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SPECTROSCOPIC STUDY OF 1, 3-DIPOLAR CYCLOADDITION REACTION OF BENZYL AZIDE AND ACRYLIC ACID

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ABSTRACT

The 1,3-dipolar cycloaddition reaction of benzyl azide with acrylic acid has been studied using B3LYP (3-21G) density functional theory (DFT). It has been demonstrated that the reaction leads to the formation of 1-benzyl-1,2,3-triazoline-4-carboxylic acid at room temperature in the absence of solvent. Upon recrystallization from ethanol the ethyl ester of the product was formed. The structure of the compound was confirmed using IR, UV, ^{1}H NMR, ^{13}C NMR and 2D-NMR. The structure of the other possible isomer has been proposed and both isomers have been studied using Gaussian 03 to predict the possibility of their formation and to calculate the vibrational frequencies and related electronic properties. It has been found that the 1,3-dipolar cycloaddition reaction of benzyl azide with acrylic acid is highly regioselective and spontaneous at 25.15^{o}C and 1 atm.

Key words: 1,3-Dipolar cycloaddition, Activation energy, Benzyl azide, Acrylic acid.

INTRODUCTION

Azides are considered very important compounds due to their industrial and biological applications[1]. Azide derivatives have been used in rubber vulcanization, polymer cross linking, dyes, tyre cord adhesives, foaming of plastics, pharmaceuticals, pesticides and herbicides[1]. One of the most useful synthetic applications of azides is the preparation of 1,2,3-triazoles via 1,3-dipolar cycloaddition. 1,2,3-triazoles are an important class of heterocycles due to their importance as synthetic intermediates and pharmaceuticals[2]. Several therapeutically interesting 1,2,3-triazoles, including anti-HIV agents[3-6], antimicrobial compounds[7], β3-selective adrenergic receptor agonists[8], kinase inhibitors[9,10] and other enzyme inhibitors[11,12] have been reported. The 1,2,3-triazole moiety is also present in a number of drugs, for example, the β-lactam antibiotic tazobactam[13] and cephalosporin

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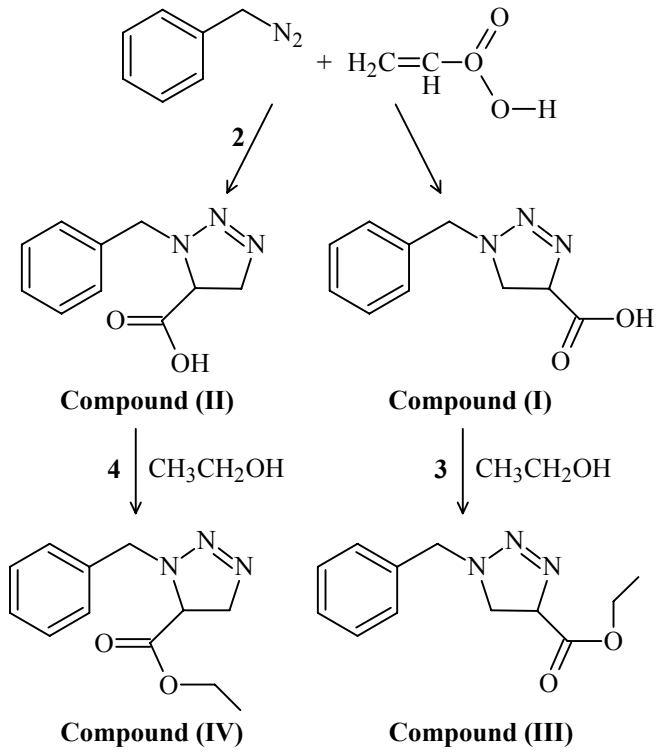
cefatrizine[14]. However, few reports were issued on calculational studies of 1,2,3-triazoles, although the B3LYP/6-31G method has been used to complete the structure of 4-phenyl and 5-phenyl-1,2,3-triazoles acting as dienes toward DMAD in microwave-assisted solvent-free Diels–Alder cycloadditions[15].

