Electronic structure and vibrational assignments of 2,5-bis[4-(n-cyclobutyldiaminomethyl)phenyl]furan

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Abstract
Several DNA minor groove binders exhibit numerous therapeutic applications. The crystal structure demonstrating 2,5-bis[4-(N-cyclobutyldiaminomethyl)phenyl]furan binding within the minor groove of DNA has been reported by Simpson et al (2000 Bioorg. Med. Chem. Lett. 10 2593). In the present study, computational investigations on the title compound have been carried out which comprise geometry optimization, HOMO-LUMO, dipole moment, Molecular electrostatic potential (MEP), thermodynamic parameters, and IR assignments using the B3LYP/6-31G** method. The true minimum was long-established by the nonappearance of negative wavenumbers. A comparison of optimized parameters with crystallographic structure demonstrates slight variations in the conformations of the cyclobutyl groups. A small HOMO-LUMO gap indicates the high chemical reactivity and inter molecule charge transferability. The vibrational spectra of the molecule calculated in 400–3800 cm⁻¹ region, reproduce reliable IR assignments. Bearing in mind the high pharmaceutical significance of minor groove binders and a variety of flexible options accessible for lead optimization will be a bountiful ground for the development of drugs targeting minor grooves.

1. Introduction
A large percentage of the currently used chemotherapeutic anticancer agents are classified into DNA-binding drugs [1]. Due to the application potential of such drugs to cancer and beyond, the development and delineation of such compounds are substantial. Functional intercalators, talented to disrupt DNA metabolism, bind to DNA duplex in between two base-pairs through a non-covalent stacking interaction that necessitates as a minimum of partial planarity, which is assisted by the realization of at least one hydrogen bond [2]. The consequences of intercalation are the decrease of DNA helical twist and enlargement of the DNA duplex [3]. The distinctive binding modes advance the stability of the duplex and improve the target specificity. The stability of ligand-DNA complexes is expected to be improved by multiple interactions. Combining covalent-binding with non-covalent recognition signifies an entropic advantage over molecules that do not confine covalently to the DNA. In vigorous cells, most of the DNA is efficiently stored and not reachable to foreign agents. On the other hand, the DNA of briskly dividing cancer cells is continuously being retrieved, modified, and replicated, with concomitant changes in structure, which can be anticipated to embrace DNA duplex in distinct forms, DNA junctions, loops, bulges, etc. DNA recognition by drugs does not seem to be contingent straight on the genetic codes of the four bases but slightly on the mode the construction of the DNA is adapted [4]. Since the early discovery of Lerman that dyes of the acridine family are intelligent enough to bind to nucleic acids implanting themselves amid the base-pairs of the polynucleotide [5], intense studies on intercalation started all over the world. It was pointed out by the crystallographers that the process of intercalation and groove binding can produce deep alterations in the nucleotide secondary structure [6], with major consequences for DNA replication and transcription. In some cases, intercalation and groove binding can occur in a selective way, which is at a particular base sequence [7]. The malleable groove width makes DNA capable to bind with any molecule which satisfies the favorable
environmental conditions [8]. Groove binders are stabilized through intermolecular interactions and naturally have higher association constants than intercalators since a cost in free energies is not required for the creation of binding sites [9]. Groove binders have established as clinical usefulness as anticancer, antiviral, and antibacterial agents [7, 10]. Apart from therapeutic use, minor groove binders are used in various other aspects of research. Compounds with the ability of binding within the minor groove can obstruct chromosome condensation in mitosis along with the outcome change in gene expression. Plausibly, the most illustrious anti-microbial DNA minor groove binding agent is pentamidine which demonstrates activity against an assortment of protozoa, for instance, Pneumocystis jiroveci. Though, like other antimicrobial minor groove binding drugs, pentamidines have notable toxicity including nephrotoxicity, cardiotoxicity, and hepatotoxicity that have provoked research for harmless agents to delicate Pneumocystis pneumonia. Pentamidine is also known to inhibit oncogenic PRL phosphatases [11], which play important roles in many cancers and clinically usable in ailments, for example, pancreatic cancer. Footprinting experiments and molecular modeling studies have demonstrated that pentamidines bind selectively within the minor groove of the AT-rich DNA duplex [12, 13]. Experiments also show that the cis conformations of pentamidines are the most favored conformation for binding with the duplex [14]. Pentamide compounds are obtained by the substitution of amidino-nitrogens by hydrophobic alkyl groups of the furamidine, which increases the binding affinity with DNA against pneumocystis carinii pneumonia [14]. Though the detection of DNA binding and the effects on biological functions are well studied, a complete understanding of the mechanism of binding or the causes of affinity, etc are yet to be accomplished. In the present effort, the electronic structure and the molecular properties of a pentamidine analog having cyclobutyl substituent namely, 2,5-bis[4-(N-cyclobutylaminomethyl)phenyl]furan have been studied and the assignment of normal modes of vibration have been carried out within the 400–3800 cm\(^{-1}\) wavenumber range, using GAUSSIAN03 program.

