New route for synthesis of 2-(2,2-dimethoxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole and DFT investigation

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ABSTRACT
Development of efficient sequences for the synthesis of the title compound (2-(2,2-dimethoxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole) (7) was described. The title compound was synthesized through several steps starting from phenylhydrazine hydrochloride and dimethyl (R)-2-(3-oxocyclohexyl)malonate. In this route, all synthesized compounds were observed by spectroscopic tools (FT-IR, NMR): Methyl-2-(2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetate (3), 2-(2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetic acid (4), N-(2,2-dimethoxyethyl)-2-(2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (5). 2-(2,2-dimethoxyethyl)-1,2,4,5,6,7-hexahydro-3H-1,5-methanoazocino[4,3-b]indol-3-one (6), 2-(2,2-dimethoxyethyl)-2,3,4,5,6,7-hexahydro-1H-1,5-methanoazocino[4,3-b]indole (7). The central step in these syntheses is the dehydrogenative reaction, which constructs the tetracyclic ring system from a much simpler tetracyclic precursor. The six-stable conformers of the compound (7) were used for further calculations such as FT-IR, NMR, NLO, and FMO analyses, performed at the B3LYP/6-311++G(d,p) level. This work revealed that (7) can be a good material to use in the non-linear optical material because its $\beta$ tensor is greater ten times than that of the urea.

1. Introduction

The (2,2-dimethoxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole ring system of intermediate 7 is a structural feature of indole alkaloid families which is characterized by the presence of the 1,5-methanoazocino[4,3-b]indole moiety bearing (2,2-dimethoxyethyl) at N-2 position and the ring system of the strychnos alkaloids [1]. Multi-functionalized 1,5-methanoazocino[4,3-b]indole tetracyclic skeleton is very important for synthetic organic chemistry and is found in many different types of natural products, such as uleine [2], epidasycarpidone [3], 20-deethyldasycarpidone [4], 20-diethyl-4-demethyldasycarpidone [5]. These natural products, which possess a wide variety of biological properties, anti-HIV, antitumor, analgesia behavior [6].

For these reasons, we first have aimed to define the new route for the synthesis of compound (7). Then, we have conducted the quantum chemical calculations to predict the other electronic properties of the compound, such as NLO properties, intramolecular interactions, e.g., because we do not have the laboratory facilities and, therefore, no experimental data to determine these properties experimentally. Thus, the new route for the synthesis of the title compound has been defined, and the electronic properties of the compound have been investigated in detail by quantum chemical tools as well.

2. Results and discussion

The synthesis of (2,2-dimethoxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole 7 began with methyl-2-(2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetate 3, which could be prepared on a multigram scale from 1 and 2 and the preparation of the starting material has been previously described [7]. Two strategic considerations guided our synthetic design: a) synthesis of organic compounds without protection b) deprotection steps are of great importance due to the atom economy. Previously we reported the synthesis of the azocino[4,3-b]indole skeleton via the acid catalyzed, as well as oxidative cyclization from appropriate tetrahydrocarbazole derivatives. The development of the synthetic pathway remains essential and challenging. We sought to develop a general intramolecular cyclization strategy for the synthesis of the azocino[4,3-b] indole and related natural products in a concise. In this regard, we selected TCB, which has not been used in strychnos alkaloids. As an alternative, herein, we report a new protocol for the cyclization of 2-substituted tetrahydrocarbazole, and synthesis of organic compounds...
without protection and deprotection steps is of great importance due to the yields. Therefore, we have decided to seek a shorter and more efficient route to the synthesis of azocino[4,3-b]indole. We chose a one-pot treatment of amide with TCB in THF at room temperature, which led to an increase in overall yield to 86% in one step from compound 5. The strategy developed here to build the azocino[4,3-b]indole system, which presents a method also advantageous in respect to alternative synthetic approaches described in the literature, synthetic entry to this tetracyclic system that may apply to the synthesis strychnos alkaloids. As the first step, the starting tetrahydrocarbazoles bearing ester group at C2-position. The ester derivative 3 was transformed into the acid 4 by treatment with 20% KOH solution in MeOH-H2O (3:1) for 6 h at room temperature. Transformation of the carboxylic acid 4 into the substituted amide 5 was prepared by followed treatment of the carboxylic acid with triethylamine and ethyl chloroformate in chloroform (CHCl3), followed by the addition of (2,2-dimethoxy)ethyamine. It was expected that the treatment of 5 with tetrachloro-1,4-benzoquinone (TCB) mediated dehydrogenative cyclization would produce the 1,5-methanoazocino[4,3-b]indole 6 in 86% yield. It is noteworthy that the construction of the tetracyclic of the 1,5-methanoazocino[4,3-b]indole that allows the introduction of the functionalized at N-2, the strategy developed here can provide a new general synthetic entry to assembling members of the strychnos alkaloids family (Scheme 1) with methods available for the construction of the tetracyclic ring substructure of strychnos alkaloids.

Finally, the reduction of amide 6 with tris(triphenylphosphine) rhodium (I) carbonyl hydrde tetrahydrofuran to give 2-(2,2-dimethoxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole 7 [8]. In this study, we developed a TCB-mediated synthesis of a new strategy to azocino[4,3-b]indoles as the vital step for the critical element of strychnos alkaloids, but also this method could be extended to the syntheses of other alkaloids, and target molecules are accessible in a few starting from 3. The application of the TCB-mediated methodology the synthesis of 2-(2,2-dimethoxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b] indole gave access to the synthesis of other natural products embodying the 1,5- methanoazocino[4,3-b] indole framework. Moreover, this synthesis provides an appealing alternative to the approach to chemical synthesis in that it typically involves the construction of the natural product, including diverse members of alkaloid families.

2.1. Molecular geometry

The conformational analysis of the title compound (7), according to the rotation of the methoxy and dimethoxy ethyl groups over the rings, has been conducted by the torsion angles of \( \chi_1 \) (C14–N19–C30–C31), \( \chi_2 \) (C24–N19–C30–C31), \( \chi_3 \) (N19–C30–C31–O35), \( \chi_4 \) (N19–C30–C31–O36), \( \chi_5 \) (C30–C31–O36–C41), \( \chi_6 \) (C30–C31–O35–C37). All conformational curves and relative energies can be found in Figure. S1 and Table S1, respectively.