Density functional theory has been used to determine the transition states and activation barriers of the 1,3-dipolar cycloadditions of azides with cycloalkynes and cycloalkenes. Exploration of reactions of azide and cyclooctyne showed that fluorine substitution was the most effective in lowering the activation energy for cycloaddition. The activation energy of azide cycloadditions to cycloalkynes decreases considerably as the ring size decreases and is lower compared to that of cycloalkene-Dipolarophiles[16]. The aim of this work is to study the reaction of benzyl azide with acrylic acid and to correlate the theoretical findings with the experimental results.

RESULTS AND DISCUSSION

Preparation



Scheme 1: Reaction of benzyl azides with acrylic acid

Benzyl azide **I** was prepared according to the procedure described in literature[17,18]. Compound **III** was prepared by mixing benzyl azide and acrylic acid without solvent and stirring at room temperature (Scheme 1).

The crude solid product was washed with water to remove any unreacted acid followed by extraction with chloroform. The solvent was removed under reduced pressure and the residue obtained was triturated with acetone. The product was recrystallized from ethanol to give compound **III** (yield 46%, melting point = 165-167^{o}C).

The IR spectrum of compound **III** (Fig. 1) shows an absorption band at 1655 cm^{-1} due to C=O group and bands at 3249, 1598, 1425, 1369 and 755 cm^{-1}, which are characteristic of the C=O harmonic, C=C, N=N, C-O-C and aromatic CH groups, respectively. These vibrational frequencies are in agreement with the calculated values as shown in Table 2.

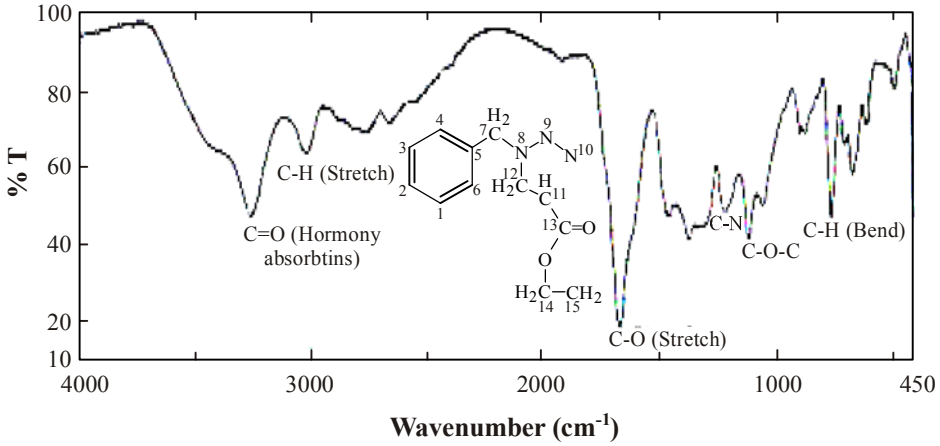


Fig. 1: IR spectrum of compound III

The ^{1}H NMR spectrum of compound **III** (Fig. 2) showed one methyl group as a triplet at δ 2.38 ppm, a doublet at δ 2.71 ppm, a singlet at δ 2.75 ppm and a quartet at δ 3.72 ppm for the three methylene groups at positions 12, 7 and 14, respectively. The methane proton appeared as triplet at δ 4.14 ppm and the aromatic protons showed a multiplet at δ 7.20-7.42 ppm.

The ^{13}C NMR spectrum of Compound **III** (Fig. 3) showed 10 signals; that were further assigned by a DEPT-135 experiment (Fig. 4) into one primaryl carbon at δ 31 ppm,

three secondary carbons at δ 49.40, 56.83 and 58.27 ppm corresponding to C-7, C-14, C-12 respectively, two quaternary carbons at δ 139.17 and 174 ppm for C-5, C-13 and 4 tertiary carbons. Four of the ^{13}C signals correspond to the mono substituted aromatic moiety. The COSY spectrum (Fig. 5) showed cross-peaks between protons on C-15 with protons on C-14 and the proton on C-11 with protons on C-12.

