

*Dedicated to the memory of
Professor Ecaterina Ciorănescu-Nenitzescu (1909–2000)*

IN SILICO STUDY OF HYDROXYL RADICAL REACTION WITH 1,2-DIMETHYL-1,2,3,4-TETRAHYDROISOQUINOLINES

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The OH· radical scavenging activity of four 1,2-dimethyl-1,2,3,4-tetrahydroisoquinolines was investigated by quantum mechanics methods. Geometry optimization of reactants and products, and transition state search revealed small differences in the activation energy, reaction enthalpy and reactivity indices (spin density, HOMO orbital localization and energy level) but all these parameters indicate the (R)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline equatorial conformer as the most susceptible to react with the OH· radical.

INTRODUCTION

Plant alkaloids are well known pharmacological active molecules; half of new potential drugs in clinical trials have vegetal origin.¹ In recent years many studies have been performed by leading international research teams to elucidate the biological action mechanisms of bis-benzylisoquinoline alkaloids, cyclophane type compounds, known as: calcium channel blockers and antioxidants.^{2,3} These compounds are extracted from the roots of the herb *Stephania tetrandrae* S. Moore and used in the traditional Chinese medicine for the treatment of hypertension and silicosis.⁴

Our previous theoretical and experimental studies refer to tetrandrine and derivate alkaloids: fangchinoline and berbamine.⁵⁻⁷

The antioxidant property of tetrandrine is related to its scavenger activity of hydroxyl radicals. Experimental evidence of the antioxidant activity of the related alkaloid cepharanthine shows differences of reactivity toward the OH radical at the two chiral centers of the molecule.⁸

In the present theoretical work this property was investigated using (R,S)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline as model, tetrahy-

droisoquinoline being structural unit of the benzylisoquinoline alkaloids but also of the more complex compounds, the bis-benzylisoquinoline (BBIQ) alkaloids. All four possible geometries, R-eq, R-ax, S-eq and S-ax (ax and eq denote axial and equatorial N-methyl) were analyzed. The R-eq conformer is shown in Figure 1.

COMPUTATIONAL DETAILS

The structures of the 1,2-dimethyl-1,2,3,4-tetrahydroisoquinolines were built using the HyperChem Release 6.01 program and the geometries were optimized by the semiempirical AM1 method (EF optimization algorithm with RMS gradient of 0.01 kcal/mol·Å). The model structures of the reactants and products were built by manual docking.

The MO quantum chemical methods permit the facile identification of reactants and products molecular geometries, but determining the transition state often remains a difficult problem.⁹⁻¹⁴

The proposed reaction is the subtraction of H atom from the C(1) by the OH· radical (Figure 2).

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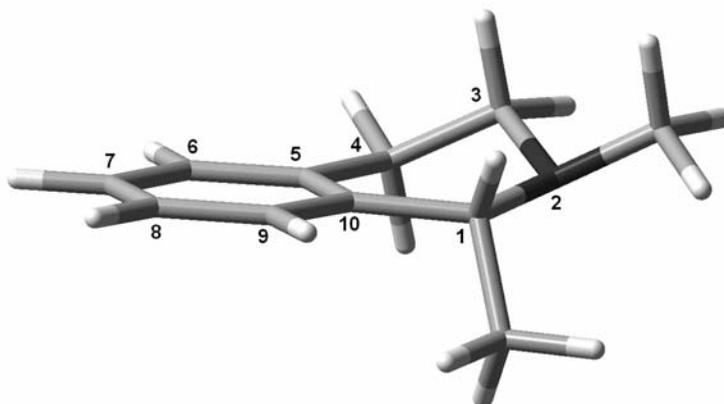


Fig. 1 – Structure of (R)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (R-eq).

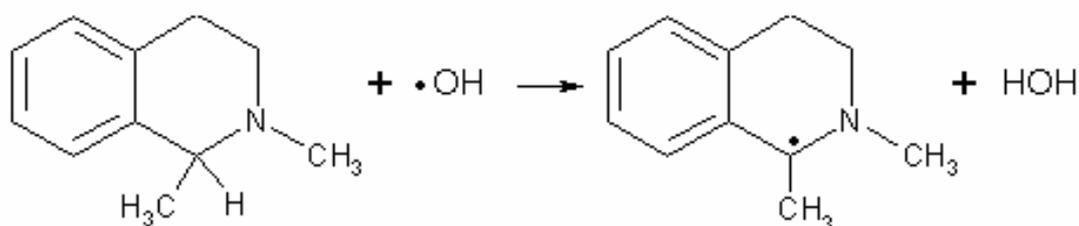


Fig. 2 – Reaction of 1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline with hydroxyl radical.