According to the FES scan results, the conformer (I) is determined as the lowest energy conformer with the electronic energy of -960.159310 hartrees, whereas the (IV) is determined the highest energy structure with the electronic energy of -960.158312 hartrees. Also, the electronic energies of all conformers are quite similar to each other: the relative energies of these conformers have been determined between 0.00- 0.63 kcal/mol in the CHCl3 (Figure 1). Also, Table S2 shows the Boltzmann population (% of six conformers obtained from the relative electronic and free energy values. Accordingly, the Boltzmann population calculated for all conformers is calculated as quite similar to each other, with the population value of 16.6-16.7 % for both the B3LYP and B3LYP-GD3BJ functionals. In this step, it should also be noted from Table S1 that the conformer (II) has the lowest \( \Delta G \) (0.00 kcal/mol) for both the B3LYP and B3LYP-GD3BJ functionals. However, the conformer (VI) has the highest \( \Delta G \) (0.90 kcal/mol) by B3LYP, while the conformer (IV) has the highest \( \Delta G \) (1.07 kcal/mol) by B3LYP-GD3BJ functional (in CHCl3).

Table 1 shows the selected geometric parameters for two stable conformers of the title compound; optimized data for the other stable structures can be seen in Table S3.

Here, we have compared the calculated parameters of the compound with the previous report of the structural related heterocyclic compound because we have no experimental data in this work. As expected, the observed bond lengths and angles of all conformers agree with the previous report: the aromatic C–C bond lengths and bond angles for all conformers have been calculated in the range of 1.39–1.42 Å and of 117.7–121.1° (by B3LYP) respectively. Besides, the dihedral angles for the RA (ring A) have been calculated between -0.2-0.0° and reported [9] them in the range of -0.2–0.3°. On the other hand, the calculated C30–C31–O35–C37 angle for (I) structure has been estimated at 170.2°, which implies that the methoxy group of the compound has deviated.

Scheme 1. Reagents and Conditions: a) AcOH, 80 °C, LiCl, H2O; b) LiOH, THF-H2O (3:1), rt; c) CH3OH–H2O, KOH, rt; d) CHCl3, (C2H5)3N, (2,2-dimethoxy)ethylamine, -10 °C; e) Tetrachloro-1,4-benzoquinone (TCB), THF, rt; f) Rh(CO) (PPH3)3, Ph2SiH2, rt.
from the planar angle (180°) with the ~10° and reported in 170.1° [9].
On the other hand, the same dihedral angle for (I) has been predicted by the B3LYP-GD3BJ level at 168.1° with the deviation of ~12° from the planar angle. Addition, C30–C31–O36–C41 angle for two conformers of the compound has been calculated by B3LYP level in -90.9° and -173.0° and by B3LYP-GD3BJ level in -89.0° and -171.4° respectively.

2.2. Vibrational analysis

In this text, the selected vibrational modes (scaled) and PED results have been given for the lowest energy conformer (I) in Table 2; full data can be found in Table S4. Also, the calculated N–H and C–H stretching modes have been scaled down by 0.960, and the remaining modes have been scaled down by 0.988 [10].

As expected, the N–H stretching (νNH) mode has occurred in the 3395 cm\(^{-1}\) of the higher spectral region of the IR and assigned as a pure mode in 3505 cm\(^{-1}\) with a strong IR intensity. In the past, the νNH mode was observed between ~3200-3500 cm\(^{-1}\) [11,12] and calculated by the same level of this work [13,14] in the range of ~3300-3550 cm\(^{-1}\). Also, the secondary amines exhibit the in-plane (ipb) and out-of-plane (opb) bending modes with variable intensity: the ipb modes can appear in the different regions of the IR spectrum while the opb modes are expected to occur in the region of 750–700 cm\(^{-1}\) [15]. From Table 2, the observed band in 3395 cm\(^{-1}\) of the compound have been assigned by PED analysis as the pyre νNH mode (100%) in 3505 cm\(^{-1}\). Also, the reported band in 1423 cm\(^{-1}\) has been assigned by PED analysis as ipb HNC mode coupled with the ring ipb HCC mode of the aromatic ring of the compound in 1445 cm\(^{-1}\). Moreover, another ipb HNC mode coupled with ipb HCC mode has been assigned by PED in 1498 cm\(^{-1}\) (50%) as a mixed-mode with the aromatic ring νCC vibration (28%). On the other hand, the opb HNC mode has been calculated in the range of 1017–310 cm\(^{-1}\); this mode has been assigned in 395 and 384 cm\(^{-1}\) as a pure mode while it has been assigned with the variable IR intensity in 1017, 753, 670, 659, 581, 446, 432, 430, 367, 350, 333 and 310 cm\(^{-1}\) as a mixed-mode with the aromatic ring modes of the compound. Also, it is known well that the νN–C and νN = C modes are hard tasks to be assigned in the fingerprint region of the IR spectrum of the related molecular system [15]. Here, it is worth to say that the νN = C mode has been accompanied by the twisting modes of the RCD in 1465 and 1225 and with ipb HNC mode in 1201 cm\(^{-1}\).

Recently, the aromatic νCH mode was observed in 3086 cm\(^{-1}\) for cetylpyridinium dipicrylamide [16] and 3012 cm\(^{-1}\) for the heterocyclic Schiff bases [17] and predicted by the same level of this work in ~3100-3000 cm\(^{-1}\) [14,18]. Also, ipb and opb HCC vibrations for the aromatic ring were observed in 1456–1131 cm\(^{-1}\) [13,19] and 1000–750 cm\(^{-1}\) [20], respectively, and assigned by PED analysis in 1476–1023 cm\(^{-1}\) and 982-750 cm\(^{-1}\) [21] and 963–525 cm\(^{-1}\) [22]. In this work, the νCH mode has been recorded in 3054 cm\(^{-1}\) and assigned in the range 3059–3053 cm\(^{-1}\). Also, ipb HCC mode has exhibited the signals in 1423, 1368, 1234 cm\(^{-1}\), and predicted between 1498-1115 cm\(^{-1}\) (Figure S3). Besides, the opb HCC signal has observed in 965 cm\(^{-1}\) and predicted in the rank of 962–430 cm\(^{-1}\), generally mixed with the HN16C modes and other bending modes.

