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Dedicated to the memory of
Professor Ioan Silaghi-Dumitrescu (1950 – 2009)

WALKING ON THE SURFACE OF PHENOTHIAZINES: A COMBINED EXPERIMENTAL AND THEORETICAL APPROACH

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Thermally induced pericyclic rearrangement reactions were studied in the case of 10-allyl-10*H*phenothiazine derivatives prepared by phase transfer catalysis. Theoretical molecular modeling based on DFT calculations performed with the B3LYP functional, indicate that 10-allyl-10*H*phenothiazine derivatives are candidate substrates for [3,3]-sigmatropic rearrangement reactions. According to computed data, aza Claisen rearrangement generates 1-allyl-10*H*phenothiazine under kinetic control and it may be followed by Cope rearrangement responsible for the formation of 3-allyl-10*H*phenothiazine under thermodynamic control.

INTRODUCTION

N-alkyl-phenothiazine derivatives are well known pharmacofores in sedatives, tranqulisers, anti-emetics, parasiticides and other drugs sucessfully employed in current medicinal practice and their preparation methods and properties were thoroughly investigated during the last 50 years[1]. Low oxidation potentials, reversible redox properties and protolytic equilibria make the suitable substituted phenothiazine derivatives, interesting candidates for contemporary materials science investigations (e.g. polymers,[2] sensors,[3] donnor-acceptor assemblies,[4] conducting charge-transfer composites[5]).

Molecular modelling became a powerful mean to predict the structure of a molecule using a set of mathematical and chemical rules. Each of the molecular modelling methods has its strengths and weaknesses and is parameterized and optimized for different types of molecules. A glance at the current literature reveals that most DFT calculations of molecules are performed with the B3LYP functional whose popularity is based on a remarkable success in predicting accurate energies and equilibrium energies.[6]

The aim of this work is the investigation of the reaction mechanism involved in the formation of C-allyl-phenothiazine during thermal treatment of the corresponding N-allyl-phenothiazine derivative. A theoretical explanation emerged by the combination of aza-Claisen and Cope sigmatropic rearrangement reactions, two of the well known and important pericyclic reactions used in synthetic organic chemistry. These [3,3]sigmatropic rearrangements involve pairwise interchanges of the two peripheral Csp^2 with their related allylic atoms and there is not any reported experimentally or theoretically data about the effective role of different parameters on stabilizing the TS geometries in the competitive reactions of allyl group rearrangement ([3,3]-sigmatropic Claisen and Cope rearrangements).[7]

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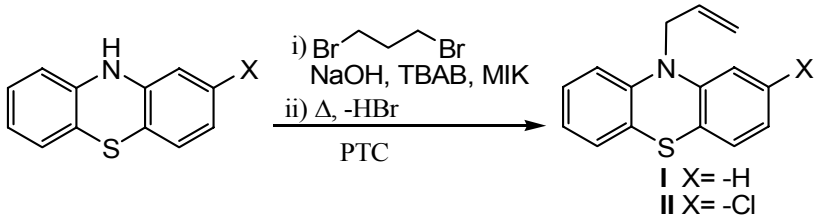
RESULTS AND DISCUSSION

Literature overview indicate the preparation of 10-allyl-phenothiazine derivatives in high yields by direct alkylation of phenothiazine with allyl bromide[8], or in moderate to low yields in the reaction of phenothiazine substrate with 1-bromo-3-chloropropane[8,9], or γ-dimetylaminopropyl chloride[10]. Reduction of 3-(2-chloro-phenothiazin-10-yl)-propionitrile followed by elimination in the intermediate quarternary ammonium hydroxide also afforded 10-allyl-phenothiazine.[11]