To determine the transition state the CHN procedure implemented in the AMPAC software package was used. The first step consisted in the geometry optimization of reactants and products systems using: TRUST algorithm, AM1 Hamiltonian, UHF approximation. Finally the transition state was refined using TS or TRUSTG procedures, associated with LFORCE or HESSEI which compute all negative and the first positive IR frequencies, respectively a few of the lowest Hessian eigenvalues, in order to characterize a potential saddle point.

Aside from this local criterion, it is also necessary to identify the minima connected through the transition state. This latter part was performed by the intrinsic reaction coordinate method (IRC), for computing minimum energy reaction pathway (MERP) in mass-weighted cartesian coordinates between the transition state

and its reactants and products. It can be thought of as the path that the molecule takes moving down the product and reactant valleys with zero kinetic energy.^{15,16}

RESULTS AND DISCUSSION

Since reactions involving neutral radicals are frontier orbital controlled processes and solvation energy effects are unimportant,¹⁷ the structures of the 1,2-dimethyl-1,2,3,4-tetrahydroisoquinolines were optimized by the semiempirical AM1 method in gas phase. The calculated heats of formation and highest occupied molecular orbital energy levels (ϵ_{HOMO}) for the four conformers are given in the Table 1.

Table 1

Heats of formation for the four conformers and highest occupied molecular orbital energy levels

Conformer	ΔH_f (kcal/mol)	ϵ_{HOMO} (eV)
R-eq	22.05	-8.989
R-ax	20.80	-9.198
S-eq	20.84	-9.054
S-ax	19.75	-9.192

The differences between heats of formation of the conformers are only of 0.4-2.30 kcal/mol, due to the position of the N-methyl. The R-eq conformer has the highest energy and a slightly different geometry of twisted half-chair with N2 atom nearly coplanar and C3 above the plane,

compared to the other conformers, where nitrogen is outside the plane (Figure 3). This particularity is probably originated in the repulsion caused by the position of the nitrogen lone pair toward methyl group.

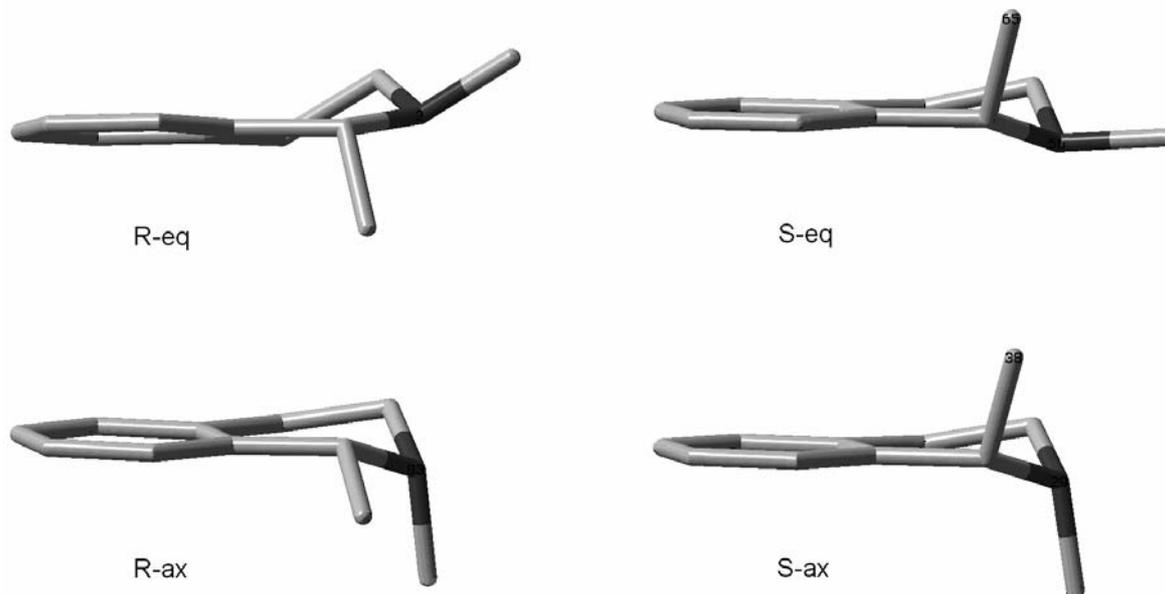


Fig. 3 – Twisted-half chair conformations of the tetrahydroisoquinolines.

