$$\mathrm{I} \rightarrow \mathrm{I}' + \mathrm{H_2} \quad (8a)$$

$$\mathrm{VII} \rightarrow \mathrm{VII}' + \mathrm{H_2} \quad (8b)$$

$$\mathrm{VIII} \rightarrow \mathrm{VIII}' + \mathrm{H_2} \quad (8c)$$

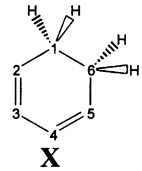


IX



IX'

$+ \mathrm{H_2}$ (8d)



X

X'

$+ \mathrm{H_2}$ (8e)

The energy values (ΔE) associated with the above aromatization processes (8a)–(8e) are listed in Table 3. The relative energy values ($\Delta\Delta E$) are expected to measure the extent of aromaticity with respect to phenantrene. The thermodynamic separations of the final and initial states are also shown in Fig. 4.

The results of dehydrogenation energies, presented in Table 3 and Fig. 4, clearly indicate that while dihydrophenantrene (**IX**) behaves analogously to **I**, **VII** and **VIII** but cyclohexadiene (**X**) behaves in anomalously. This may look disturbing, at least initially, because benzene is the quintessential prototype of aromatic compounds. It became obvious very quickly that a variation in the dihedral angle of the –C=C–C=C– moiety is

Table 5
Energy (ΔE) and relative eneregy ($\Delta\Delta E$) of aromatization of compounds **I**, **VII**, **VIII**, **IX** and **X** as well as their ionization energy ($-\epsilon_{\mathrm{HOMO}}$)

Level of theory	Process	Aromatization energy (kcal/mole)				$-\epsilon_{\mathrm{HOMO}}$ (hartree) of non aromatic compound
		Hydride acceptor: $Li^{(+)}$		Hydride acceptor: $H_3C^{(+)}$		
		ΔE	$\Delta\Delta E$	ΔE	$\Delta\Delta E$	
HF/3-21G	**I** → **I′**	−86.31	8.84	−227.50	8.84	0.40
	VII → **VII′**	−85.37	9.78	−226.56	9.78	0.43
	VIII → **VIII′**	−91.64	3.51	−232.83	3.51	0.28
	IX → **IX′**	−95.15	0.00	−236.34	0.00	0.28
	X → **X′**	−118.52	−23.37	−259.71	−23.37	0.30
HF/6-31G(d)[a]	**I** → **I′**	−74.56	9.05	−212.11	9.06	0.39
	VII → **VII′**	−73.32	10.29	−210.87	10.30	0.42
	VIII → **VIII′**	−80.39	3.22	−217.95	3.22	0.27
	IX → **IX′**	−83.61	0.00	−221.17	0.00	0.28
	X → **X′**	−54.62	28.99	−192.18	28.99	0.30
B3LYP/6-31G(d)[a]	**I** → **I′**	−80.40	6.75	−231.62	6.75	0.31
	VII → **VII′**	−78.77	8.48	−229.89	8.48	0.63
	VIII → **VIII′**	−84.62	2.53	−235.84	2.53	0.21
	IX → **IX′**	−87.15	0.00	−238.37	0.00	0.21
	X → **X′**	−75.38	11.77	−226.60	11.77	0.21

[a] Single point calculations using the geometry optimized at the HF/3-21G level of theory.