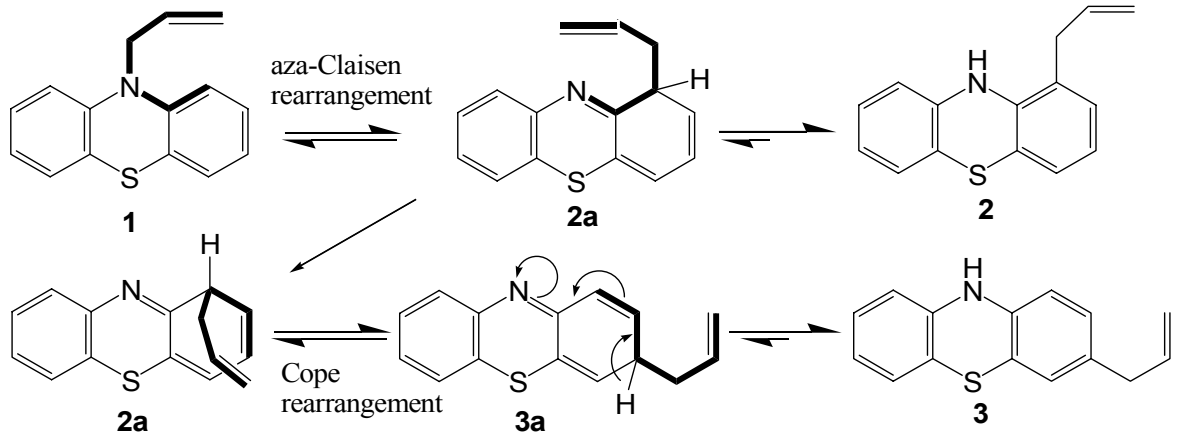
Here we propose a one pot procedure for the preparation of 10-Allyl-10*H*-phenothiazine **I** and 10-allyl-2-chloro-10*H*-phenothiazine **II** respectively, under phase transfer catalysis (PTC) conditions. The procedure involves two consecutive reaction steps: the N-alkylation of phenothiazine substrate with 1,3-dibromopropane at room temperature, followed by dehydrohalogenation of the bromoalkyl chain of the intermediate at 100 ^{o}C under alkaline conditions (NaOH conc.) as presented in scheme 1.



Scheme 1

When **1** was injected into the GC-MS system, the formation of a mixture of two compounds with the same molecular weight ($M^{+\cdot}$=239 a.m.u.) was observed. The 300 MHz ^{1}H-NMR spectrum of the mixture obtained by heating **1** at 230 ^{0}C under Ar in Kugelrohr supports the formation of a mixture of 10-allyl-phenothiazine and 3-allyl-phenothiazine **3**, based on the assignment of key signals due the methylene protons in the allyl system. In the 10-allyl-phenothiazine spectrum the methylene protons appear at 4.50 ppm (m, 2H) deshielded by the heterocyclic nitrogen atom, while the methylene protons in the structure of 3-allyl-phenothiazine appear at 3.39 ppm (m, 2H), deshielded by the anisotropy of the aromatic ring. The ratio of the two regioisomers **1:3** is 1:2, favourable to C-substituted allyl-phenothiazine. The substitution pattern of phenothiazine ring in position 3 was confirmed by ^{1}H-^{1}H homonuclear couplings identified in 1D- and 2D-NMR spectra.

In order to explain the formation of 3-allyl-phenothiazine upon thermal treatment of 10-allyl-phenothiazine, we suggest two successive thermally activated [3,3]sigmatropic rearrangement reactions as shown in Scheme 2. The Aza-Claisen[12] rearrangement of **1** may generate 1-allyl-10*H*-phenothiazine **2** and may be followed by Cope rearrangement[12b,13] of **2** which generates 3-allyl-10*H*-phenothiazine **3**.



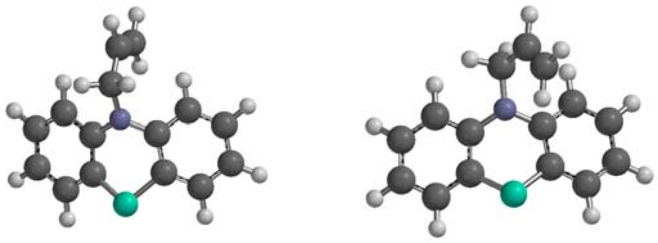
Scheme 2

The proposed mechanism shown in Scheme2 was employed in confronting the experimental data with the computed data.

