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A comparative study of two novel unsymmetrically substituted triazacyclohexanes

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ABSTRACT

Novel unsymmetrically N-substituted *N,N′*-R_1N''-R_2-1,3,5-triazacyclohexanes (1b and 2b; R_1 = p-chlorophenyl or p-methoxyphenyl and R_2 = butyl or cyclohexyl) have been synthesized in a good yield from condensation reaction by excess amine. Both triazacyclohexane rings have chair conformation. However, 1b adopts diaxial orientation of aryl groups and an equatorial form of alkyl group whereas 2b prefers an axial orientation of the alkyl group and diequatorial forms of aryl groups. 1b is consolidated by weak C-H···π interactions. Intra-molecular C-H···O or C-H···N hydrogen bonds and C-H···π may be effective in the stabilization of 2b. Both compounds have showed moderate antimicrobial activity, but 1b exhibits higher activity than 2b. All experimental results are found in good support to theoretical data. Findings of research may be helpful guide for the medicinal chemists and the field is further open for pharmacokinetics studies.

1. Introduction

Preparation of 1,3,5-triazacyclohexane by primary amines and formaldehyde began over a century ago. Various triazines were synthesized by using the procedure given by Miller and Wagner [1]. There are various studies by considering their usages in industrial chemistry of catalysis for the polymerization and trimerization of olefins as reported by Baker et al. [2]. Therefore, interest in 1,3,5-triazacyclohexane as ligand has been underlined by former researchers [3]. These compounds adopt a chair conformation by eee, eea, eaa or aaa, with e and a corresponding to equatorial and axial orientations. All of them have axial repulsions involving substituent or lone pairs of electrons on nitrogen atoms.

Further, we have recently reported some novel unsymmetrically substituted triazacyclohexanes and they prefer eaa conformer by R_1 substituents in axial and R_2 in equatorial forms [4]. In the current work, we have investigated crystal structures of two novel unsymmetrically substituted 1,3,5-triazacyclohexanes compounds: 1,3-bis(P-chlorophenyl)-5-buthyl)-1,3,5-triazane (1b) and 1,3-bis(P-methoxyphenyl)-5-cyclohexyl)-1,3,5-triazane (2b) for comparison. They are bound to aliphatic as well as aromatic substituents. Structures of the synthesized compounds were characterized by FTIR and their crystal structures were confirmed by X-ray diffraction. These two compounds have also been screened for their anti-bacterial and anti-fungal activities. Density functional theory (DFT) has been used to research conformational analysis, characteristic infra-red bands and electronic properties which correspond to the relationships between structure and activity.

2. Experimental

The synthesis of 1b and 2b was conducted by the procedure reported by some of us [4]. The starting materials from Aldrich were used as received with pro-analysis grade. Manipulations were performed under aerobic conditions. For the preparation of 1b; 10 ml of ethanol were dissolved in n-butylamine (0.4956 ml, 5 mmol) and p-chloroaniline (1.27 g, 10 mmol). Then an aqueous solution of formaldehyde in water (37%, 2.52 ml, 36 mmol) was added under stirring. After 24 h the final mixture was filtered and

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dried to yield the required product (1.093 g, 60.00%). For the preparation of 2b; the same procedure of 1b elaboration was used with a solution of cyclohexylamine (0.57 ml, 5 mmol) and p-methoxyaniline (1.23 g, 10 mmol) in 10 ml of pure ethanol, to which an aqueous solution of formaldehyde in water (37%, 2.52 ml, 36 mmol) added under stirring. The mixture kept at room temperature for a day. The precipitate was obtained with a yield of 80% (1.53). After some days of recrystallization in hexane, good crystals were produced. The purity of these products was confirmed by R_f = 0.13 and 0.40 (Chloroforme/Petroleum Ether (7/3)) and melting point of 140 and 108 C°, respectively.