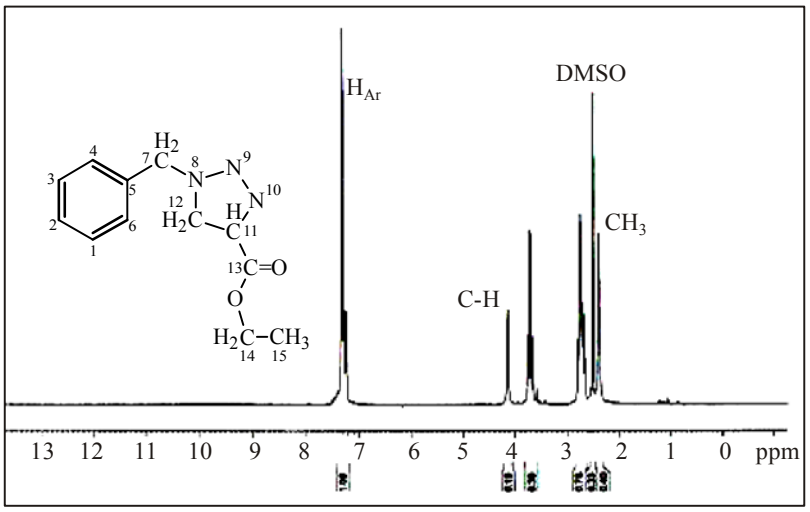


Fig. 2: ^{1}H NMR spectrum of Compound III

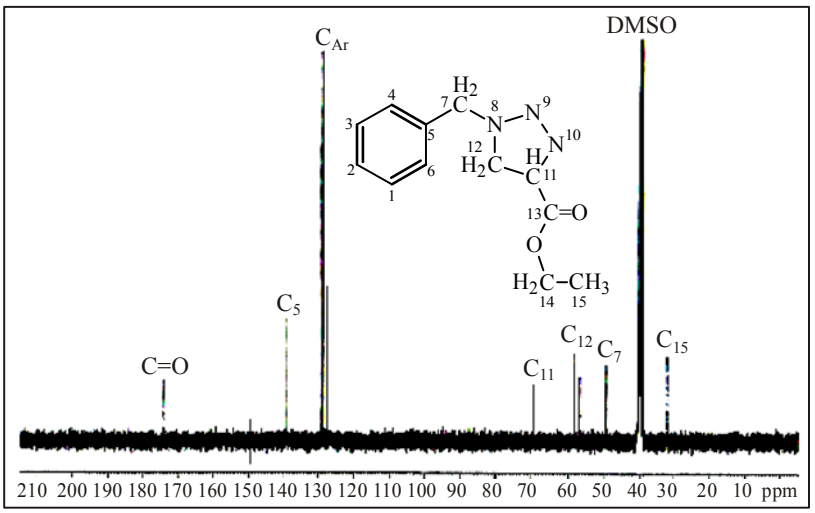


Fig. 3: ^{13}C NMR spectrum of Compound III

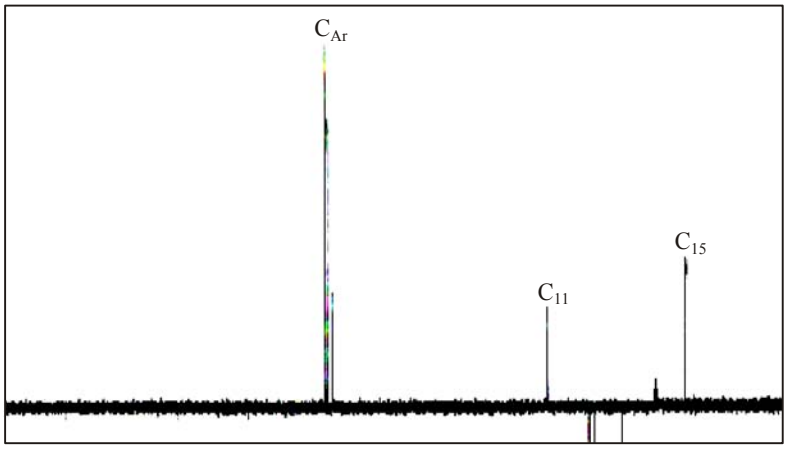


Fig. 4: DEPT 135 spectrum of Compound III

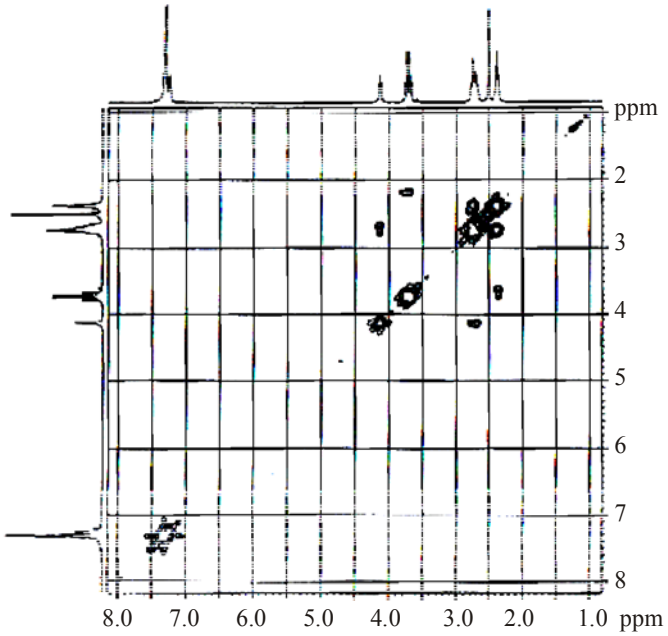


Fig. 5: COSY spectrum of Compound III

Computational methods

Gaussian 03 / DFT = B3LYP / (3-21G*)[19-22] was used to calculate the structural properties, electronic spectra and IR frequencies of the products of the title reaction (Scheme 1). The energy of orbitals (**εHOMO** and **εLUMO**), electronic energy ($\mathbf{E_{elec}}$), activation energy ($\mathbf{E_b}$) and energy of reaction ($\mathbf{\Delta E_R}$) were calculated and are listed in Table 1.

Table 1: Energy of orbital (εHOMO and εLUMO), energy of reaction (ΔE_R), bonding energy (E_b) and electronic energy (E_{elec}) of products I and II in gaseous state at (T = 25°C)

E_{elec} (eV)	E_b (eV)	ΔE_R (eV)	εHOMO (eV)	εLUMO (eV)	Molecular formula	Compounds
-18986.8960	-117.7380	-1.2700	-6.7891	-1.3899	$C_{10}H_{11}O_2N_3$	I