THEORETICAL METHODS

As general calculation methods, in this study, we used Density functional theory (DFT), which is a way of calculating the electronic structure of many-molecule systems, in order to predict their behaviour and properties. In order to perform all the calculations at a homogeneous computational level that provides quantitative accuracy at a reasonable computational cost, all of the calculations described in this paper have been performed using Becke`s hybrid three parameter functional (B3LYP) and the 6-31G (d) basis level of theory [14]. This level of theory has been proven to yield accurate activation parameters and geometries [15,16].

Geometries of the molecules containing phenothiazine derivatives are influenced by the presence of heteroatoms electron lone pairs, oriented towards the median plane of the molecular π orbital of the benzene rings[17]. When visualizing the 3D design of 10-allyl-10H-phenothiazine substrate **I**, apparently the distance between C_1 and C_γ is shorter in the allyl-*intra* conformation (figure 1a) and we assumed that this conformer, with the allyl chain oriented in a position that favours the conjugation of the lone pair of electrons from the nitrogen with the benzene π systems, was the right one. This presumption was dispelled when the accurate geometries were calculated. Molecular modelling calculations gave two reasons for choosing the allyl-*extra* conformer (figure 1b): first, the molecule tends to expel the allyl group (for steric reasons), towards the median plane of the molecular π orbital of the benzene rings, above the axis that passes through N and S, and second, the barrier energies for transposing the allyl group, were smaller in this case.



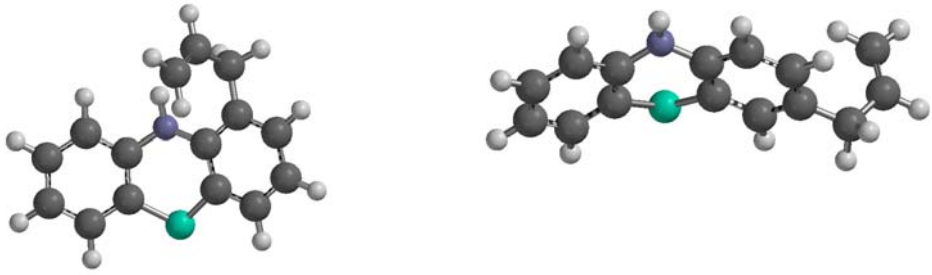
a **b**

Fig. 1 – B3LYP/6-31G optimised conformations of 10-allyl-10*H*-phenothiazine **I**
a) allyl-*intra,* where computed distance between C_1-Cγ is 3.487Å
b) allyl-*extra,* where computed distance between C_1-Cγ is 3.584 Å

The geometry of each species **1-3** was fully optimized using the Gaussian 98 software package with the 6-31G* basis set and the density functional theory (specifically, the Becke3LYP functional) and the nature of the stationary point checked by vibrational analysis [18,19]. All points were characterized as minima or transition structures by calculating the harmonic vibrational frequencies, using analytical second derivatives. Also, the pathway for each reaction was obtained by using the intrinsic reaction coordinate (IRC) with mass-weighted coordinates [20,21].

A reversible aza Claisen rearrangement seems favoured by the almost equal interatomic distances C_1-Cγ=3,487 A in **1** (fig 1a) and N_{10}-Cγ=3,479 A in **2** (fig 2a).

For the investigation of the reaction pathway, it was necessary to calculate the transitions states (TS) energies and the obtained values were related to the most stable conformation of the substrates. The transitions states (TS) energies were computed using the SPARTAN '06 Semi-Empirical Program[22], method: B3LYP and the 6-31G (D) Basis level of theory. The calculations were made with the Estimating Force Constant matrix by central-differences and a restricted hybrid HF-DFT SCF calculation was performed using Pulay DIIS + Geometric Direct Minimization [20].A summary of the energy data is given in Figure 3.



a **b**

Fig. 2 – B3LYP/6-31G optimised conformations of
a) 1-allyl-10*H*-phenothiazine **2** where the computed distance between N-Cγ is 3.479 Å
b) 3-allyl-10*H*-phenothiazine **3** where the computed distance between C_1-Cγ is 4.579 Å.

