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Dihydropyridine Isomerism in the Chemical Delivery System Series

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A theoretical study was performed for three structural isomers of the dihydropyridine-targetor based chemical delivery systems of estradiol and azidothymine. The relative thermodynamic stabilities reflected by the calculated heats of formation (ΔH_f) indicated, in good agreement with available experimental evidence, preferential formation of the 1,4-dihydropyridine isomers as a result of thermodynamic product control. The increased relative stability of the 1,4-isomers, as compared to the 1,2-and 1,6-dihydropyridine, is explained by favorable electronic interactions (hyperconjugation, homoaromaticity) existent in these derivatives.

INTRODUCTION

Dihydropyridine – pyridinium salt redox targetor (carrier)-based chemical delivery systems (CDS) have been extensively investigated because of their potential use in the therapy of central nervous systemic diseases.[1–3] Indeed, covalently attached dihydropyridine molecules provide for specific transport of various drug molecules across the blood brain barrier and into the central nervous system.[4,5] Since improved therapeutic indices can be expected from this approach, the CDS method might have numerous applications in medicinal chemistry.

A practical means of the synthesis of the CDS is the dithionite reduction of their synthetic precursors, the corresponding quaternary pyridinium salts.[6,7] This method preferentially results in the 1,4-dihydropyridine isomer, accompanied by small amounts of 1,2-and 1,6-derivatives of the other two possible structural isomers. The selectivity of

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this reaction is important since the 1,4-isomers of the dihydropyridines have been shown to be suitable, safe, non-toxic drug targetors.

Although the subject of numerous studies, the mechanism and selectivity of the dithionite reduction are not completely or unambiguously understood. The stability of particular isomers, such as the 1,4-dihydropyridines, in the mentioned examples, is also of interest. Recent theoretical investigations of simple model molecules have been used to analyze the nature of product control (kinetic *vs.* thermodynamic) of the dithionite reduction[8] and the stability of the dihydropyridine isomers.[9]

The study of the isomerism of the 1,4-dihydro-1-methyl-3-pyridine carboxylates of estradiol (estradiol-CDS) and azidothymidine (AZT-CDS) (Figure 1), two thoroughly examined chemical delivery systems,[10,11] is reported here.

The AM1, MNDO and PM3 molecular orbital approximations have been used for this theoretical study, based on their well-documented ability to accurately predict heats of formation and geometries.

METHODS

Theoretical studies were performed using the AM1,[12] MNDO[13] and PM3[14] molecular orbital methods included in the MOPAC (version 5.10) package. A Tektronix Computer Aided Chemistry (CaChe™) Worksystem, run on an Apple Macintosh™ II computer, was used for all computations. The structural input was generated using a Macintosh interface and all starting geometries were found by using molecular modeling (MM2) to optimize the geometries. The Broyden-Flecher-Goldfarb-Shanno method[15–18] was used to optimize the geometries as a function of the total molecular energy. All geometries variables were optimized. The dynamic »level shift« method[19] was used to improve the convergence of the self-consistent field (SCF). The »precise« option was implemented to tighten the convergence criteria for all optimizations. The closed-and open-shell species were investigated using the restricted Hartree-Fock (RHF) approach.

RESULTS AND DISCUSSION

The mechanism of the dithionite reduction has been subject of numerous studies. It is now generally accepted that the formation of sulfinic acid adducts occurs and that they represent key intermediates in the reaction; the adducts are then transformed to dihydropyridines, either by direct decomposition[20,21] or through a heterolytic dissociation to the pyridinium salts and sulfoxilate ions, the active reducing agents.[22] A step by step analysis of the relative thermodynamic stabilities for the 1,2-, 1,4-and 1,6-isomers of the intermediates and products of the reduction of some simple pyridinium salts[8] suggested that the preferential formation of the 1,4-isomers is ruled by thermodynamic rather than kinetic factors. Further studies performed for the same model molecules[9] indicated that several factors, including the geometries and favorable electronic interactions, contribute to higher stability of the 1,4-dihydropyridine isomers.

The study of the isomerism to the CDS of the estradiol and azidothymidine (Figure 1) is discussed herein. Numbering of the compounds used in computations is indicated in Figure 2.