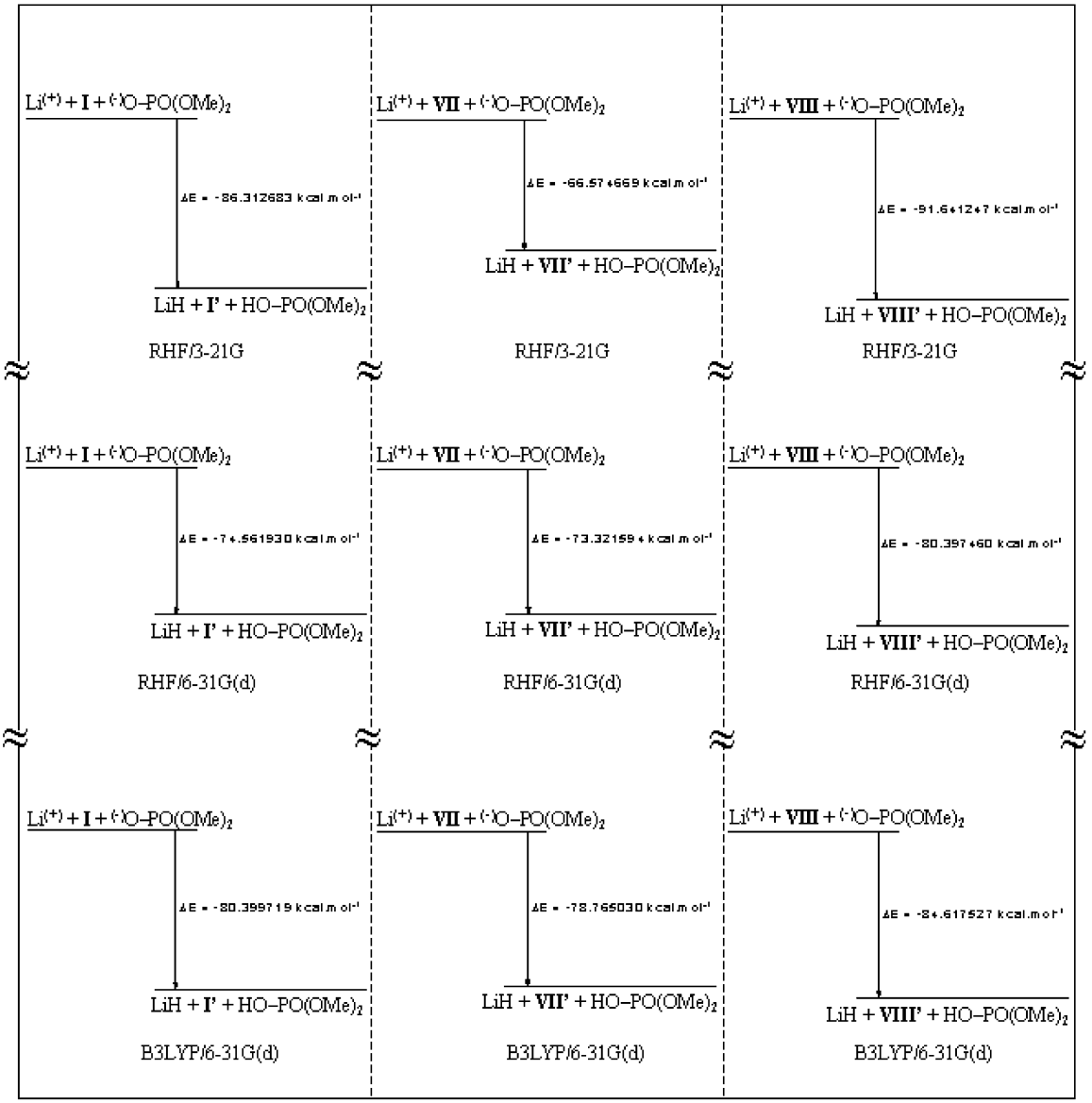


Fig. 5. Ionic aromatizations energies of three selected compounds (**I**, **VII** and**VIII**) using $Li^{(+)}$ as the hydride acceptor.

responsible for the unexpected behavior. In compound **I**, **VII**, **VIII**, and **IX** the torsional angle is predetermined by the biphenyl unit which contains the $-CH_2-CH_2-$ bridge. Thus, the equivalent dihedral angle in **X** is markedly different as shown in Table 4. Consequently, it is prudent to choose dihydrophenantrene (**IX**) as the standard comparison rather than cyclohexadiene (**X**). It should be pointed out that, at least these levels of theory, all aromatization process, via dehydrogenation yielded positive energy values. For the formation of benzene the range was 0.5–51 kcal/mole