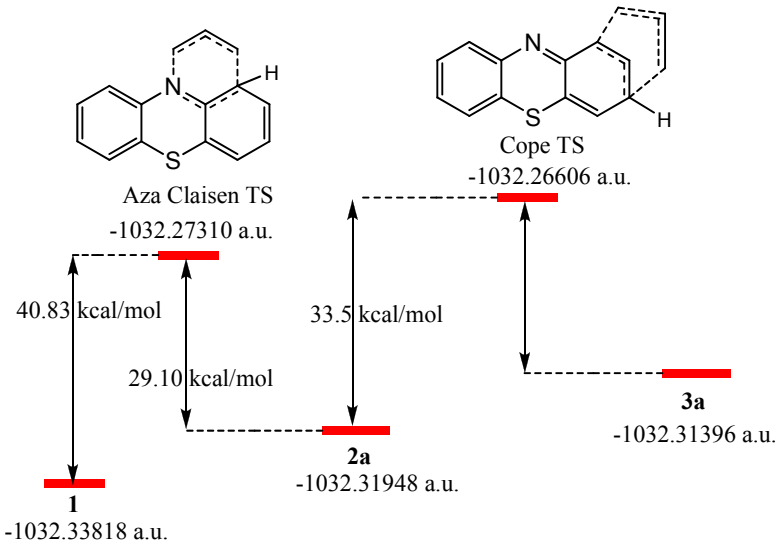


Fig. 3 – Total (a.u.) and relative energies (kcal/mol) for species involved in the pericyclic reactions.

From figure 3 one can see that **1** requires a considerable amount of energy (40.83 kcal/mol) to get to the aza Claisen rearrangement transition state. When 1-allyl-1*H*-phenothiazine **2a** is formed, the energy barrier required for returning the system to **1** diminishes to 29.10 kcal/mol. This decrease in energy barrier is due actually to the higher relative energy (11.7 kcal/mol) of the **2a** intermediate with sp^3 character at C_1. The energy barrier of 33.5 kcal/mol required for Cope rearrangement of **2a** is smaller than the one required for the aza Claisen rearrangement and suggests the possibility of Cope rearrangement TS to occur, in competition with a faster decay of **2a** intermediate back to starting substrate **1**. The significant increase in the relative energy of 3-allyl-3*H*-phenothiazine **3a** suports the expected sp^3 character of C_3 in this intermediate. According to these theoretical data, the system needs more energy for aza Claisen rearrangement than for Cope rearrangement, which is in line with the failure of isolating the **2** regioisomer.

1*H*-phenothiazine **2a** and 3*H*-phenothiazine **3a** are high energy intermediates with quinon-imine structures which are involved in tautomerism leading to more stable 10*H*-phenothiazine tautomers **2** and **3** respectively (scheme 2). After the proton migration to NH group the energy decreases in **3** down to -8.8 kcal/mol relative to **1** as shown in figure 4**.** A summary of the energy data computed with B3LYP/6-31G (d) method is given in figure 4.

According to theoretical data, the aza Claisen rearrangement generates 1-allyl-10*H*phenothiazine **2** through kinetic control (low activation energy), but its isolation is not possible, due to the reversibility of the reaction, while the formation of 3-allyl-10*H*phenothiazine **3** seems to be favored by thermodynamic control.

10-allyl-2-chloro-10*H*phenothiazine **II** prepared according to scheme 1, was also subjected to

thermal treatment and a complex mixture of products was obtained. Scheme 3 presents the allyl-2-chloro-10*H*phenothiazine products obtained by aza Claisen and Cope rearrangement reactions.