The relative thermodynamic stability of the three isomers of the estradiol-CDS and AZT-CDS, as reflected by the calculated heats of formation, are presented in Table I. In agreement with experimental results,[1–5] including an indirect statistical method in which the relative stability of the 1,4-and 1,2-methyldihydropyridines was deter-

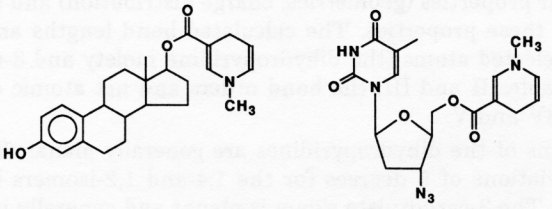
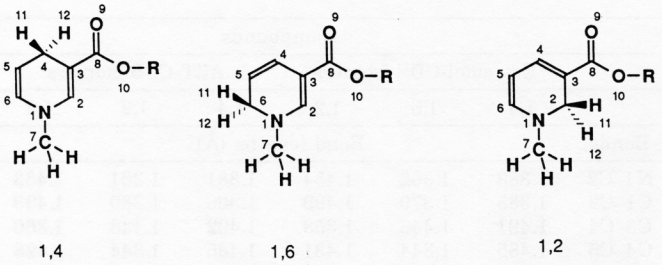


Figure 1. Chemical delivery systems (CDS) of estradiol (left) and azidothymidine (AZT) (right).



1,4 1,6 1,2

Figure 2. Structures of the dihydropyridine isomers and the numbering used in computations. R represents the estradiol and azidothymidine (AZT) moieties.

TABLE I

Calculated heats of formation (Δ_fH) of CDS isomers

Compound/ isomer	$\Delta_f H$(kcal/mol) Method used		
	AM1	MNDO	PM3
Estradiol-CDS			
1,2-isomer	−101.07	−79.01	−102.41
1,4-isomer	−104.49	−81.19	−105.66
1,6-isomer	−103.50	−80.40	−103.48
AZT-CDS			
1,2-isomer	−51.38	−69.81	−80.98
1,4-isomer	−54.59	−72.24	−64.36
1,6-isomer	−53.31	−71.42	−82.16

mined,[23] the 1,4-isomers were found to be more stable than either the 1,2- or 1,6-structural isomers. The order of stability was consistently the same (1,4 > 1,6 > 1,2), regardless of the semiempirical method used. Although differences in the calculated ΔH_f were generally within the error limits of the procedures, due to the structural similarity in the isomer series, the real situation was well reflected.

As reported earlier,[9,24] the differences in the stability of the three isomers could be explained by different electronic interactions that favor the 1,4-derivative. Various

calculated molecular properties (geometries, charge distribution) and the HOMO structure should reflect these properties. The calculated bond lengths and angles and dihedral angles for selected atoms (the dihydropyridine moiety and 3-carboxylic group) are presented in Tables II and III; the bond orders and net atomic charges are summarized in Tables IV and V.

The ring systems of the dihydropyridines are generally planar (Tables II and III) with maximum deviations of 5 degrees for the 1,4-and 1,2-isomers but close to zero for the 1,6-isomers. The 3-carboxylate group is planar and generally in the same plane with the dihydropyridine moieties (with the exception of the 1,4-isomer of AZT-CDS).

TABLE II

Calculated AM1 geometries for CDS isomers

	Compounds					
	Estradiol-CDS isomers			AZT-CDS isomers		
	1,4	1,6	1,2	1,4	1,6	1,2
Bonds	Bond lengths (Å)					
N1–C2	1.383	1.362	1.454	1.381	1.361	1.453
C1–C2	1.385	1.379	1.499	1.366	1.380	1.499
C3–C4	1.491	1.446	1.358	1.492	1.446	1.360
C4–C5	1.485	1.344	1.431	1.485	1.344	1.428
C5–C6	1.349	1.494	1.371	1.349	1.494	1.372
C1–C6	1.405	1.455	1.371	1.406	1.454	1.367
C1–C7	1.435	1.433	1.434	1.436	1.434	1.433
C3–C8	1.458	1.453	1.461	1.455	1.450	1.456
C8–O9	1.235	1.236	1.236	1.235	1.236	1.236
C8–O10	1.376	1.377	1.373	1.381	1.382	1.378
Angle	Bond angles (degrees)					
3–2–1	122.5	132.0	114.5	122.5	122.7	114.2
8–3–2	121.6	122.0	117.0	121.6	122.1	117.2
2–1–6	118.1	121.0	120.7	118.2	121.3	121.1
1–6–5	122.3	114.7	123.2	122.3	114.5	123.1
6–5–4	122.8	122.4	120.9	122.9	122.4	120,7
2–1–7	120.7	122.1	116.3	120.7	121.9	116.5
10–8–3	115.6	115.7	145.4	114.2	114.2	114.1