In the past, the νC=O stretching mode for the aromatic rings of the propolisbenzofuran B molecule was reported by the same level of this work in the range of 1268–1081 cm\(^{-1}\) as a pure mode, and between 1305-790 cm\(^{-1}\) as a mixed-mode with the modes [23]. Here, the PED analysis has demonstrated the νC=O modes with a strong IR intensity in 1126 (56%), 1066 (69%), and 948 cm\(^{-1}\) (59%). Also, the mixed νC=O modes with the other stretching and bending modes of the compound have been assigned in 1057, 1036, 1017, 876, and 830 cm\(^{-1}\) (Figure S3). It should be noted that the observed and calculated data of the vibrational modes of the compound agree with each other.

2.3. NMR analysis

The representative results of observed and Boltzmann-weighted \(^1\)H and \(^13\)C NMR chemical shifts of the title compound have been given in Table 5; full calculated NMR data for all stable conformers can be seen from Table S5a and Table S5b, respectively. Also, Table S5c, for each stable conformer, shows the correlation equations obtained from the linear regression analysis to show the relationship between the observed and calculated NMR shifts without using the Boltzmann distribution law. Besides, the relationship between the observed and calculated averaged
NMR shifts by using the Boltzmann statistics for the title compound can be found in Table S5d.

From Table 3, the $^{13}$C chemical shifts for the aromatic ring have occurred in the region of the NMR spectrum in 102.2–136.9 ppm; the unsaturated ring carbon shifts have given the signals in 25.1–53.6 ppm. As expected, the chemical shift for C31 atom neighboring to two electronegative oxygen atoms has occurred in 106.8 ppm and predicted by As expected, the chemical shift for the H17 atom bonded to the nitrogen atom of the compound has been observed in 8.52 ppm and calculated at 7.5 ppm (in CHCl$_3$). Also, the $^1H$ NMR shifts for the H18 and H34 atoms have been reported in 4.27 and 4.63 ppm and predicted (CHCl$_3$) in 3.8 and 4.2 ppm, respectively. Besides, the $^1H$ shifts for the aromatic ring atoms (H7–H10) have exhibited the signals in 7.04–7.64 ppm and calculated in 7.2–7.7 ppm (in vac.) and 7.3–7.8 ppm (in CHCl$_3$). Recently, the $^1H$ chemical shifts for the H–N and CH$_2$O groups of a polynamidoamine compound was observed [26] in 8.03 ppm and 3.45 ppm, respectively. In this work, we have reported these chemical shifts in 8.52 ppm (H17) and 3.38 ppm (H42–H44) ppm, whereas they have been calculated in 7.5 and the range of 2.9–3.8 ppm (CHCl$_3$).

From Table S5c, it should be seen that the regression coefficients for six conformers have been calculated in the range of 0.9914–0.9952 for $^{13}$C shifts and the rank of 0.9674–0.9769 for $^1H$ chemical shifts (B3LYP, in CHCl$_3$). Besides, the regression coefficient for the relationship between the recorded by experiment and calculated Boltzmann averaged NMR shifts has found to be R$^2$ = 0.9947 for $^{13}$C and R$^2$ = 0.9754 for $^1H$, respectively (B3LYP, in CHCl$_3$). Thus, these results have demonstrated that the observed and calculated NMR shifts agree with each other.

### Table 1. The selected optimized parameters of two conformers of the compound (7) at 6-311++G(d,p) basis set in CHCl$_3$.

| Bond Length (Å) | Exp.* | B3LYP | B3LYP-GD3BJ |
|-----------------|-------|-------|--------------|
|                 |       | I     | II           | I             | II            |
| C1–C2           | 1.39  | 1.41  | 1.41         | 1.41          | 1.41          |
| C1–C6           | 1.38  | 1.39  | 1.39         | 1.39          | 1.39          |
| C4–C5           | 1.41  | 1.42  | 1.42         | 1.43          | 1.43          |
| N16–C4          | 1.38  | 1.38  | 1.38         | 1.38          | 1.38          |
| C11–C15         | 1.36  | 1.37  | 1.37         | 1.37          | 1.37          |
| C14–C15         | 1.50  | 1.51  | 1.51         | 1.50          | 1.51          |
| N19–C30         | 1.46  | 1.46  | 1.46         | 1.45          | 1.45          |
| O35–C31         | 1.39  | 1.40  | 1.42         | 1.40          | 1.42          |
| O35–C37         | 1.42  | 1.43  | 1.43         | 1.43          | 1.43          |
| O36–C31         | 1.40  | 1.43  | 1.41         | 1.43          | 1.40          |
| O36–C41         | 1.39  | 1.42  | 1.43         | 1.42          | 1.43          |

| Bond angle (°) |
|----------------|
|                 |
| C1–C2–C3       | 121.2 |
| C4–C5–C15      | 106.5 |
| C4–N16–C11     | 108.9 |
| C2–C3–C4       | 117.6 |
| C5–C15–C11     | 107.0 |
| C5–C15–C14     | 131.9 |
| C12–C13–C14    | 108.3 |
| N19–C30–C31    | 111.8 |
| N19–C24–C20    | 119.4 |
| C30–C31–O35    | 107.0 |
| O35–C31–O36    | 110.3 |

| Dihedral angle (°) |
|--------------------|
| C1–C2–C3–C4       | 0.3   |
| C4–C5–C6–O35      | -0.2  |
| C4–C5–C15–C41     | 0.2   |
| C5–C4–N16–C11     | 0.8   |
| N16–C4–C5–C6      | -179.0|
| N16–C4–C5–C15     | -0.7  |
| N19–C30–C31–O35   | -67.5 |
| C30–C31–O35–C37   | 170.1 |
| O35–C31–O36–C41   | -119.5|
| O36–C31–O35–C37   | -71.6 |
| O35–C31–O36–C41   | 123.3 |

* Available experimental data are taken from Ref. [9].
Table 2. The observed and calculated vibrational frequencies (in cm\(^{-1}\)) of the lowest energy structure (I) of the compound (7), at B3LYP/6-311++G(d,p) level in CHCl\(_3\).