The same theoretical procedure was applied to **II** and calculations showed that for the aza Claisen rearrangement of 10-allyl-2-chloro-10*H* phenothiazine **II**, the system requires lower activation energy (35.2 kcal/mol) as compared to unsubstituted substrate **I** (40.83 kcal/mol), which means that the rearrangement reactions may take place even faster. Table 1 contains the total energy values (a.u.) for the structures involved in aza Claisen and Cope rearrangement of **II.**

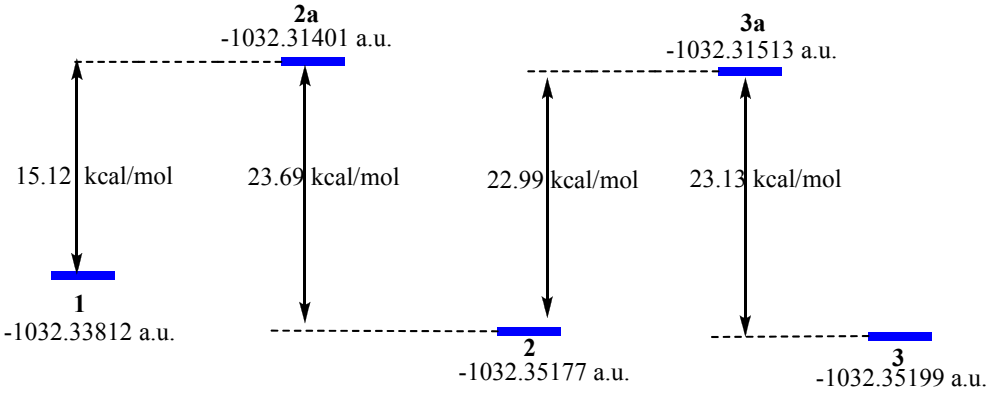
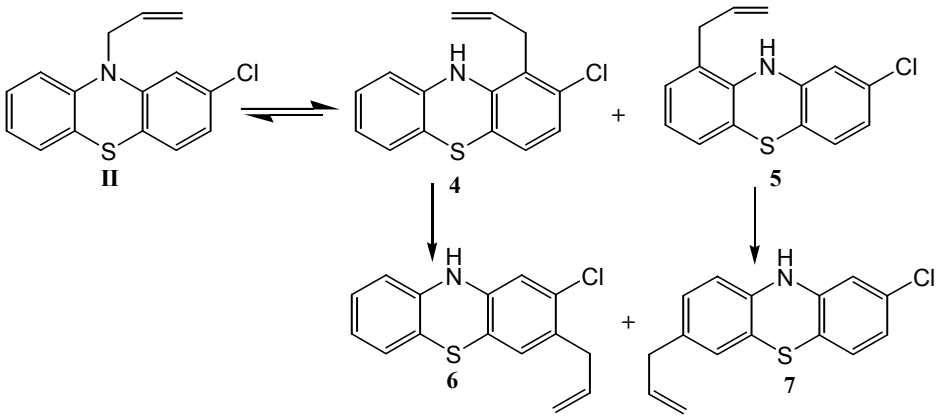


Fig. 4 – Total (a.u.) and relative energies (kcal/mol) for allyl-phenothiazine species involved in tautomerism.



Scheme 3

Table 1

Total energy values (a.u.) for structures involved in aza Claisen and Cope rearrangement reactions of 10-allyl-2-chloro-10*H*phenothiazine **II**

Cpd.	**II**	Tautomer C*H*phenothiazine			
		4a	**5a**	**6a**	**7a**
Energy (a.u.)	-1491.93105	-1491.90229	-1491.90226	-1491.90490	-1491.90589
Cpd.		Tautomer N*H*phenothiazine			
		4	**5**	**6**	**7**
Energy (a.u.)		-1491.94217	-1491.944417	-1491.94504	-1491.94642