The plots of HOMO show similar localizations on the saturated cycle, in principal on C1 and N2 atoms (Figure 4).

From Table 1 one may observe that the R-eq conformer has the highest value of ϵ_{HOMO} *i.e.* the highest electrodonor ability and therefore an increased antioxidant property in this series. It was

found that this antioxidant property is lost in the acidic medium.⁸ At the protonated species the HOMO orbital has a different distribution being localized on the aromatic cycle and is more lower energetically (*e.g.* $\epsilon_{\text{HOMO}} = -12.92$ eV for the R-eq conformer) proving a decrease of the antioxidant activity.

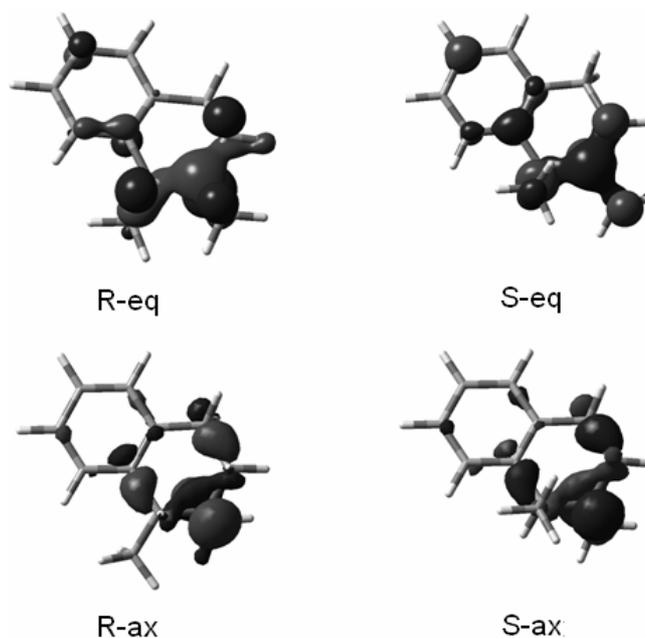


Fig. 4 – HOMO orbitals of R-eq, R-ax, S-eq and S-ax conformers.

In the analysis of the chemical reaction course three points of the potential energy 3N-6 dimensional hypersurface have a special importance: the minima corresponding to the reactants and products and the saddle point corresponding to the transition state.

The transition states for the hydrogen abstraction reactions (Fig. 2) as a proof of antioxidant property of (R,S)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolines

were determined by CHN and TS/TRUSTG procedures.

The geometries of the transition states for the four reactions are very similar. In the Figure 5 is shown the transition state of the R-eq reaction with the •OH radical and the characteristic geometrical parameters for all transition states are given in the Table 2.

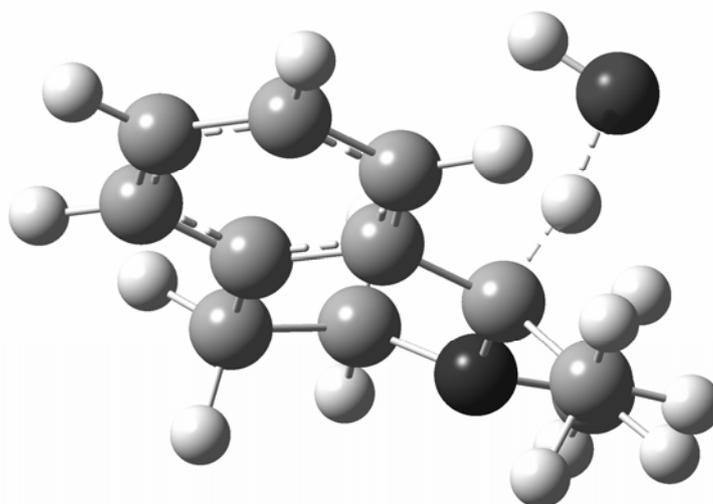


Fig. 5 – The transition state geometry of the hydrogen subtraction from R-eq.