| Exp. | Scaled | \(I_{\text{IR}}\) | PED % |
|------|--------|------------------|-------|
| 3395 | 3505   | 109              | sNH (100) |
| 3059 | 3050   | 49               | sCH RA (94) |
| 3041 | 3033   | 7                | s\(v_{\text{CH}}\) (93) |
| 3000 | 2992   | 38               | s\(v_{\text{C}=\text{H}}\) (87) |
| 2969 | 2954   | 23               | sCH RD (98) |
| 2952 | 107    | 40               | s\(v_{\text{CH}_2}\) (93) |
| 2849 | 52     | 61               | s\(v_{\text{CH}_2}\) (88) |
| 2928 | 70     | 75               | sCH2 RC (79) |
| 2918 | 64     | 64               | sCH2 RC (90) |
| 2917 | 71     | 71               | s\(v_{\text{C}=\text{H}}\) (98) |
| 2911 | 84     | 84               | sCH2 RCD (82) |
| 2908 | 3      | 3                | sCH2 RCD + s\(v_{\text{CH}_2}\) (90) |
| 2882 | 72     | 72               | s\(v_{\text{C}=\text{H}}\) (81) + s\(v_{\text{C}=\text{H}}\) (12) |
| 2878 | 69     | 69               | sCH2 RCD (99) |
| 2870 | 75     | 75               | s\(v_{\text{C}=\text{H}}\) (90) |
| 2831 | 2841   | 91               | s\(v_{\text{C}=\text{H}}\) (93) |
| 2782 | 149    | 149              | sCH RD (98) |
| 1618 | 1633   | 10               | s\(v_{\text{C}=\text{H}}\) (67) |
| 1594 | 1574   | 11               | s\(v_{\text{C}=\text{H}}\) (54) |
| 1512 | 1512   | 4                | sCH2 RD (73) |
| 1498 | 6      | 6                | s\(v_{\text{HCC RA} + \text{ipb HNC}}\) (50) |
| 1484 | 12     | 12               | s\(v_{\text{C}=\text{H}}\) + s\(v_{\text{C}=\text{H}}\) (70) |
| 1478 | 8      | 8                | sCH2 RCD (89) |
| 1471 | 10     | 10               | s\(v_{\text{C}=\text{H}}\) (49) |
| 1467 | 42     | 42               | s\(v_{\text{C}=\text{H}}\) (52) + s\(N_{16}\)C |
| 1464 | 10     | 10               | s\(v_{\text{C}=\text{H}}\) (91) |
| 1461 | 8      | 8                | s\(v_{\text{C}=\text{H}}\) (75) + s\(v_{\text{C}=\text{H}}\) (14) |
| 1461 | 50     | 50               | s\(v_{\text{HCC RA} + \text{ipb HCC RA}}\) (50) |
| 1454 | 4      | 4                | s\(v_{\text{C}=\text{H}}\) (77) |
| 1423 | 52     | 52               | s\(v_{\text{HCC RA} + \text{ipb HNC}}\) (46) |
| 1406 | 9      | 9                | s\(v_{\text{C}=\text{H}}\) (53) |
| 1386 | 24     | 24               | s\(v_{\text{C}=\text{H}}\) (60) |
| 1384 | 4      | 4                | s\(v_{\text{C}=\text{H}}\) (30) |
| 1368 | 11     | 11               | s\(v_{\text{HCC RA} + \text{ipb HCC RA}}\) (44) |
| 1347 | 3      | 3                | s\(v_{\text{C}=\text{H}}\) (39) |
| 1331 | 16     | 16               | s\(v_{\text{C}=\text{H}}\) (52) |
| 1308 | 60     | 60               | s\(v_{\text{C}=\text{H}}\) (10) + s\(v_{\text{C}=\text{H}}\) (14) |
| 1276 | 22     | 22               | s\(v_{\text{C}=\text{H}}\) (44) |
| 1236 | 13     | 13               | s\(v_{\text{HCC RA} + \text{ipb HCC RA}}\) (53) |
| 1193 | 38     | 38               | s\(v_{\text{C}=\text{H}}\) (36) + s\(v_{\text{C}=\text{H}}\) (15) |
| 1159 | 2      | 2                | s\(v_{\text{C}=\text{H}}\) (80) + s\(v_{\text{C}=\text{H}}\) (13) |
| 1137 | 56     | 56               | s\(v_{\text{N}_{19}\text{C}}\) (48) |
| 1127 | 1126   | 166              | s\(v_{\text{C}}\) (56) |
| 1073 | 1066   | 299              | s\(v_{\text{C}}\) (69) |
| 1012 | 1017   | 30               | s\(v_{\text{C}}\) (53) |
| 1000 | 21     | 21               | s\(v_{\text{C}}\) (38) |
| 965  | 962    | 18               | s\(v_{\text{C}}\) (13) |
| 930  | 948    | 141              | s\(v_{\text{C}}\) (59) |
| 900  | 913    | 9                | s\(v_{\text{C}}\) (28) |
| 753  | 4      | 4                | s\(v_{\text{C}}\) (36) |
| 737  | 97     | 97               | s\(v_{\text{C}}\) (74) |

(continued on next page)
Table 2 (continued)

| Exp. | Scaled | \(I_{\text{IR}}\) | PED %a |
|------|--------|-----------------|--------|
| 432  | 1      | opb (HN\(_2\)C + HCC RA) (61) |
| 384  | 42     | opb HN\(_2\)C (63) |
| 367  | 18     | opb (HN\(_2\)C + COC) (33) |
| 310  | 10     | opb HN\(_2\)C (25) |

a The vibrational assignments of the compound are given for the lowest energy conformer. The abbreviations are as: IR, IR intensity; \(\nu\), symmetric stretching; \(\nu\) as, asymmetric stretching; \(\omega\), wagging; \(\tau\), twisting; \(\rho\), rocking; \(\sigma\), scissoring; \(\alpha\), in-plan ring deformation; \(\beta\), non-planar ring deformation; ipb, in-plane bending; opb, out-plane bending; sb, symmetric bending; \(\chi\), torsion; R, ring.