2. Methodology

The crystallographic geometry of the molecule namely 2,5-bis[4-(N-cyclobutyl diaminomethyl)phenyl]furan has been extracted from the PBD ID: 1FMQ (www.rscb.org). The optimization of the geometry of the molecule without any constraint, in vacuum, has been carried out through the B3LYP/6-31G** density functional method as implemented in GAUSSIAN03 software [15]. The optimized coordinates of the molecule have been considered for the calculation of Mullikan atomic charges, the dipole moment of the molecule, molecular electrostatic potential, HOMO-LUMO, IR assignments, and thermodynamic properties of the molecule in the ground state, as has been adopted in our earlier papers [11, 16, 17].

3. Results and discussion

3.1. Geometry optimization

The molecular geometry of 2,5-bis[4-(N-cyclobutyl-aminomethy)phenyl]furan, optimized through B3LYP/6-31G** method, exhibit syn-conformation (figure 1). The absence of negative IR wavenumbers indicates true minima. The comparisons of geometrical parameters indicate that the core rings have robust conformations while substituents conformations have slight variations (table S1 is available online at stacks.iop.org/IOPSN/1/024005/mmedia). Bond lengths of the optimized geometry of the molecule are rather elongated to that of the

![Figure 1. Optimized geometry of 2,5-bis[4-(N-cyclobutyl diaminomethyl)phenyl]furan as obtained through B3LYP/6-31G** method.](image-url)
crystallographic structure, the most change being for C–N bonds. Changes in bond angles have also been observed at both terminal carbon atoms where the cyclobutyl group is attached. The dihedral angles of cyclobutyl rings show variations i.e. the conformation of cyclobutyl rings is different in crystallographic and gas-phase states. These rings have been twisted from the original coordinates albeit the whole molecule adopts cis conformation.

3.2. Partial atomic charges

Although the quantum theory of atoms in molecules describes electron transfer in buried atoms with realistic accurateness, these are not suitable to construct point-charge models for classical force-fields [18]. The quantum theory method can be used to construct accurate force-fields using multi-centered polyatomic multipole expansions, but these are more complicated than the simple point-charge based force-fields often used. Instead, electrostatic potential derived point charges have reasonable accuracy for reproducing the electrostatic potential surrounding the material, but these do not accurately describe electron transfer for buried atoms. All the nitrogen and oxygen atoms bear fractional negative charges while all hydrogen atoms possess partial positive charges [table S2]. The interior or buried carbon atoms retain partial positive charges while exterior carbon atoms that are bonded with hydrogen atoms bear negative partial charges. The calculated charges also exhibit symmetrical nature as atoms are chemically arranged. The higher positive charges have been found on C14 and C18 atoms with values 0.317 and 0.305 and most negative on C7 and C31 atoms with electronic charges $-0.214$ and $-0.224$. The vector sum of individual bond dipole moments, of the molecule as obtained through calculation is 3.073 Debye. Thus, the molecule is a little bit polar in nature.

3.3. Molecular electrostatic potential

Molecular reactive behavior is most often regarded as a well-known tool for the elucidation and prediction of molecular reactive performance towards electrophiles. The electrophiles have a tendency to go to those regions where electrostatic potential residues most negative. Moreover, the nucleophilic processes can be dealt with by considering electrostatic and polarization both effects. The surface of the molecule is generally taken as an outer contour of the electronic density that reflects the specific features of the molecule including $\pi$-electrons, strained bonds, lone pairs, etc [19]. Hydrogen bonding and other non-covalent interactions can be understood and anticipated well with the electrostatic potential. In pharmaceutics, the positive and negative electrostatic potential areas can provide characteristic understanding into the initial phases of ligand-receptor and enzyme-substrate interactions. In the present exertion, the electrostatic potential surface of the molecule has been calculated using the B3LYP/6-31G** method on the isosurface of 0.001 electrons/bohr$^3$. The positive and negative potentials appear near hydrogen and oxygen/nitrogen(electronegative) atoms while most of the regions are green i.e. electrostatically neutral (figure 2).

3.4. HOMO-LUMO orbitals

The prominent roles are played by HOMO and LUMO frontier orbitals in governing chemical reactions. Higher the gap between LUMO and HOMO represents greater hardness as well as a higher stability of the molecule [20]. It is not always HOMO and/or LUMO involved in chemical reactivity but symmetry also plays a role. The total electronic energy of the molecule is $-1304.2450$ Hartree whereas HOMO and LUMO energies of the molecule are $-0.1903$ and $-0.0351$ Hartree, respectively. The high chemical reactivity of the molecule is indicated by the small value of the HOMO–LUMO gap. The HOMO lobes are highly concentrated on carbon atoms of the phenyl rings and less intense on nitrogen and oxygen atoms while virtual orbitals, delocalized in LUMO, are highly concentrated around single bonds of the molecule in the central region (figure 3). These results clearly suggest...
that the molecule is bioactive and intermolecular charge transfer can take place easily. Thermodynamical parameters of the molecule are also calculated using the same functional and basis set (table 1). The zero-point vibrational energy of the molecule is 339.578 cal mol\(^{-1}\).