Oxford Diffraction Xcalibur (Atlas, Gemini ultra) diffractometer with Mo Kα radiation (λ = 0.71073 Å) was performed for X-ray diffraction intensities at 273 K for 1b and 110 K for 2b. Unit cell determination, data reduction, position of H atoms, crystal structure and analyses were performed by the same procedures and programs as described earlier [4]. Antimicrobial activities of the compounds were also conducted under the same conditions as in earlier examples [4]. A Nexus Nicolet spectrometer was used for the infrared spectra in the range of 400–4000 cm^{-1} by 120 scans at a resolution of 8 cm^{-1}. The compounds (about 100 μg) were scraped and then compressed together with 23 ± 2 mg of KBr in a cold 150 MPa isostatic press in order to obtain a 200–250 μm thick pellet.

2.1. Methodology

All ab initio computations were performed with the Gaussian 09 [5]. The DFT method was used to optimize 1b and 2b. The functional used was B3LYP and the basis set for all atoms was 6-31G(d). Starting geometries of 1b and 2b were derived from their X-ray structures. Frequency computations based on the same geometry optimization method were used to confirm the nature of the stationary points. No imaginary frequencies were encountered. Calculations of electronic energy, density of state (DOS), electrostatic potential surface (EPS), geometrical parameters, energies of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) and uncorrected harmonic wavenumber were performed. Harmonic wavenumbers were scaled by 0.9613 [6].

3. Results and discussion

3.1. Structural analysis

Single crystals of 1b and 2b compounds have allowed to solve their crystal structures. Fig. 1 represents the atomic details of the compounds. CCDC 1412174 and 1412175 contain supplementary crystallographic data for the compounds. It is worth to mention that they crystallize with orthorhombic lattice, but the lattice parameters are rather different as well as their space groups; P_{nma} with a = 22.8310 Å, b = 13.8735 Å, c = 5.8766 Å, V = 1861.4 $Å^3$ for 1b and C_{mc21} with a = 20.4100 Å, b = 15.9480 Å, c = 6.3050 Å, V = 2052.3 $Å^3$ for 2b. The number of the formula groups per unit cell is four in each network.

1b prefers eaa chair conformer. Similar results were obtained for previous unsymmetrically substituted triazacyclohexanes [4,7]. However, 2b adopts eea chair form. Torsion angles around C-N for 1b are in the range of 54.4° (53.8°) and 58.6° (55.7°) with a mean of 56.5° (54.8°) for 1b. For 2b, these angles are between 58.0° (59.2°) and 60.3° (55.9°) with a mean value of 59.2° (57.6°). Theoretical values have been given in the parenthesis. Further, Table 1 shows the structural parameters of the compounds. CH_2-N bond lengths are between 1.452 Å (1.453 Å) and 1.466 Å (1.468 Å) with a mean of 1.459 Å (1.461 Å) for 1b and 1.449 Å (1.452 Å) and 1.479 Å (1.481 Å) with a mean of 1.464 Å (1.467 Å) for 2b which are similar to those in comparable compounds [4,7,8]. Angles of CH_2-N-CH_2 are 107.1°–109.8° (109.2°–110.1°) with a mean value of 108.5° (109.7°) for 1b and 106.9°–110.1° (106.9°–110.4°) with a mean of 108.5° (108.7°) for 2b. The root mean square deviations between the experimental and calculated bond lengths, angles and torsion angles are found to be 0.024 Å, 0.78° and 2.75° for 1b and 0.009 Å, 0.76° and 1.65° for 2b, respectively.

All nitrogen atoms have distinctly pyramidal geometry with aryl and alkyl N-C bonds inclined at 34.22°–41.50° and 45.66°–47.43° relative to their CH_2-N-CH_2 planes correspondingly. In addition, it is observed that nitrogen atoms of aliphatic amines are associated with larger out-of-plane angles compared with nitrogens of aromatic amines. For comparison, the corresponding out-of-plane angle of N-C (aryl) is 37.5°–42.2° in aniline [9], 27.0° in *N*,*N*-dimethylaniline [10], 36.9° - 37.4° in p-fluoro aniline [11] and the N-C (alkyl) is 46.1°–52.2° in cyclohexylamine [12]. Corresponding