Table 3. The observed and Boltzmann-averaged computed \(^1\)H and \(^{13}\)C NMR chemical shifts of the title compound at B3LYP/6-311++G(d,p) level of the theory.

| 13C  | Exp. | Vac. | CHCl\(_3\) | \(^1\)H Exp. | Vac. | CHCl\(_3\) |
|------|------|------|-----------|--------------|------|-----------|
| C1   | 118.7| 125.4| 125.2     | H7           | 7.04 | 7.3       |
| C2   | 119.2| 127.2| 126.7     | H8           | 7.04 | 7.3       |
| C3   | 102.2| 114.1| 115.4     | H9           | 7.27 | 7.3       |
| C4   | 136.9| 143.4| 144.0     | H10          | 7.64 | 7.9       |
| C5   | 127.9| 134.4| 134.8     | H17          | 8.52 | 6.9       |
| C6   | 110.5| 124.6| 124.3     | H18          | 4.27 | 3.7       |
| C11  | 135.3| 137.6| 141.0     | H21          | 2.10 | 2.0       |
| C12  | 28.9 | 30.7 | 30.7      | H22          | 2.31 | 2.3       |
| C13  | 25.1 | 29.9 | 29.7      | H23          | 1.53 | 1.6       |
| C14  | 53.6 | 61.5 | 61.9      | H25          | 2.31 | 2.5       |
| C15  | 121.5| 127.3| 126.7     | H27          | 2.56 | 2.9       |
| C20  | 32.4 | 33.2 | 33.2      | H28          | 2.31 | 2.4       |
| C24  | 44.7 | 50.5 | 51.5      | H29          | 1.78 | 1.6       |
| C26  | 33.2 | 36.6 | 36.7      | H32          | 2.63 | 3.1       |
| C30  | 57.9 | 68.5 | 69.3      | H33          | 2.96 | 3.0       |
| C31  | 106.8| 112.5| 113.1     | H34          | 4.63 | 4.3       |
| C37  | 52.6 | 56.0 | 57.0      | H38          | 3.38 | 3.5       |
| C41  | 53.2 | 56.5 | 57.3      | H39          | 3.38 | 3.4       |
|      |      |      |           | H40          | 3.38 | 3.1       |
|      |      |      |           | H42          | 3.47 | 3.5       |
|      |      |      |           | H43          | 3.47 | 3.5       |
|      |      |      |           | H44          | 3.47 | 3.3       |
|      |      |      |           | H45          | 2.31 | 2.5       |
|      |      |      |           | H46          | 3.01 | 3.2       |

Table 4. The NLO properties for compound (7), at B3LYP/6-311++G(d,p) level in CHCl\(_3\).

|     | I     | II    | III   | IV    | V     | VI    |
|-----|-------|-------|-------|-------|-------|-------|
| \(\mu\) (Debye) |       |       |       |       |       |       |
| \(\mu_x\) | 0.00  | 0.00  | 0.00  | 0.00  | 0.00  | 0.00  |
| \(\mu_y\) | 0.00  | 0.00  | 0.00  | 0.00  | 0.00  | 0.00  |
| \(\mu_z\) | 3.22  | 4.04  | 3.90  | 3.56  | 5.59  | 5.54  |
| \(\mu\)  | 3.22  | 4.04  | 3.90  | 3.56  | 5.59  | 5.54  |
| \(\alpha\), esu (x10\(^{-24}\)) |       |       |       |       |       |       |
| \(\alpha_x\) | 42.91 | 42.80 | 42.78 | 42.74 | 42.85 | 42.77 |
| \(\Delta\alpha\) | 17.56 | 17.39 | 16.83 | 18.89 | 18.66 | 17.64 |
| \(\beta\), esu (x10\(^{-30}\)) |       |       |       |       |       |       |
| \(\beta_x\) | -4.21 | -3.71 | 1.39  | 1.30  | 2.47  | 1.10  |
| \(\beta_y\) | 2.61  | 1.09  | 1.77  | 2.17  | -1.00 | -0.99 |
| \(\beta_z\) | -3.55 | -4.24 | -4.77 | -4.85 | -2.74 | -3.26 |
| \(\beta\)  | 6.09  | 5.74  | 5.28  | 5.47  | 3.82  | 3.58  |

a The abbreviations are as \(\mu\), the static dipole moment; \(\alpha\) the linear polarizability, \(\Delta\alpha\), the anisotropy of the polarizability; \(\beta\), the frequency independent first-order hyperpolarizability according to the x, y, z components of the coordinate system.
2.4. NLO (non-linear optic) analysis

Nowadays, the optical properties of both organic and inorganic compounds [27, 28, 29] have significantly been investigated by the experimental studies supported by the computational tools, because to look for the availability of using in optoelectronic devices. Moreover, it was reported [30] in the molecular systems having the \( \pi \)-electron delocalization based on the molecular geometry could be shown the molecular systems having the same as each other for both phases. Again, the dipole moment value for the lowest energy structure \( \Delta \) in vac. Recently, the electronic chemical potential, and conformers have been determined as follows:

\[ \Delta E: \text{VI}(5.011) > \text{V}(4.961) > \text{IV}(4.972) > \text{III}(4.954) > \text{II}(4.932) \]

\[ \mu: \text{VI}(3.012) > \text{III}(3.029) > \text{IV}(3.043) > \text{II}(3.049) > \text{VI}(3.049) > \text{I}(3.060) \]

\[ \eta: \text{V}(2.505) > \text{VI}(2.505) > \text{IV}(2.486) > \text{I}(2.481) > \text{III}(2.477) > \text{II}(2.466) \]

\[ \omega: \text{I}(1.887) > \text{II}(1.885) > \text{V}(1.862) > \text{VI}(1.855) > \text{III}(1.852) > \text{IV}(1.812) \]

\[ \Delta \alpha: \text{I}(1.236) > \text{II}(1.233) > \text{IV}(1.224) > \text{III}(1.223) > \text{VI}(1.217) > \text{V}(1.203) \]

On the other hand, the reactivity descriptors obtained from the G3D3BJ functional, including the empirical dispersion corrections, can be found in Table S7a. Accordingly, the reactivity parameters have been changed as follows:

\[ \Delta E: \text{V}(4.989) > \text{VI}(4.969) > \text{IV}(4.936) > \text{III}(4.918) > \text{I}(4.902) > \text{II}(4.756) \]

\[ \mu: \text{V}(-2.970) > \text{II}(-2.992) > \text{VI}(-3.007) > \text{III}(-3.012) > \text{IV}(-3.023) \]

\[ \Delta \alpha: \text{I}(-1.036) \]

\[ \eta: \text{V}(2.495) > \text{VI}(2.485) > \text{IV}(2.468) > \text{III}(2.459) > \text{I}(2.451) > \text{II}(2.378) \]

\[ \omega: \text{I}(1.882) > \text{II}(1.880) > \text{IV}(1.851) > \text{III}(1.845) > \text{VI}(1.820) > \text{V}(1.768) \]

\[ \Delta \alpha: \text{I}(1.258) > \text{II}(1.239) > \text{III}(1.225) > \text{IV}(1.225) > \text{VI}(1.210) > \text{V}(1.191) \]

According to B3LYP results, the tendency for the intermolecular interactions is possible than the intramolecular charge transfer for the structure VI because of its highest \( \Delta E \) value, or vice versa for the conformer II. Also, it is clear from Table 5 that the conformer V has the highest electronic chemical potential, and conformer II has the lowest chemical potential. The hardest conformers are estimated as \( \text{VI} \) and \( \text{V} \), while the soft conformer is predicted as the conformer II, by the \( \eta \) values of the conformers. Also, the conformer I has the highest capacity to accept electrons, and the structure \( \text{V} \) has the lowest ability to accept electrons. According to \( \Delta N \) values, \( \text{V} \) has a higher electron transfer capability to a specific molecular system/site, in comparison to the other stable structures. Figure 2 shows the HOMO and LUMO densities for the lowest energy conformer; the frontier molecular orbital densities of the other stable structures.

