Structural elucidation of antihemorrhage drug molecule Diethylammonium 2,5-dihydroxybenzene sulfonate - an insilico approach

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Abstract. Ab-initio computational study of antihemorrhage drug molecule diethylammonium 2,5-dihydroxybenzene sulfonate, popularly known as ethamsylate, has been attempted using Gaussian 09. The optimized molecular geometry has been envisaged using density functional theory method at B3LYP/6-311 basis set. Different geometrical parameters like bond lengths and bond angles were computed and compared against the experimental results available in literature. Fourier transform infrared scanning of the title molecule was performed and vibrational frequencies were also computed using Gaussian software. The presence of O-H---O hydrogen bonds between C₆H₅O₅S- anions and N-H---O hydrogen bonds between anion and cation is evident in the computational studies also. In general, satisfactory agreement of concordance has been observed between computational and experimental results.

Keywords: Ethamsylate, diethylammonium 2,5-dihydroxybenzene sulfonate, computational, Gaussian, FTIR

1. Introduction
Ethamsylate is a haemostatic agent used to improve coagulation and reduce bleeding. It works by enhancing irregular platelet adhesion [1, 2]. The synthesis, biological action and toxicity studies were first described in US patent No. US3351526 in 1967 [3]. The use of this drug to control hemorrhagic brain damage in infants and its consequences were described by D. Elbourne et al [4]. The crystal structure of ethamsylate was explained by Harrison et al [5] wherein the authors discuss about the formation of molecular salt between sulfonic acid group and secondary amine moiety. The authors visualise a helical structure formed out of C₆H₅O₅S- anions connected via O-H---O hydrogen bonds and similar hydrogen bonds helping in cross linking chains. Further cation to anion linking is achieved through N-H---O hydrogen bonds. The crystalline structure analysis of another analogous molecule bis(diethylammonium) 2,5-dihydroxy-1,4-benzenedisulfonate was provided by Solans et al[6].

Ab-initio computational modelling has been emerged as a powerful tool in analyzing molecular geometry and structure. It is also helpful in predicting vibrational frequencies of molecules. Same authors have carried out similar studies for molecule 4-nitro2-phenoxyaniline in 2015 [7]. In the...
current study, authors have employed quantum chemical methods for these investigations using Gaussian 09 software package.

2. Experimental

2.1 Instrumentation

The FTIR scanning of the title molecule has been performed in a Perkin-Elmer spectrophotometer within the range 4000-400 cm\(^{-1}\). Crystal structure data has been incorporated from the single crystal X-ray diffraction study presented in literature method [5] and the same has been utilized for comparison with computed results.

2.2 Computational studies

The molecular labelling and optimized geometry of diethylammonium 2,5-dihydroxybenzene sulfonate has been configured by Gaussian 03W program package [8] using Density Functional Theory (DFT) approximations at 6-311++G(d,p) and 6-31++G(d,p) basis sets. The designated molecule has 34 atoms and DFT analysis reveals 95 expected IR vibrations (Fig 1).

![Figure 1. Diethylammonium 2,5-dihydroxybenzene Optimized molecular geometry with atom labelling using DFT-B3LYP/6-311g](image-url)

In Density Functional Theory approach, the hybrid functional consisting the exact exchange-functional of Becke (B3) [9-11] together with gradient-corrected correlational functional of Lee, Yang and Parr (LYP) [12] were utilized using split-valence polarised 6-31G (d,p) and 6-311G (d,p) basis sets. For comparison, computation was also attempted using Hartree-Fock approximation at 3-21 G (d,p) basis set. Overall, adequate concurrence could be observed between computational and experimental results.

3. Results and discussions

3.1 Infrared frequency assignment
IR vibrational frequencies computed using Density Function theory and Hartree Fock approximation were listed and compared against experimental FTIR results in table 1. Computed data shows characteristic twin peaks between 3700 – 3400 cm$^{-1}$ typical of aromatic $\text{–OH}$ stretching and H bonded $\text{–OH}$ stretching. However such peaks were not very apparent in the experimental FTIR spectrum, probably due to multiple inter molecular and intra molecular hydrogen bonding involving all the $\text{-OH}$ groups. In their study Harrison et al [5] have described the presence of O-H---O hydrogen bonds between $\text{C}_6\text{H}_5\text{O}_5$ anions and N-H---O hydrogen bonds between anion and cation. Multiple peaks were seen between 3100 – 2700 cm$^{-1}$ expected of CH stretching vibrations and the same has been corroborated in the experimental spectrum as well. Strong peaks at around 1700 and 1600 cm$^{-1}$ hint at NH scissoring and phenyl stretching vibrations. Other notable peaks obtained between 1200 – 1400 cm$^{-1}$ were archetypal of CH out of plane bend. Further, presence of sharp peaks at 1080 and 1020 cm$^{-1}$ vindicates C-O stretching vibrations.