Table 2

The geometrical parameters for the transition states				
Parameter	R-eq	R-ax	S-eq	S-ax
C1--H1 (Å)	1.21	1.22	1.22	1.21
H1···O (Å)	1.51	1.46	1.46	1.44
H···O-H (°)	101.4	102.8	102.0	102.1

The spin density of the atoms involved in the reaction is given in table 3. One may observe that the spin distribution is the normal one. As it is expected, for reactants and products the odd electron is localized on the hydroxyl radical and respectively on the C1 atom of the substrate conjugated with the aromatic nucleus, whilst for the transition state this electron is shared by the O and C1 atoms.

The values of the activation energy and the reaction enthalpy have been calculated both from the data obtained with CHN and IRC procedures (Table 4).

The two procedures give similar results which mean that the first step in the CHN procedure, the reactants and products optimization was efficient.

The obtained values of activation energy are small, normal for hydrogen abstraction radical reactions in agreement with literature values of

2-10 kcal/mol, obtained for simple compounds like: metan derivatives, propanol, formaldehyde derivatives, small organic acids.¹⁹⁻²⁵ The hydrogen abstraction reaction by hydroxyl radicals is thermodynamically controlled one due to relative stability of the radical product. This explains the order allyl ~ benzyl > tert > sec > pri > allyl ~ vinyl for C-H bond reactivity.²² The benzyl type radical produced by hydrogen abstraction from 1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline is supplementary stabilized by the proximity of the nitrogen atom.

The R-eq conformer has the lowest activation energy. This theoretical result is an argument which supports the experimental results described in the work of Kogure *et al.* concerning the reactivity of the R center of the cepharanthine alkaloid.⁸

Table 3
Spin density

Conformer	Atom	Spin density		
		Reactants	Transition states	Products
R-eq	C1	0.0312	0.2990	0.7464
	H1	-0.0125	-0.1257	-0.005
	O	1.0200	0.7895	0.0014
	H(O)	-0.0312	-0.0244	-0.0001
R-ax	C1	0.342	0.3450	0.8148
	H1	-0.0159	-0.1384	-0.0005
	O	0.9295	0.7945	0.0012
	H(O)	-0.0313	-0.0250	-0.0001
S-eq	C1	-0.0097	0.3468	0.7681
	H1	0.00012	-0.1339	-0.0003
	O	1.0239	0.7887	0.0007
	H(O)	-0.0313	-0.0246	0
S-ax	C1	0.0357	0.3689	0.7960
	H1	-0.0128	-0.1347	-0.0002
	O	1.0232	0.7869	0.0006
	H(O)	-0.0313	-0.0246	0

Table 4

The activation energies and the reaction enthalpies for the hydrogen abstraction reactions

Conformer	CHN procedure		IRC procedure	
	E _a (kcal/mol)	ΔH (kcal/mol)	E _a (kcal/mol)	ΔH (kcal/mol)
Req	6.7	-52.11	6.83	-51.24
Rax	6.9	-51.54	8.3	-49.93
Seq	8.92	-50.43	8.72	-49.68
Sax	9.43	-49.45	9.26	-49.49

CONCLUSIONS

The antioxidant properties of the bis-benzylisoquinoline alkaloids were related to their scavenger activity of reactive oxygen species, especially of derivated radicals. Thus, experimental evidence of cepharanthine antioxidant activity showed differences of reactivity toward the ·OH radicals at the two chiral centers of the molecule.

Our theoretical work used the (R,S)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline as structure model of the bis-benzylisoquinoline alkaloids for the explanation of these reactivity differences.

Geometry optimization of reactants and products, and transition state search revealed small differences in activation energy, reaction enthalpy, geometry and reactivity indices. Taking into

account the variation of all these parameters, the equatorial R conformer appears as the most susceptible to react with the ·OH radical. This result supports the experimental finding of Kogure *et al.*, on the antioxidant activity of the R chiral center of the more complex bis-benzylisoquinoline alkaloid, cepharanthine.

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