### Table 5. The quantum chemical reactivity identifiers for the compound (7), at B3LYP/6-311++G(d,p).

| Conformers | I       | II      | III     | IV      | V       | VI      |
|------------|---------|---------|---------|---------|---------|---------|
| **Vacuum** |         |         |         |         |         |         |
| HOMO       | -0.200  | -0.200  | -0.198  | -0.200  | -0.197  | -0.201  |
| LUMO       | -0.018  | -0.019  | -0.016  | -0.016  | -0.015  | -0.017  |
| \( \Delta E \) | 4.941   | 4.926   | 4.957   | 4.981   | 4.956   | 5.019   |
| \( \mu \)  | -2.958  | -2.988  | -2.916  | -2.939  | -2.894  | -2.965  |
| \( \eta \)  | 2.471   | 2.463   | 2.478   | 2.490   | 2.475   | 2.509   |
| \( \omega \) | 1.771   | 1.812   | 1.715   | 1.734   | 1.692   | 1.751   |
| \( \Delta N \) | 1.197   | 1.213   | 1.176   | 1.180   | 1.169   | 1.181   |
| **CHCl₃**  |         |         |         |         |         |         |
| HOMO       | -0.204  | -0.203  | -0.202  | -0.203  | -0.203  | -0.204  |
| LUMO       | -0.021  | -0.021  | -0.020  | -0.020  | -0.019  | -0.020  |
| \( \Delta E \) | 4.961   | 4.932   | 4.954   | 4.972   | 5.009   | 5.011   |
| \( \mu \)  | -3.060  | -3.049  | -3.029  | -3.043  | -3.012  | -3.049  |
| \( \eta \)  | 2.481   | 2.466   | 2.477   | 2.486   | 2.505   | 2.505   |
| \( \omega \) | 1.887   | 1.885   | 1.852   | 1.862   | 1.812   | 1.855   |
| \( \Delta N \) | 1.233   | 1.236   | 1.223   | 1.224   | 1.203   | 1.217   |

*HOMO and LUMO energies, \( \Delta E \), \( \chi \), \( \eta \), \( \omega \) and \( \Delta N \) max are given in eV. Abbreviations are \( \Delta E \), Energy Gap; \( \chi \), electronic chemical potential; \( \eta \), global hardness; \( \omega \), electrophilicity; \( \Delta N \), max. charge transfer capability index.*

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conformers have been given in Figure S5. As known well, the HOMO implies the nucleophile attack site as an electron donor, and LUMO demonstrates the electrophilic attack site as an electron-accepting for the related reactions. Accordingly, the whole indole part and partly the unsaturated rings and oxygen atoms of the compound are responsible for the nucleophilic attack reactions. On the other hand, the indole part of the compound is the only crucial region for the electrophilic attack reaction.

3. Conclusions

In summary, we have completed the synthesis of 2-(2,2-dimethoxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole in 51% overall yields from 3. Further, we have also shown that the tetracyclic 1,5-methanoazocino[4,3-b]indole. The application of this strategy could be other styrchnos alkaloids bearing 1,5-methanoazocino[4,3-b]indole. The observed FT-IR and NMR spectroscopic data were compared with those of the calculated data, and the results for both analyses were found to be quite compatible with each other. After, the six stable conformers of the compound (7) were predicted by PES scan, and their energies obtained from the re-optimization at 6–311++G(d,p) basis set demonstrated that the (I) was the lowest energy structure in CHCl3. The calculated β values of all conformers of the compound (7) revealed that this compound could be a good material to use in the optoelectronic devices because of the β tensors of the six stable conformers were calculated to be greater than that of the urea. Also, the calculated η and μ tensors implied that the conformer II was the soft structure and had the lowest electronic chemical potential value. Besides, the η and AN tensors indicated that conformers I and V were predicted as the best electrophile and the highest electron transfer capability, respectively.

4. Experimental section and computational methods

4.1. General

1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were recorded with a Bruker instrument DPX-400 MHz High-performance Digital FT-NMR Spectrometer in CDCl3andDMSO-d6 as the solvent and with tetramethylsilane (TMS) as the internal Standard at 25 °C. Chemical shifts are expressed in terms of parts per million (ppm), and the δ coupling constants are given in Hz. IR spectra were obtained as KBr pellets using a Mattson 1000 FT-IR spectrometer. The scan range was from 400 to 4000 cm-1, and 128 scans were accumulated to get 4.0 cm1 resolution, and the DTGS KBr detector used to register the FT-IR spectra. Elemental analyses were performed on a Costech ECS 4010 analyzer. Melting points were determined in a capillary tube on a Gallen Kapp apparatus and uncorrected. Reactions were monitored by thin-layer chromatography (silica gel 60 F254). Reagents were obtained from Sigma and used as received and used without further purification.

4.2. Methyl-2(2,3,4,9-1H-carbazol-2-yl)acetate (3)

A mixture of phenylhydrazine hydrochloric acid (1) (2.5 g, 17.28 mmol) and ketone (2, dimethyl (R)-2-(3-oxocyclohexyl)malonate) (3.94 g, 17.28 mmol) in ethanol (100 mL) was heated 12 h under nitrogen atmosphere. After being cooled, the mixture was evaporated in vacuo. The residue was treated with 30 mL of 10% NaHCO3 and extracted with AcOEt. The aqueous layer further extracted with AcOEt. The organic layer was dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel, eluting with methanol n-hexane (1:5) to give 2 (4.9, 95%) as a solid, mp 86–88 °C; IR (KBr); 3371, 2937, 1724 cm-1; 1H NMR (400 MHz, CDCl3) δ 8.25 (s, 1H), 7.42 (d, J = 7.4 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.23–7.13 (m, 2H), 3.68 (s, 3H), 2.91–2.80 (m, 1H), 2.78–2.65 (m, 1H), 2.59–2.48 (m, 1H), 2.43–2.05 (m, 5H), 1.69–1.57 (m, 1H); 13C NMR (100 MHz, CDCl3); δ 174.7, 135.1, 133.8, 127.5, 122.0, 119.3, 118.1, 110.3, 109.5, 52.1, 41.3, 32.7, 28.9, 28.4, 19.7; [Found: C, 74.24; H, 7.19; N, 5.63. C13H15NO2 requires: C, 74.85; H, 6.74; N, 5.76%].