Expectedly IR data from Hartree-Fock method are slightly higher in magnitude compared to that from DFT as the anharmonicity in vibrational modes have not been taken into account (fig.2 and fig.3). As the electron correlation was also considered, DFT offers calculations closer to reality specifically after applying suitable scaling factor. The vibrational frequencies were scaled by multiplying with a factor 0.92 for HF methods and for DFT methods the equation $(1.0087-0.0000163*x)*x$ was used where x = unscaled frequency.

![Figure 2. Computed IR data compared.](image-url)
Figure 3. FTIR Spectrum (Experimental)

Table 1. IR frequencies assigned

| Wave No. | Int. | Wave No. | Int. | Wave No. | Int. | Exptl. | Assignment          |
|----------|------|----------|------|----------|------|--------|---------------------|
| 3765     | 77   | 3492     | 40   | 3520     | 47   | 3300   | OH str              |
| 3491     | 333  | 3484     | 35   | 3513     | 45   |        | OH str H bonded     |
| 3177     | 403  | 3112     | 19   | 3080     | 18   |        | CH str              |
| 3129     | 4    | 3066     | 16   | 3041     | 19   |        | CH str              |
| 3117     | 4    | 3050     | 15   | 3025     | 17   |        | CH str              |
| 3078     | 416  | 3024     | 10   | 2993     | 14   |        | CH str              |
| 3069     | 23   | 3020     | 12   | 2989     | 15   |        | CH str              |
| 3015     | 33   | 3013     | 27.8 | 2981     | 32   |        | CH str              |
| 3009     | 29   | 2985     | 23   | 2980     | 30   |        | CH str              |
| 2996     | 42   | 2980     | 2    | 2956     | 18   | 2990   | CH str              |
| 2995     | 40   | 2945     | 13   | 2950     | 1    | 2800   | CH str              |
| 2987     | 18   | 2940     | 9    | 2921     | 6    |        | CH str              |
| 2983     | 1    | 2939     | 13   | 2915     | 10   |        | CH str              |
| 2952     | 85   | 2751     | 1581 | 2912     | 2    |        | CH str              |
| 2947     | 2    | 2626     | 107  | 2911     | 15   |        | CH str              |
| 2928     | 12   | 1741     | 870  | 2798     | 1327 |        | NH str symm         |
| 2926     | 16   | 1648     | 22   | 2665     | 223  |        | NH str asym         |
| 1762     | 524  | 1622     | 2    | 1750     | 823  | 1731   | NH sciss            |
| 1675     | 2    | 1595     | 69   | 1628     | 19   | 1620   | Ph str              |
| 1628     | 18   | 1533     | 0.2  | 1602     | 2    |        | Ph str              |
| 1595     | 106  | 1528     | 149  | 1584     | 59   |        | NH bend             |
| 1542     | 3    | 1527     | 1    | 1529     | 1    |        | CH bend             |
| 1532     | 147  | 1526     | 5    | 1526     | 3    |        | CH bend             |
| 1529     | 3    | 1520     | 11   | 1524     | 2    |        | CH inplane bend     |
| 1523     | 12   | 1514     | 30   | 1520     | 12   |        | CH inplane bend     |
| 1520     | 32   | 1511     | 26   | 1515     | 142  |        | CH inplane bend     |
| 1515     | 29   | 1476     | 0.6  | 1512     | 21   |        | CH out of plane bend|
| 1484     | 110  | 1467     | 2    | 1508     | 29   |        | CH out of plane bend|
3.2 Molecular geometry

The optimized geometrical representation using DFT B3LYP 6-311G with correlated atom labelling basis set has been presented in fig. 1. The bond lengths and bond angles computed via Density Function theory and Hartree Fock approximation models show necessary concurrence with each other and also with the experimental single crystal XRD data presented in literature [fig.4 and fig.5]. Further computational data also substantiate the presence of N-H—O hydrogen bonds which help in proton transfer from anion to cation to facilitate formation of the molecular salt, diethylammonium 2,5-dihydroxybenzene sulfonate. This was evidenced by enhanced bond lengths of 2.6, 2.3 and 2.75 between atom number 10 and 16.
4. Conclusions

Computational modelling and molecular mechanics are slowly emerging as valid tools for studying structure and properties of molecules. The current study also shows sufficient concordance between experimental and theoretically predicted results. In the hind sight, slight deviations are expected from experimental values as theoretical assessment has been performed assuming single molecule in space without any intermolecular interactions or possible multi layered stacking effects. DFT methods
produced results closer to experimental ones compared to HF approximations as system anharmonicity is neglected in the latter and hence probably over-estimated.

5. References

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