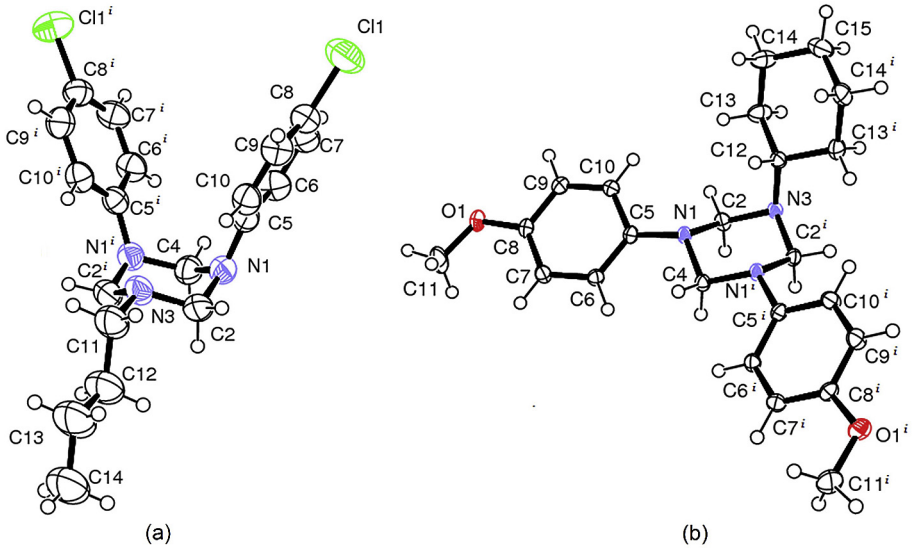

Fig. 1. Molecular structures of 1b (a) and 2b (b) with the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

Table 1
Structural parameters of the compounds.

1b	X-Ray	DFT	2b	X-Ray	DFT
Bond distances (Å)					
Cl1-C8	1.744	1.761	N1-C5	1.417	1.420
N1-C5	1.410	1.420	C4-N1	1.454	1.457
N1-C2	1.452	1.453	N1-C2	1.479	1.481
C4 -N1^{i}	1.466	1.468	O1-C8	1.374	1.369
N3-C2^{i}	1.461	1.469	O1-C11	1.421	1.416
N3-C11	1.468	1.466	N3-C2^{i}	1.449	1.452
N1- C4	1.466	1.468	N3-C12	1.480	1.490
C2- N3	1.461	1.469	C5-C6	1.399	1.401
C5-C6	1.403	1.406	C2-N3	1.144	1.147
C5-C10	1.389	1.404	C5-C10	1.408	1.411
C6-C7	1.372	1.391	C6-C7	1.407	1.401
C11-C12	1.497	1.543	C7-C8	1.385	1.395
C12-C13	1.508	1.535	C8-C9	1.399	1.404
C13-C14	1.490	1.532	C9-C10	1.377	1.385
C8-C7	1.368	1.395	C12-C13	1.526	1.543
C8-C9	1.374	1.392	C13-C14^{i}	1.524	1.538
C10-C9	1.385	1.395	C14 -C15	1.512	1.532
C11-C12	1.497	1.543	C15-C14^{i}	1.512	1.532
C12-C13	1.508	1.535			
C13-C14	1.490	1.532			
Bond angles (°)					
C5-N1-C2	118.22	118.91	C5-N1-C4	116.59	116.45
C5-N1-C4	118.58	118.20	C5-N1-C2	114.22	116.16
C2-N1-C4	109.76	110.13	C4-N1-C2	110.05	110.43
N1-C2-N3	111.32	112.13	C8-O1-C11	117.03	117.89
C2^{i}-N3-C2	107.10	109.17	N3-C2-N1	111.69	112.02
C2i -N3-C11	114.43	114.49	C2i-N3-C2	106.94	106.90
C10-C5-C6	116.95	118.19	C2 -N3-C12	113.73	115.22
C10-C5-N1	122.93	123.11	N1^{i}-C4-N1	108.65	109.74
C6-C5-N1	119.91	118.62	C6-C5-C10	117.58	117.42
N1-C4-N1^{i}	111.80	113.09	C6-C5-N1	124.06	123.51
C7-C8-C9	120.50	120.49	C10-C5-N1	118.31	119.04
C7-C8-Cl1	119.76	119.68	C5-C6-C7	121.59	121.51
C9-C8-Cl1	119.77	119.83	C8-C7-C6	119.69	120.13
C9-C10-C5	121.25	120.89	O1-C8-C7	125.38	125.16
C8-C9-C10	119.80	119.73	O1-C8-C9	115.19	115.85
C7-C6-C5	121.78	121.24	C7-C8-C9	119.42	118.99
N3-C11-C12	117.30	118.26	C10-C9-C8	120.51	120.51
C8-C7-C6	119.70	119.43	C9-C10-C5	121.19	121.43
C11-C12-C13	113.40	113.24	N3-C12-C13^{i}	110.79	110.31
C14-C13-C12	111.80	111.91	C13^{i}-C12-C13	108.83	109.21
			C14-C13-C12	111.42	112.83
			C14-C15-C14^{i}	110.60	110.14
Torsion angles (°)					
C5-N1-C2-N3	−81.70	−85.35	C5-N1-C2-N3	166.33	165.41
C4-N1-C2-N3	58.60	55.68	C4-N1-C2-N3	−60.30	−59.15
C2^{i}-N3-C2-N1	−61.40	−57.51	N1-C2-N3-C2^{i}	58.94	58.94
N1-C2-N3-C11	170.70	172.66	N1-C2-N3-C12	−67.48	−70.45
C5-N1-C4-N1^{i}	85.80	87.56	C5-N1-C4-N1^{i}	−169.80	−168.81
C2-N1-C4-N1^{i}	−54.30	−53.78	C2-N1-C4-N1^{i}	58.00	55.89