3.5. Infra-red wavenumbers
In larger molecules, IR spectra are used to ascertain the specific groups present in the molecules. The absorption peaks of the molecule in the wavenumber range 400 to 3800 cm\(^{-1}\) calculated at B3LYP/6-31G** level have been assigned (figure 4, table S3). The molecule is structurally symmetric showing syn conformation with no imaginary wavenumbers exhibiting slightly different wavenumbers at the two sides of the molecule. The prominent peaks observed in the IR spectrum consist of rocking, ring deformation, bending, symmetric and asymmetric stretching, wagging, scissoring, etc. NH\(_2\) twisting is observed at 344.92 and 355.86 cm\(^{-1}\) while the molecule as a whole shows rocking vibration at 391.87 cm\(^{-1}\). The ring out of plane deformations has been observed at 416.30 and 419.41 cm\(^{-1}\) wavenumbers though. the experimentally reported average value is 411 cm\(^{-1}\)\[21\]. C–Ho u t - o f - p l a n e bending vibration is obtained experimentally around 474 cm\(^{-1}\)\[21\], in contrast, to theoretically observed values at 577.89 and 589.45 cm\(^{-1}\). The oxygen atom of the central furan ring, exhibit out of plane deformation at 689.07 cm\(^{-1}\). C–C–C and C–H out of plane distortions are observed at a little bit more wavenumbers than experimentally reported tenets. Aromatic C–C stretching modes have been found in the range 994 to 1033 cm\(^{-1}\) whereas furan ring C–H twisting at 970.39 cm\(^{-1}\). The normal modes at 1055.04, 1056.00, 1244.12, and 1334.89 cm\(^{-1}\) are assigned as C–H scissoring, C–H rocking, C–N stretching, and C–H wagging, respectively. In-plane H–C–C bending is displaying by the molecule at 1094.82 and 1097.21 cm\(^{-1}\) while ring –CH–C–C stretching is observed in the range 1300 to 1317 cm\(^{-1}\). CH\(_2\) scissoring modes are detected at 1355.61, 1388.56, 1488.52, and 1489.62 cm\(^{-1}\). Asymmetric and symmetric C–H stretching vibration modes of CH\(_2\)-groups of the molecule are exhibited in the range 3042 to 3067 and 3069 to 3120 cm\(^{-1}\) while asymmetric and symmetric aromatic C–H stretching vibrations in the range 3189 to 3208 and 3214 to 3224 cm\(^{-1}\) respectively. NH\(_2\) groups in the molecule exhibit three types of vibrational modes: symmetric NH\(_2\) stretching at 3472.26 and 3492.66 cm\(^{-1}\), asymmetric NH\(_2\) stretching at 567.78 and 3582.82 cm\(^{-1}\) and N–H stretching at 3506.63 and 3515.98 cm\(^{-1}\) respectively.

4. Conclusion
The geometrical parameters of 2,5-bis[4-(N-cyclobutyldiaminomethyl)phenyl]furan calculated using the B3LYP/6-31G** method have been compared with the crystallographic structure (table S3). The conformation of core rings is robust enough while the conformation of cyclobutyl rings has significant deviations. The MEP map and HOMO-LUMO energy calculations obviously advocate that the molecule is bioactive with easy intermolecular charge

![Figure 3. LUMO and HOMO orbitals of the molecule estimated through the DFT/B3LYP/6-31G** method.](image)
Table 1. Computed thermodynamical parameters of 2,5-bis[[4-(n-cyclobutyl-diaminomethyl)phenyl]]furan.

| Rotational Temperature (K) | Rotational constant (GHz) | Thermal Energy (cal mol⁻¹ K⁻¹) | Molecular capacity at constant volume (cal mol⁻¹ K⁻¹) | Entropy (cal mol⁻¹ K⁻¹) |
|----------------------------|----------------------------|---------------------------------|-----------------------------------------------------|------------------------|
|                            |                            | translational rotational vibrational Total | translational rotational vibrational Total | translational rotational vibrational Total |
| 0.0185, 0.0016, 0.0016     | 0.3848, 0.0335, 0.0325     | 0.889                           | 2.981                                               | 355.754                |
|                            |                            | 0.889                           | 2.981                                               | 357.531                |
|                            |                            | 355.754                         | 2.981                                               | 357.531                |
|                            |                            | 0.0185                          | 106.491                                             | 112.452                |
|                            |                            | 0.0016                          | 106.491                                             | 112.452                |
|                            |                            | 0.0016                          | 2.981                                               | 37.881                 |
|                            |                            | 0.0016                          | 116.470                                             | 116.470                |
|                            |                            | 0.0016                          | 2.981                                               | 198.320                |
transference. Good correlation is also observed with the infrared (IR) assignments of the normal vibrational modes of the computed and experimental wavenumbers with a scale factor of 0.96 as reported by us previously [16]. It has been proven that the molecule recognizes both strands of the duplex binding within the minor groove [13]. In view of the high pharmaceutical significance of the molecule and also the range of flexible options available for lead optimization, these computations will be a productive ground for the development of drugs targeting minor grooves.

Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

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