-18986.8190	-117.6606	-1.1930	-6.5498	-1.2267	$C_{10}H_{11}O_2N_3$	II

The activation energy and energy of reaction were calculated from Eq. 1 and 2.

$$E_b\,(M) = E_{elec}\,(M) - \Sigma\, E_{elec}\,(A) \qquad ...(1)$$

$$\Delta E_R = E_b\,(\text{Products}) - \Sigma E_b\,(\text{Reactives}) \qquad ...(2)$$

Based on the values of energies in the Table 1, compound **I** is more stable than **II** since the bonding energy of compound **I** is – 117.74 eV, while that of compound **II** is – 117.66 eV, and reaction pathway 1 with the reaction energy – 1.270 eV is more favored than compound **II** whose reaction energy is – 1.19 eV. Therefore compound **I** was considered the product of the reaction and its ester **III** was the isolated product. Figure 6, shows the fully optimized structure of compound **I**, along with the distribution of partial charges and bond lengths (A).

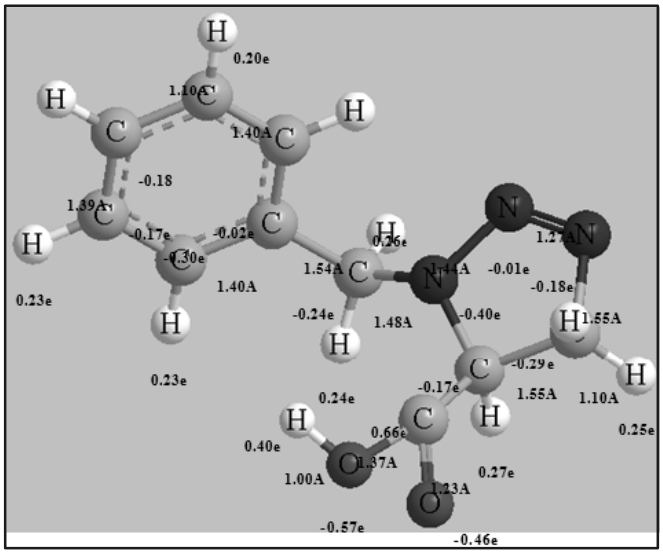


Fig. 6: Fully optimized structure of Compound I

The infrared spectrum of this compound was calculated from the fully optimized structure of compound **I** (Fig. 7).