angle for a tetrahedral arrangement is 54.7°. Axial and equatorial N-C bonds in 1b are displaced by 21° and 10° outwards from standard chair form, respectively, where as these bonds are displaced by 7° and 13° outwards from ideal chair form for 2b.

The dihedral angles between N atom lone-pair orbital and the aromatic p orbital are 27° and 15° for 1b and 2b correspondingly. In absence of steric effects, this dihedral angle would be expected to be 0° to provide maximum overlap. Nitrogen and chloro atoms of 1b deviate from the phenyl planes by 0.031 Å - 0.146 Å and 0.055 Å, respectively, giving out-of-plane angle of 1.25°−5.94° with a mean of 3.09° for aryl C-N bonds and 1.81° for aryl C-Cl bonds. Oxygen atoms of methoxy group of 2b deviate by 0.031 Å giving out-of-plan angle of 1.38° for aryl C-OMe bonds. A non-planar equilibrium geometry of aniline was found by aryl C-N bond inclined at 2.4° to the aromatic plane [13].

1b is stabilized by weak C-H ⋯ π intermolecular interactions (C2-H2A: 0.970 Å, H2A ⋯ Cg: 2.877 Å, C2 ⋯ Cg: 3.577 Å, ∠C2H2ACg: 129.86°) with H ⋯ *Cg* distances of 2.877 Å, where Cg are the center of gravity of the phenyl ring, leading to the formation of chains parallel to the b axis (Fig. 2a). For the 2b, there are intramolecular C10-H10⋯O1 (C10-H10: 0.930 Å, H10⋯O1: 2.704 Å, C10⋯O1: 3.374 Å, ∠C10H10O1: 129.63°) and C4-H6B⋯N3 (C4-H6B: 0.923 Å, H6B⋯N3: 2.730 Å, C4⋯N3: 3.653 Å, ∠C4H6BN3: 179.56°) hydrogen bonds and weak C11-H11C⋯Cg (C11-H11C: 0.961 Å, H11C⋯Cg: 3.474 Å, C11⋯Cg: 4.320 Å, ∠C11H11CCg: 148.21°) intermolecular interactions. In the crystal structure of 2b, the molecules are stacked in alternating layers along the b axis (Fig. 2b).