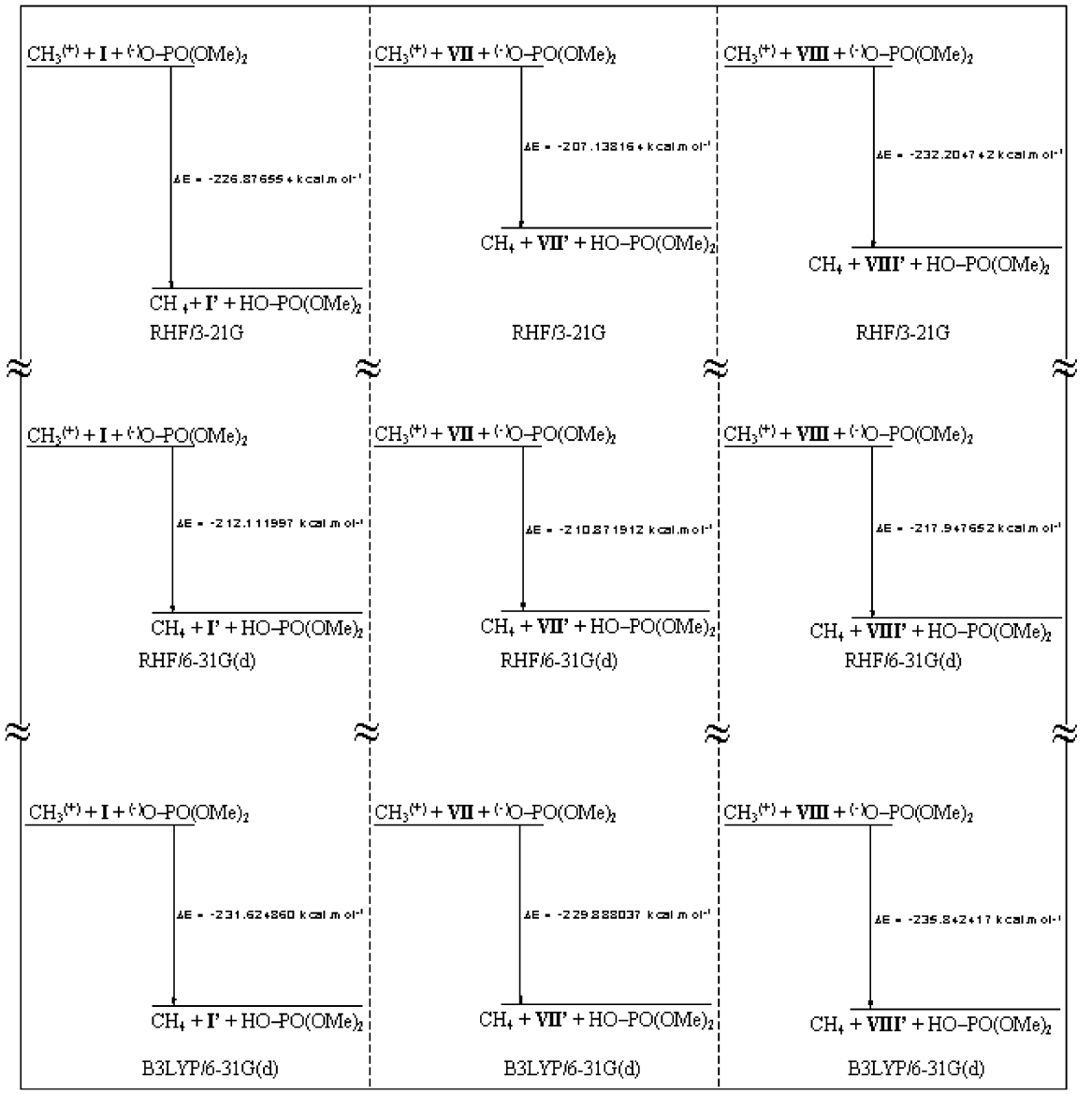
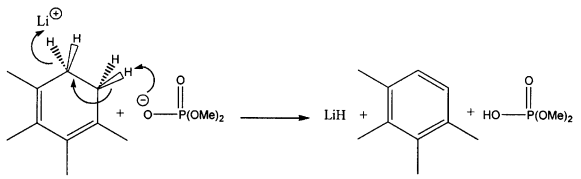


Fig. 6. Ionic aromatizations energies of three selected compounds (**I**, **VII** and**VIII**) using $CH_3^{(+)}$ as the hydride acceptor.

while for the other compounds the values fell within 16–32 kcal/mole.

In contrast to the above results the putative reaction mechanism suggest an ionic aromatization. Such process is illustrated in general way in (Eqs. (9a) and (9b)) for phenantrene (**IX**) and benzene (**X**) using a weak ($Li^{(+)}$) and a strong ($H_3C^{(+)}$) hydride abstractor and, of course, the model phosphate ion as the proton acceptor.



(9a)

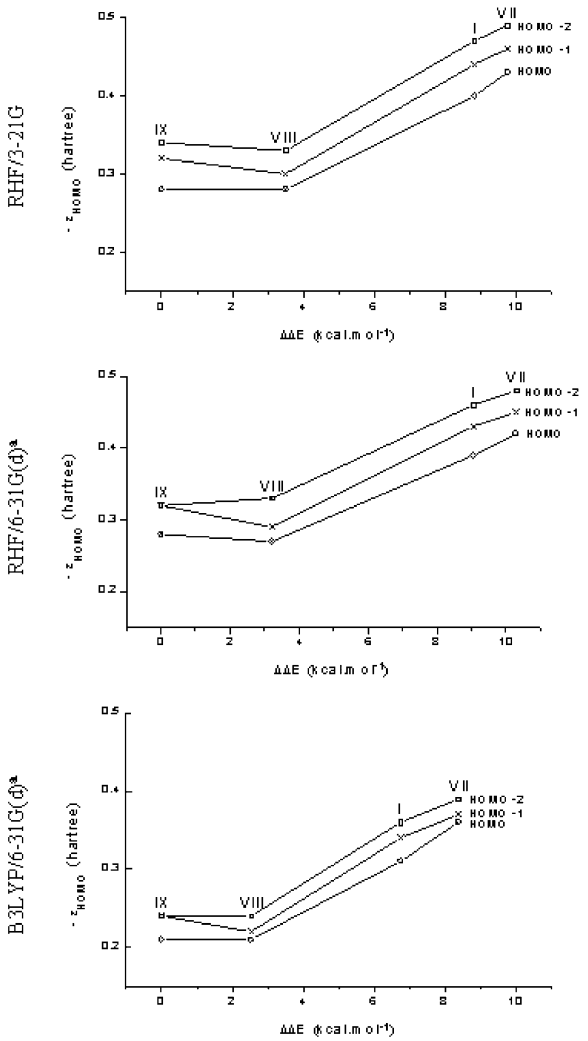
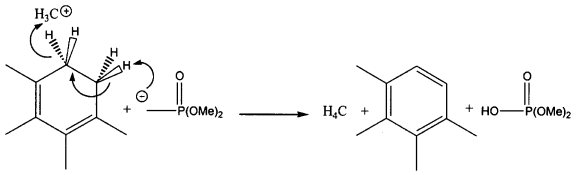