TABLE III

Calculated (AM1) dihedral angles (degrees)

Angle	Compound					
	Estradiol CDS isomers			ZT CDS isomers		
	1,4	1,6	1,2	1,4	1,6	1,2
8–3–2–1	–177.8	179.8.	–178.6	–4.4	179.7	179.2
10–8–3–2	–1.3	–0.3	1.6	9.1	2.6	0.9
3–2–1–6	4.9	0.7	2.0	–4.4	0.9	–1.0
2–1–6–5	–4.6	–0.8	–4.8	4.0	–1.2	2.4
1–6–5–4	–1.3	0.5	179.6	–1.0	0.8	179.7
6–2–1–7	–164.9	179.1	164.0	–165.3	179.4	–170.9
9–10–8–9	179.5	179.0	179.2	179.9	179.8	179.7

TABLE IV

Calculated (AM1) bond orders

Bond	Compound					
	Estradiol CDS isomers			AZT CDS isomers		
	1,4	1,6	1,2	1,4	1,6	1,2
N1–C2	1.111	1.204	0.925	1.121	1.213	0.924
C2–C3	1.687	1.554	0.981	1.676	1.545	0.981
C3–C4	0.976	1.056	1.709	0.975	1.054	1.691
C4–C5	0.994	1.850	1.125	0.994	1.852	1.137
C5–C6	1.848	0.993	1.631	1.850	0.993	1.613
C6–N1	1.009	0.921	1.158	1.007	0.920	1.171
C1–C7	0.941	0.945	0.949	0.940	0.944	0.947
C3–C8	0.978	0.988	0.975	0.985	0.995	0.983
C8–O9	1.771	1.765	1.763	1.778	1.770	1.768
C8–O10	1.002	0.999	1.015	0.986	0.984	0.999

TABLE V

Calculated (AM1) net atomic charges

Atom	Compound					
	Estradiol CDS isomers			AZT CDS isomers		
	1,4	1,6	1,2	1,4	1,6	1,2
N1	−0.227	−0.268	−0.271	−0.225	−0.285	−0.274
C2	0.068	0.113	0.041	0.074	0.118	0.048
C3	−0.252	−0.276	−0.235	−0.256	−0.278	−0.245
C4	−0.055	−0.044	0.025	−0.055	−0.046	0.037
C5	−0.211	−0.245	−0.311	−0.208	−0.241	−0.318
C6	−0.054	−0.024	0.059	−0.054	0.023	0.071
C7	−0.071	−0.073	−0.074	−0.072	−0.075	−0.071
C8	0.364	0.375	0.358	0.367	0.379	0.362
O9	−0.366	−0.373	−0.371	−0.361	−0.369	−0.368
O10	−0.292	−0.295	−0.279	−0.297	−0.300	−0.286

The carbon atom of the *N*-methyl groups is deviated from the plane of the dihydropyridine in the case of 1,4-and 1,2-isomers by 10–15 degrees while for the 1,6-isomers it is essentially coplanar. The conjugation of the carboxylate groups with the 2,3-double bond is stronger in the case of the 1,6-isomers, as reflected by both the planarity of that part of the molecule and by the decreased C2–C3 double bond character and increased C3–C8 double bond character (Tables II–IV).

The greater homoaromatic contribution in the case of the 1,4-isomers relative to the 1,2-and 1,6-systems could explain the greater stability in the former case. The homoaromaticity of the 1,4-dihydropyridine is due to the contributions of the two double bonds (C2–C3 and C5–C6), and the N1 lone pair as well as the hyperconjugation of the CH_2 group. In the other two isomers, the diene structure represents classical butadiene structures (C3–C4 and C5–C6 double bonds separated by the C4–C5 central bond in the 1,2-structures, respectively, C2–C3 and C4–C5 double bonds separated by C3–C4 in the 1,6-isomers) less stabilized by resonance than the dienamine structure in the 1,4-isomer.

Data generated by the PM3 method (Table I) better reflect this assumption. While calculated heats of formation were rather similar for 1,2-and 1,6-isomers (–1.1 Kcal/mol apart), differences between ΔH_f of the 1,4-isomer and the 1,6-or 1,2-ones were larger (2.2 Kcal/mol and 3.3 Kcal/mol respectively).