3.2. FTIR studies

FTIR spectra have been used to analysis the chemical bonding

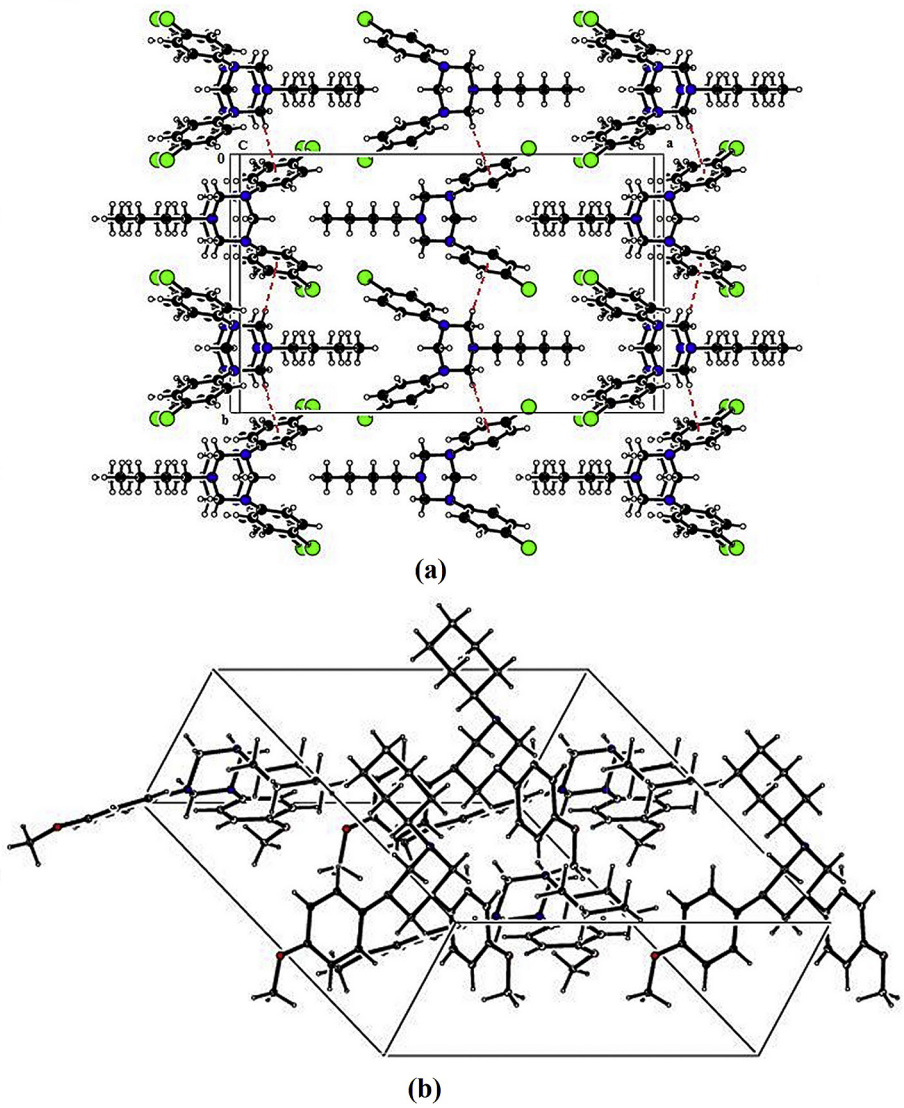

Fig. 2. Packing view of 1b (a) and 2b (b).

and structure, and are given in Fig. 3. The characteristic bands of 1b are as follows: CH aromatic stretching at 3090-3030 cm^{-1}, aliphatic CH_3 stretching at 2954 cm^{-1}, aliphatic CH_2 stretching at 2930 cm^{-1}, aromatic rings at 1592 cm^{-1}, amine III CN stretching at 1357 cm^{-1} CN ph-NR_2 stretching 1280 cm^{-1} and C-Cl stretching at 737 cm^{-1}. The computed values of these modes are 3108-3057, 2962, 2926, 1591, 1351, 1274 and 752 cm^{-1} correspondingly. Similar bands of 2b are as follows: CH aromatic stretching at 3060-3036 cm^{-1}, aliphatic CH_3 stretching at 2996 cm^{-1}, aliphatic CH_2 stretching at 2931 cm^{-1}, aromatic rings at 1619-1510 cm^{-1}, amine III CN stretching at 1355 cm^{-1} and methoxy O-C stretching at 1040 cm^{-1}. The theoretical values are found as 3101–3032, 2976, 2921, 1614–1507, 1348 and 1042 cm^{-1} respectively. All bands are observed in the expected regions and similar bands were shown earlier [3,4,14]. As seen from Fig. 3, the theoretical frequencies are generally in good agreement with the experimental values.