4.3. 2-(2,3,4,9-Tetrahydro-1H-carbazol-2-yl)acetic acid (4)

To a solution ester (2.0 g, 8.22 mmol) was dissolved in THF (10 mL), 20 mL of 20% KOH solution in MeOH-H2O (3:1) was added. The mixture was stirred at rt for 6 h under nitrogen atmosphere. After removal of the solvent, the residue was treated with 40 mL of 10% hydrochloric acid and extracted with AcOEt. The precipitate was filtered, dried and recrystallized from diethyl ether, the carboxylic acid 4 was obtained as a white solid (1.6 g, 88%), mp 204–206 °C; IR (KBr); 3391, 2917, 2833, 1701, 1416, 1344, 1217, 1011, 973 cm-1; 1H NMR (400 MHz, CDCl3) δ 12.21 (bs, 1H), 8.19 (bs, 1H), 7.93 (d, J = 7.3 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.35–7.18 (m, 1H), 2.89–2.87 (m, 1H), 2.83–2.75 (m, 1H), 2.69–2.57 (m, 1H), 2.51–2.39 (m, 4H), 2.37–2.33 (m, 1H), 2.23–2.18 (m, 1H), 1.97–1.88 (m, 1H); 13C NMR (100 MHz, CDCl3); δ 179.2, 136.1, 134.4, 127.2, 122.8, 119.3, 118.6, 111.5, 110.5, 52.3, 41.4, 31.7, 29.4, 28.3, 18.8; [Found: C, 73.42; H, 6.48; N, 6.19. C13H15NO2 requires: C, 73.34; H, 6.59; N, 6.11%].

4.4. N-(2,2-dimethoxyethyl)-2-(2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (5)

Acid 4 (1.5 g, 6.54 mmol) and triethylamine (1.8 mL 13.0 mol) were dissolved in 40 mL absolute chloroform, the reaction mixture was cooled to -10 °C and ethyl chloroformate (1.3 g 12.0 mmol) was dropwise added in to reaction mixture under nitrogen atmosphere. After the mixture was stirred at -10 °C for 4 h, (2,2-dimethoxy)ethylamine (2.2 mL 19.5 mmol) was added into the reaction mixture and the resulting mixture was stirred at -10 °C for 6 h. To the mixture 50 mL of 10% sodium hydroxide (20 mL) and then extracted with chloroform. The organic layer was separated and dried over anhydrous magnesium sulfate and evaporated, which was then purified by silica gel chromatography (EtOAc-acetone, 6:1). The resulting residue was crystallized in diethyl ether, the amide product 5 was obtained as a white solid (1.6 g, 78%), mp 153–154 °C; IR (KBr); 3443, 3231, 2947, 2933, 2861, 1635, 1532, 1461, 1358, 1017, 1019, 729 cm-1; 1H NMR (400 MHz, CDCl3); δ 8.19 (br s, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 7.3 Hz, 1H), 7.19 (td, J = 7.9, 0.8 Hz, 1H), 7.05 (td, J = 7.9, 0.8 Hz, 1H), 5.63 (t, J = 4.6 Hz, 1H), 4.43 (t, J = 5.3 Hz, 1H), 3.59–3.48 (m, 2H), 3.42 (s, 3H), 3.40 (s, 3H), 2.75 (t, J = 6.2 Hz, 2H), 2.51 (dd, J = 15.6, 5.1 Hz, 1H), 2.14 (dd, J = 15.6, 9.3 Hz, 1H), 2.23–2.29 (m, 2H), 2.33–2.26 (2H), 1.87–1.81 (m, 1H); 13C NMR (100 MHz, CDCl3); δ 172.3, 136.9, 134.8, 127.4, 122.6, 119.7, 118.3, 111.7, 111.1, 102.6, 54.6, 54.2, 38.8, 36.3, 32.7, 31.3, 29.5, 21.3; [Found: C, 73.42; H, 6.48; N, 6.19. C18H24N2O3 requires: C, 72.83; H, 6.74; N, 8.85%].
4.5. 2-(2,2-dimethoxyethyl)-1,2,4,5,6,7-hexahydro-1H-1,5-methanoazocino[4,3-b]indol-3-one (6)

Amide (5) (1.0 g, 3.16 mmol) was dissolved in 20 mL absolute THF under nitrogen atmosphere. TCB (0.93 g, 3.79 mmol) was added in one portion and stirred for 7 h at rt under nitrogen atmosphere a poured into a 30 mL of 10% NaOH solution. After the extraction with EtOAc (2 × 50 mL). Combined organic layer were dried over dried over anhydrous magnesium sulfate and evaporated, which was then purified by silica gel chromatography (EtOAc). After removing all volatile components by rotary evaporation. In vacuo, the resulting residue was crystallized in dichloromethane-acetone (9:1), the title compound 6 was obtained as a white solid (1.6 g, 86%), mp 230–232°C; IR (KBr): 3183, 2928, 2831, 1618, 1467, 1412, 1331, 1232, 1152, 755 cm⁻¹; 1H NMR (400 MHz, CDCl3); δ 8.42 (br s 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.18 (td, J = 7.7, 1.0 Hz, 1H), 7.09 (td, J = 7.7, 1.0 Hz, 1H), 4.87 (t, J = 2.4 Hz, 1H), 4.57 (dd, J = 7.5, 3.1 Hz, 1H), 4.23 (dd, J = 14.1, 3.4 Hz, 1H), 3.63–3.55 (m, 1H), 3.51 (s, 3H), 3.44 (s, 3H), 3.37–3.29 (m, 1H), 3.09 (dd, J = 14.1, 7.3 Hz, 1H), 2.91–2.83 (m, 2H), 2.79–2.77 (m, 1H), 2.68–2.64 (m, 1H), 2.41–2.36 (m, 1H); 13C NMR (100 MHz, CDCl3); δ 169.3, 135.9, 132.6, 124.2, 123.0, 121.0, 118.6, 114.5, 114.2, 103.8, 55.6, 54.8, 52.6, 42.4, 40.5, 41.1, 36.4, 32.1.; [Found: C, 68.65; H, 7.11; N, 8.83. C32H22N2O5 requires: C, 68.77; H, 7.05; N, 8.91%].