Fig. 7. Correlations of ionizations energies (in terms of $-\epsilon_{HOMO}$) of selected dihydroaromatic compounds (**I**, **VII**, **VIII** and **IX**) and the relatives dehydrogenetion energy ($\Delta\Delta E$) measuring aromatic character of the products formed (**I**′, **VII**′, **VIII**′ and **IX**′) relative to phenantrene (**IX**′).



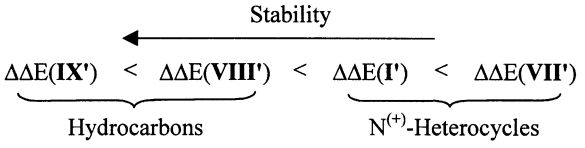
(9b)

The energy values for such ionic aromatizations as shown in Eqs. (9a) and (9b) as well as in Scheme 2 were calculated for **I**, **VII**, **VIII**, **IX** and **X** at three levels of theory. The numerical values are summarized in Table 5. Illustrative examples are also shown in Figs. 5 and 6.

As expected the $\Delta\Delta E$ values given in Tables 3 and 5, Fig. 7 are practically identical as they measure the extent of aromaticity of the products. However the energy change (ΔE) associated with aromatization process does depend on whether the reaction was carried out under covalent or ionic condition. In the ionic reactions, such as Eqs. (9a) and (9b) and Scheme 2, the reaction starts with an ion pair and finishes with neutral species. Consequently, the energy of

neutralization is part of the ΔE values observed. Thus, the values are relatively large negative numbers indicating great exothermicity.

The results, summarized in Tables 3 and 5, suggest the following extent of aromatic character for the four polycyclic compound (**I**, **VII**, **VIII** and **IX**) studied:



(10)

Clearly, a quaternary nitrogen in the ring makes the polycyclic compounds less aromatic than the fully carbon containing rings. This would suggest that $N^{(+)}$ heterocycles are more reactive with their π-system than the polyaromatic hydrocarbons. In particular, for nucleophilic addition, the LUMO energy of the aromatic compounds may be illustrative. In fact the LUMO energy of the $N^{(+)}$ heterocycle are all negative while they are all positive to the hydrocarbons aromatics.

$$\epsilon_{\mathrm{LUMO}}(\mathbf{I}' \text{ or } \mathbf{VII}') < 0 < \epsilon_{\mathrm{LUMO}}(\mathbf{VIII} \text{ or } \mathbf{IX}') \qquad (11)$$

One more point has to be made in comparing $\mathbf{I}'$ and $\mathbf{VII}'$. The $\Delta\Delta E$ values computed for $\mathbf{I}'$ at any level of theory is always less, by a small but noticeable magnitude (0.94–1.73), than that of compound $\mathbf{VII}'$. Clearly the heteroatom substitution on the ring acts as relatively small perturbation on the effect the quaternary nitrogen made when it was introduced in the aromatic ring.

In relating ionization energy, within Koopmann's theorems, with the aromatizations energy, the negative of the orbital energies were plotted against the $\Delta\Delta E$ values. While $\Delta\Delta E$ increased about 3 kcal/mole on going from **IX** to **VIII** however $-\epsilon$ hardly varied. However, $-\epsilon$ has monotonically increased on going from **VIII** to **I** and then to **VII** together with an increase in $\Delta\Delta E$. Although the relationship cannot be expected to be linear nevertheless a nearly linear trend is clearly seen. This would suggest that in the aromatization process the ease of hydride ion removal parallels the stabilization energy of the aromatic compound to be formed.

Acknowledgements

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