3.3. Structure and activity relationship

Values of minimum inhibitory concentrations for both compounds are presented in Table 2. Investigation of anti-bacterial screening exhibits that 1b shows promising activity against *Escherichia coli*. Furthermore, it demonstrates good activity against *Salmonella typhi*, *Staphylococcus areus and Bacillus subtilus*. However, 2b has poor activity against *Escherichia coli*, *Salmonella typhi* and *Staphylococcus areus*. Table 2 also indicates that both compounds are inactive against *Fusirium moneliforme* and exhibit inhibitory effect against *Aspergillus flavus*. Further, 1b and 2b are inactive against *Pencillium chrysogenum* and *Aspergillus niger*, respectively. However, 1b and 2b show inhibitory effects against *Aspergillus niger* and *Pencillium chrysogenum* correspondingly.

By comparing with our previous data [4], it is found that 1b is the most promoter among the compounds. Anti-bacterial activity of 1b is very close to the compound 4a which has similar structure by the two p-chlorophenyl substituents in the axial position. 1b has same antifungal effect with compound 4a towards *Aspergillus flavus, Aspergillus niger* and *Fusirium moneliforme*, but a different effect towards *Pencillium chrysogenum*. Hence, the biological effect of the compounds increases by the presence of two p-chlorophenyl substituents in the axial position. The data of the biological effect on 1,3,5-triazacyclohexene derivatives, however, which contain p-methoxyphenyl substituent such as 2b, is not available for comparison.