Computed energy values for 1-allyl-2-chloro-1*H*phenothiazine **4a** and 9-allyl-2-chloro-9*H*phenothiazine **6a** are very similar, as well as the ones for 3-allyl-2-chloro-3*H*phenothiazine **5a** and 7-allyl-2-chloro-7*H*phenothiazine **7a,** thus illustrating the possible migration of the allyl group in **II** towards any of the two aromatic rings of the phenothiazine core. Four stable C-allyl-2-chloro-10*H*phenothiazine regioisomers **4-7** may be obtained. The energy decreased in **4-7** down to -6.97÷-9.6 kcal/mol relative to **II** suggests the formation of these regioisomers in thermodynamic control, similar to the one described for **I.**

EXPERIMENTAL

Bruker Avance, 300MHz spectrometer
GC-MS Shimadzu QP 2010

General procedure for 10-allyl-10Hphenothiazine preparation by PTC

A mixture of 0.05 mol phenothiazine and 1.4 mmole TBAB were solved in 50 ml of MIK, 0.05 mol 1, 3-dibrome-propane (d=1.98 g/cm^3) were added and then 50 ml of NaOH solution 50% was added. The mixture was vigorously stirred at room temperature for 24 hours, than it was refluxed for additional 24 hours. Water was added to the resulted reaction mixture and the 2 layers were separated. The organic layer was washed with water and dried over Na_2SO_4 anh. and then the solvent was removed by vacuum distillation.

The obtained product can be purified either by recrystallization from ethyl alcohol, by vacuum distillation or by column chromatography (silica gel 60, petroleum ether: toluene 10:1 v/v).

10-Allyl-phenothiazine I

0.05 mole (10g) phenothiazine, 1.4 mmole (0.5g) TBAB solved in 50 ml of MIK, 0.05 mole (10,1g; 5.1 ml) 1, 3-dibrome-propane, 50 ml of NaOH solution 50% ether: toluene 10:1 v/v). The product was collected as light yellowish oil η =70% (8.4 g)

EI-SM (m/e): 239(M^+, 18%); 199 (29%); 198 (100%); 167 (11%); 154 (11%)

^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm): 4.50 ppm (m ,2H, -CH_2), 5.2 ppm (m, 2H, =CH_2) 5.88 ppm (m, 1H, =CH), 6.74 ppm (d, 2H, ^{3}J=8.8 Hz, $H_{1,9}$), 6.81 ppm (t, ^{3}J=7.6 Hz, 2H, $H_{3,7}$), 7 ppm (m, 4H, $H_{2,4,6,8}$)

^{13}C NMR (300 MHz, $CDCl_3$): δ(ppm) 51.3 ppm (-CH_2-); 115,2 ppm (arCH, $C_{1,9}$), 117.6 (=CH_2), 122.3 ppm(arCH, $C_{3,7}$), 122.9 ppm(arC_q, $C_{4a,6a}$), 127 ppm (arCH, $C_{2,8}$), 127,4 ppm (arCH, $C_{4,6}$), 133,3 ppm (=CH), 144,3 ppm(C_q, $C_{9a,10a}$).

10-Allyl-2-cloro-phenothiazine II

0.05 mol (11,73 g) 2-cloro-phenothiazine, 0.05 mole (10,1g; 5.1 ml) 1, 3-dibrome-propane,1.4 mmole (0.5 g) TBAB, 30 ml MIK, 30 ml NaOH 50%

The product was purified by column chromatography (silica gel 60, petroleum ether: toluene 10:1 v/v). White crystals, m.p. 75^{0}C. η =70% (7g)

SM (m/e): 273(M^+, 20%), 275 (6%); 232 (100%); 234 (25%); 197 (15%).

CONCLUSIONS

10-allyl-10*H*phenothiazine derivatives **I, II** can be successfully prepared by one pot procedure based on phase transfer catalysis conditions. Thermal treatments (≈210 ^{0}C) of these substrates must be avoided due to generation of regioisomers mixtures. Theoretical modeling based on DFT calculations performed with the B3LYP functional indicate 10-allyl-10*H*phenothiazine derivatives **I, II** as substrates for [3,3]sigmatropic rearrangement reactions which proceed under thermal activation.

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