4.6. 2-(2,2-dimethoxyethyl)-2,3,4,5,6,7-hexahydro-1H-1,5-methanoazocino[4,3-b]indole (7)

To a mixture compound 6 (1.0 g, 3.18 mmol) and 0.36 g (0.4 mmol) diphényl silane was added under nitrogen atmosphere. The mixture was stirred at rt for 8 h. After completion reaction, the mixture was diluted with diethyl ether. After the extraction with 1H HCl aq. The aqueous layer was basified with 10% NaOH aq and extracted with EtOAc (2 × 20 mL). The organic layer was separated and dried over anhydrous magnesium sulfate and evaporated, which was then purified by silica gel chromatography (EtOAc). The resulting residue was crystallized in petroleum ether, the amine product 7 was obtained as a white solid (0.86 g, 91%), mp 141–143°C; IR (KBr): ν 3395, 3291, 3054, 2928, 2831, 1618, 1581, 1467, 1423, 1368, 1331, 1232, 1152, 1127, 1107, 1012, 1002, 965, 930, 900 cm⁻¹; 1H NMR (400 MHz, CDCl3); δ 8.82 (s, 1H), 7.64 (dd, J = 6.4 and 2.2 Hz, 1H), 7.27 (dd, J = 6.6, 1.3 Hz, 1H), 7.04 (m, 2H), 4.63 (t, J = 5.4 Hz, 1H), 4.27 (m, 1H), 3.47 (s, 3H), 3.38 (s, 3H), 3.01 (dd, J = 17.3, 6.7 Hz, 1H), 2.96 (dd, J = 12.8, 5.6 Hz, 1H), 2.63 (dd, J = 11.3, 4.3 Hz, 1H), 2.56 (d, J = 16.9 Hz, 1H), 2.44–2.18 (m, 1H), 2.1 (m, 1H), 1.78 (m, J = 12.3 Hz, 1H), 1.53 (m, J = 12.3 Hz, 1H); 13C NMR (100 MHz, CDCl3); δ 136.9, 135.3, 127.9, 121.5, 119.2, 118.7, 110.5, 106.8, 102.2, 57.9, 53.6, 53.2, 52.6, 44.7, 33.2, 32.4, 28.9, 25.1; [Found: C, 71.85; H, 8.12; N, 9.41. C34H22N2O5 requires: C, 71.97; H, 8.05; N, 9.33%]

4.7. Computational and theoretical methods

All quantum chemical calculations were performed by G09W [35] package by using the DFT method. First, the stable conformers of the final production (6) of the synthesis process of this work were predicted by PES (potential energy surface) scan by the B3LYP level [36,37] in the vacuum (vac.). For this purpose, each torsion angle of χ1 (C14–N19–C30–C31), χ2 (C24–N19–C30–C31), χ3 (N19–C30–C31–O35), χ4 (N19–C30–C31–O36), χ5 (C30–C31–O36–C41), χ6 (C30–C31–O35–C37) were changed within intervals of 10° in 36 steps, according to the rotation of the methoxy and dimethoxy ethyl groups over the rings. Then, the six stable conformers of the title compound were used for further calculations of this study. Next, the total and relative energetic parameters were obtained from the frequency calculations in the vacuum and CHCl3 phases. Besides, the calculated vibrational frequencies of the lowest energy conformer were assigned by the VEDA package [38] via the PED (potential energy distribution) analysis and compared with the observed values of the title compound. The NMR chemical shifts were calculated by GIAO (Gauge-Independent Atomic Orbital) [39,40] approach by subtracting the shielding constants of TMS. In this step, the averaged NMR chemical shifts of the title compound have been calculated by using the Boltzman statistics [41]. The NLO analysis was performed to predict the nonlinear optical behavior of the compound, and the static dipole moment (μ), the mean polarizability (α), the anisotropy of the polarizability (Δα), the frequency independent first-order hyperpolarizability (β) tensors [42,43] of all conformers were calculated from the equations given below

\[ \mu = \left( \mu_x^2 + \mu_y^2 + \mu_z^2 \right)^{1/2} \]

\[ \alpha_i = \frac{(\alpha_{xx} + \alpha_{yy} + \alpha_{zz})}{3} \]

\[ \Delta \alpha = 2^{1/2} \left( (\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{yy} - \alpha_{zz})^2 + (\alpha_{zz} - \alpha_{xx})^2 + 6(\alpha_{xx}^2 + \alpha_{yy}^2 + \alpha_{zz}^2) \right)^{1/2} \]

\[ \beta = \left( \beta_x^2 + \beta_y^2 + \beta_z^2 \right)^{1/2} \]

where,

\[ \beta_x = (\beta_{xx} + \beta_{yy} + \beta_{zz}) \]

\[ \beta_y = (\beta_{xy} + \beta_{yx} + \beta_{yy}) \]

\[ \beta_z = (\beta_{zx} + \beta_{xz} + \beta_{zz}) \]

Also, the DFT-based reactivity tensors, which are the ionization energy (I), electron affinity (A) [44], electronic chemical potential (γ), global hardness (η), electrophilicity (ω) and the maximum charge transfer index (ΔNmax) [45, 46, 47], were calculated with the equations given below

\[ I = - \text{EHOMO} \]

\[ A = - \text{ELUMO} \]

\[ \chi = \frac{I + A}{2} \]

\[ \eta = \frac{I - A}{2} \]

\[ \omega = \frac{\mu^2}{2\eta} \]

\[ \Delta N_{max} = \frac{I + A}{2(I - A)} \]

Also, the geometry optimizations, frequency calculations, and FMO analysis for each conformer have been repeated by using the B3LYP-GD3BJ functional, including the empirical dispersion corrections [48]. PCM (polarized continuum model) was used for all calculations conducted in CHCl3 [49, 50].

Declarations

Author contribution statement

Nesimi Uludag: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Goncağül Serdaroglu: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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