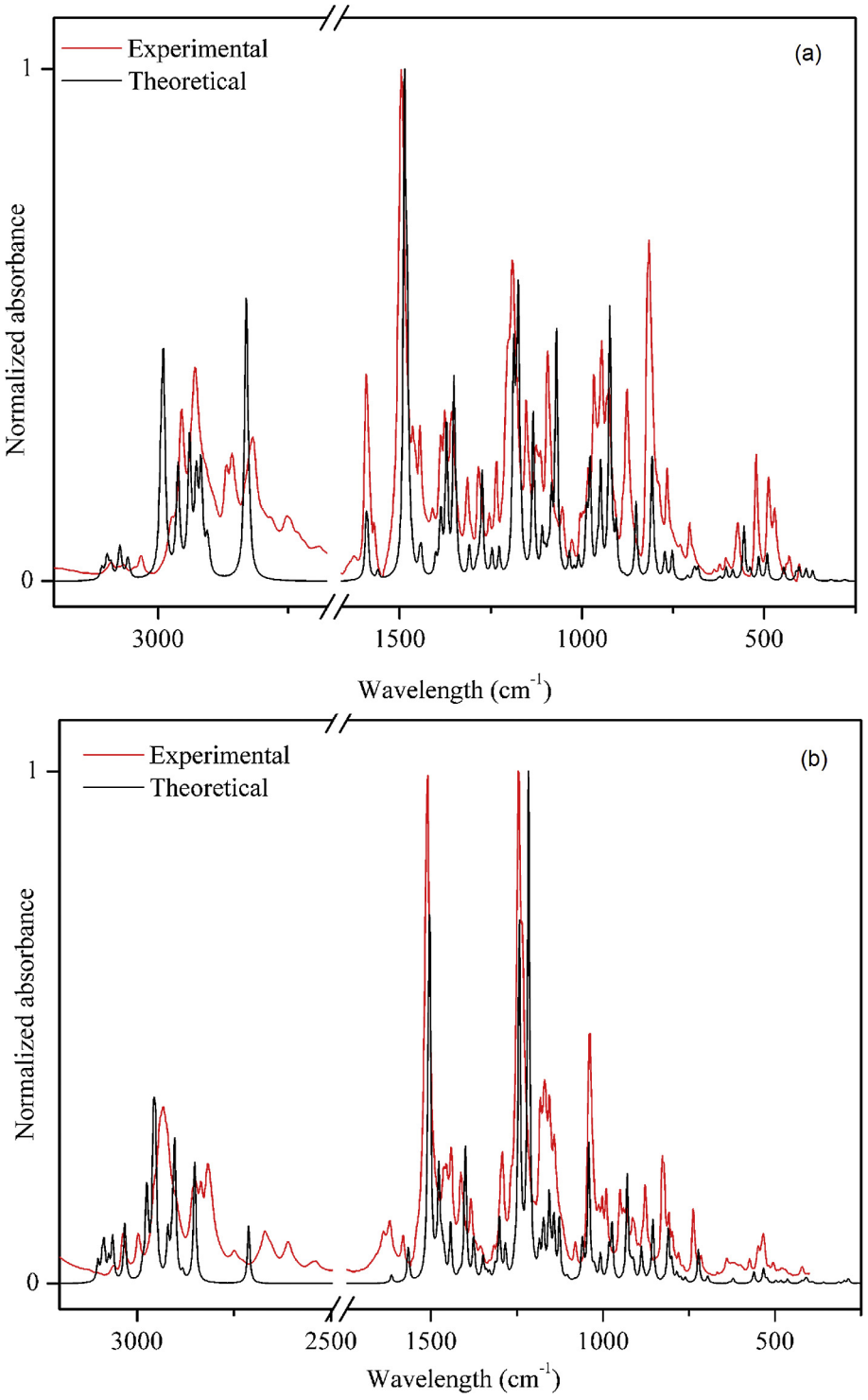

Fig. 3. Experimental and theoretical IR spectra of 1b (a) and 2b (b).

DFT was also used to research the relationships between biological activity and chemical structure which are based on the fundamental hypothesis that biological properties are functions of the molecular structure [15,16]. For example, anti-bacterial activity is related with the function of LUMO. Compounds which have low LUMO energy are more highly motivated to accept electrons than those with higher energy since incoming electrons are received in LUMO. Therefore, they indicate higher activity [4]. When we investigate some energetic descriptors of 1b and 2b, it is found that their LUMO energies are −0.356 eV and −0.066 eV correspondingly. 1b has higher activity. Computational findings are in good agreement with measured values. The investigated molecules have same band gap and chemical hardness as 4.955 eV and 2.478 eV, respectively, though they have different frontier molecular energies (HOMO: −5.311 eV for 1b and −5.021 eV for 2b). Moreover, DOS spectra of the compounds are given in Fig. 4 together with models

Table 2
Screening of anti-bacterial and anti-fungal activities.

Compound	*Escherichia coli*	*Salmonella typhi*	*Staphylococcus areus*	*Bacillus subtilus*
1b	14	18	25	17
2b	9	10	15	21
Penicilin	18	25	40	17
Dmso	–	–	–	–
Compound	*Aspergillus niger*	*Aspergillus flavus*	*Pencillium chrysogenum*	*Fusirium moneliforme*
1b	–	–	+	+
2b	+	–	–	+
Greseofulvin	–	–	–	–
Control	+	+	+	+