The more significant participation of the ring nitrogen lone electron pair to the π-p conjugation in the 1,4-isomers is reflected by a lower net charge density on N1, as compared to the other two isomers (Table V). The charge densities are –0.227 and –0.225 for the 1,4-isomers of the estradiol-CDS and AZT-CDS, respectively, as compared to –0.268 and –0.265 for the 1,6-isomers and –0.271 and 0.274 for the 1,2-isomers. In the same Table, the contribution of the sp^3 C4 to the homoaromaticity of the 1,4-isomers can be noticed: net charges on C4 are –0.055 for the 1,4-isomers as compared to the 0.024 and 0.023 for C6 of the 1,6-isomers and 0.041 and 0.048 for the C2 of the 1,2-isomers. By examination of the LCAO type HOMO's (AM1) for the three isomers, π-type orbital profiles are suggested for all derivatives. The contributions to the HOMO are given below for the estradiol-CDS:

$$\Psi^{1,4}_{HOMO} = 0.402\ N1\ p_z - 0.144\ C2\ p_z - 0.350\ C3\ p_z + 0.134\ C4\ p_z - 0.309\ C5\ p_z - 0.186\ C6\ p_z + 0.223\ H11s - 0.215\ H12s$$

$$\Psi^{1,6}_{HOMO} = 0.307\ N1\ p_z - 0.167\ C2\ p_z - 0.358\ C3\ p_z + 0.163\ C4\ p_z + 0.305\ C5\ p_z - 0.079\ C6\ p_z - 0.202\ H11s - 0.204\ H12s$$

$$\Psi^{1,2}_{HOMO} = 0.329\ N1\ p_z - 0.080\ C2\ p_z + 0.339\ C3\ p_z + 0.114\ C4\ p_z - 0.394\ C5\ p_z - 0.195\ C6\ p_z + 0.209\ H11s - 0.209\ H12s$$

and the AZT-CDS:

$$\Psi^{1,4}_{HOMO} = 0.558\ N1\ p_z + 0.101\ C2\ p_z + 0.356\ C3\ p_z - 0.125\ C4\ p_z + 0.\ 297\ C5\ p_z + 0.190\ C6\ p_z + 0.201\ H11s - 0.205\ H12s$$

$$\Psi^{1,6}_{HOMO} = 0.431\ N1\ p_z + 0.231\ C2\ p_z + 0.503\ C3\ p_z - 0.237\ C4\ p_z - 0.433\ C5\ p_z - 0.114\ C6\ p_z - 0.201\ H11s - 0.205\ H12s$$

$$\Psi^{1,2}_{HOMO} = 0.464\ N1\ p_z + 0.119\ C2\ p_z - 0.446\ C3\ p_z - 0.139\ C4\ p_z + 0.513\ C5\ p_z + 0.254\ C6\ p_z + 0.209\ H11s - 0.209\ H12s$$

Hyperconjugation occurs in each case, but the contribution of the sp^3 carbon atoms and the attached hydrogens is more pronounced in the case of the 1,4-isomers. The more important contribution of the nitrogen electrons to the HOMO of the 1,4-derivatives is also obvious.

In conclusion, the hyperconjugation and homoaromaticity contribute to the higher stability of the 1,4-isomers. There is no significant contribution of the rest of the molecules (estradiol and AZT parts) to these effects. These results are in agreement both with experimental evidence and the calculations performed for simple model compounds.

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SAŽETAK

Dihidroperidinski izomerizam u kemijskom prijenosnom sustavu

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S pomoću molekulske metode AM1 teorijski su proučena tri strukturna izomera dihidropiridina, koji predstavljaju temelj kemijskomu prijenosnom sustavu estradiola i azidotimidina. Relativne termodinamičke stabilnosti izomernih dihidropiridina odražavaju se u njihovim izračunanim toplinama stvaranja (ΔH_f). Teorijski rezultati se slažu s eksperimentalnim pokazateljima koji upućuju na to da, kao rezultat termodinamičke kontrole produkata, pretežito nastaju 1,4-dihidropiridinski izomeri. Veća relativna stabilnost 1,4-izomera u usporedbi s 1,2- i 1,6-dihidropiridinima objašnjava se postojanjem povoljnijih elektronskih interakcija (hiperkonjugacija, homoaromatičnost) u njima.