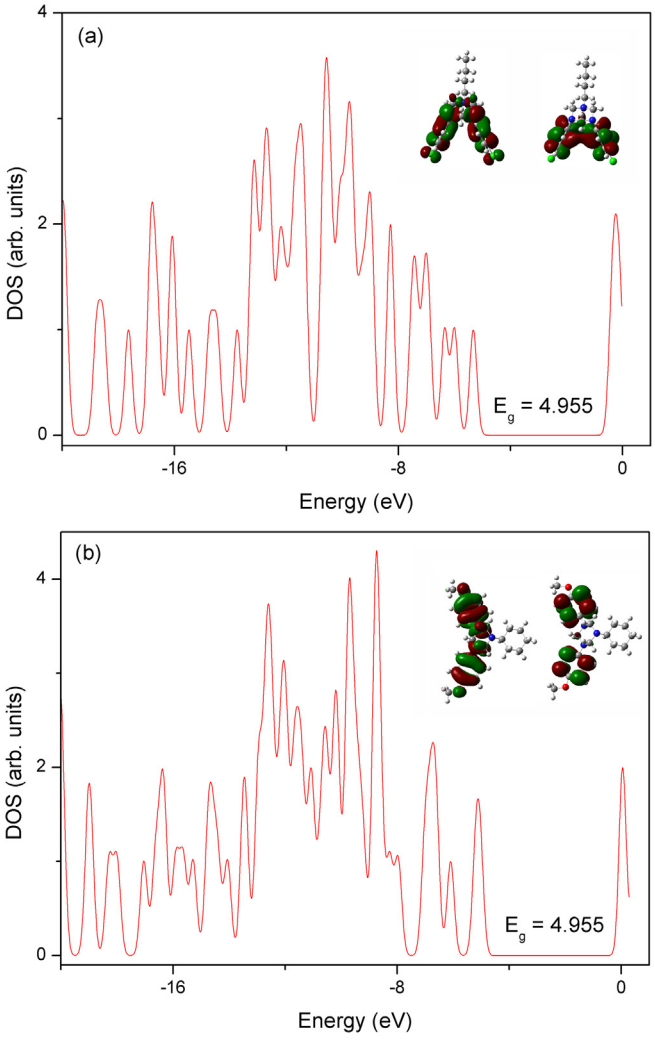

Fig. 4. DOS spectra and frontier orbitals of 1b (a) and 2b (b).

of frontier orbitals of molecules. HOMOs of 1b and 2b are localized on almost all atoms of their R_1 substituents while their LUMOs are localized on almost all atoms of their R_1 substituents except Cl halogen or O-CH_3 groups and without N-R_1 regions. Thus, HOMOs have antibonding characters whereas LUMOs show bonding characters.

Nucleophilicity and electrophilicity are the fundamental basis of chemical reactivity. Certain electrophilic or nucleophilic sites of the compound can bind to nucleophilic or electrophilic region of the receptor. One of the important approach for the analysing of the drug and receptor binding mechanism is EPS [17]. Electrostatic potential maps of 1b and 2b are given in Fig. 5. According to results, electrophiles interact red areas which seem as the most probable candidates as active sites for the compounds while nucleophiles attack blue regions.

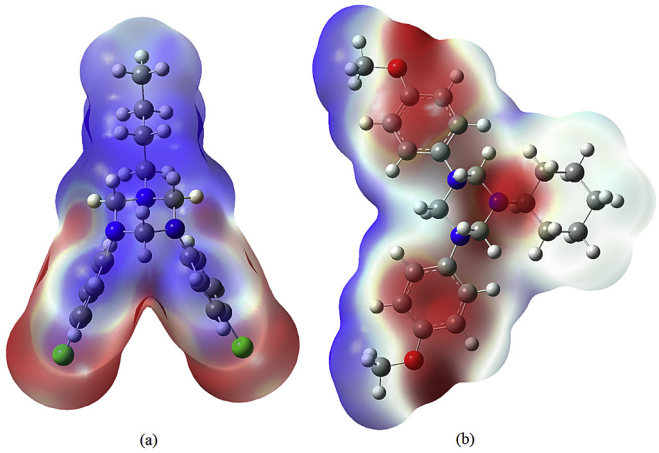

Fig. 5. Electrostatic potential maps of 1b (a) and 2b (b).

4. Conclusions

The study related with two new unsymmetrically substituted (1,3,5) triazacyclohexanes derivatives prepared from two amines and formaldehyde allowed to clarity the conformational consequences and showed that the triazacyclohexane rings prefer chair conformation by an equatorial form of alkyl group and diaxial orientation of aryl groups for 1b and diequatorial forms of aryl groups and an axial orientation of alkyl group for 2b. Both structures crystallize in orthorhombic lattice systems by different space group and hall symbol. 1b has halogen chloro atoms as pharmacophore and it showed better antimicrobial activity proving probably the relation between structure and activity, as compared with the used microorganisms. The biological activity of 1,3,5-triazacyclohexene derivatives increases with the presence of two p-chlorophenyl substituents in the axial position. It has been also found theoretically that the compound 1b with lower energy for the lowest unoccupied orbital concluded its higher activity. For the all investigations, there are good agreements between the experimental and theoretical findings.

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