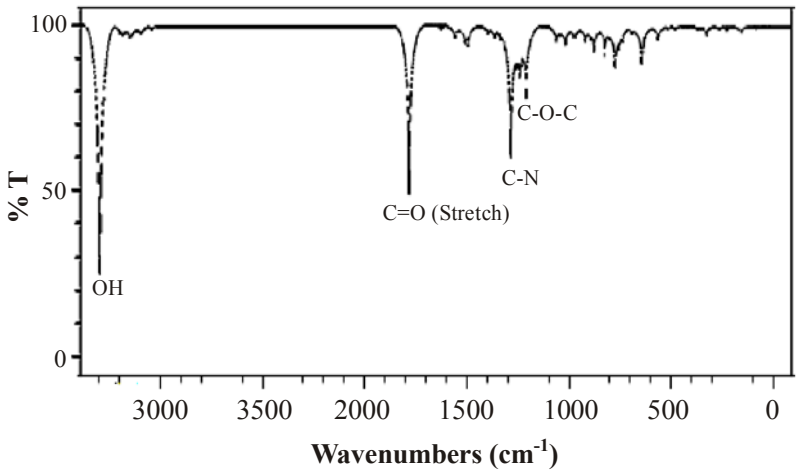


Fig. 7: Theoretically derived IR spectrum of compound I

The possibility of esterification of compound **I** in ethanol is studied as shown in Scheme 1, path 3. Figure 8 shows the fully optimized structure of compound **III**, distribution of partial charges and bond lengths (A).

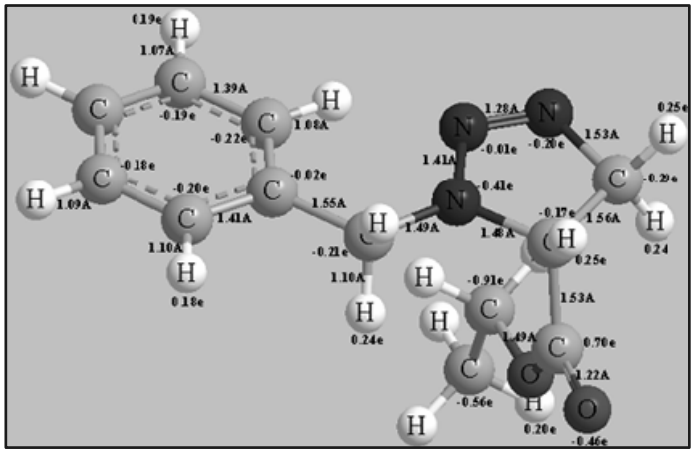


Fig. 8: Fully optimized structure of compound III

From the fully optimized structure of compound **III** the harmonic vibrations are calculated with the conclusion that the infrared spectrum of compound **III** is similar to that depicted in Fig. 9.

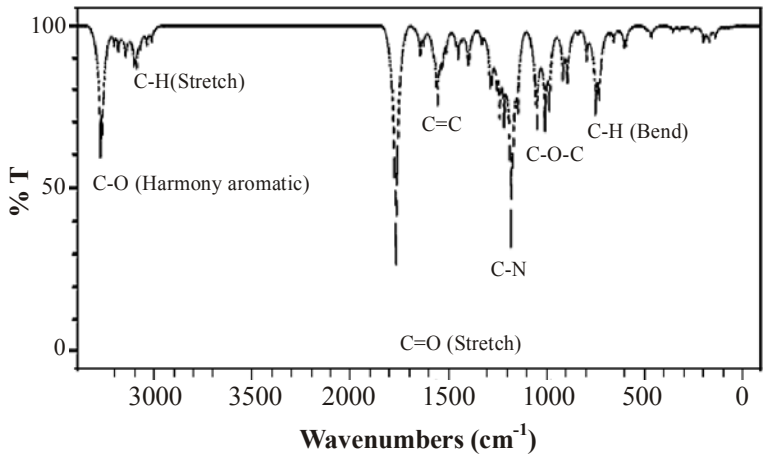


Fig. 9: Theoretically derived IR spectrum of Compound III

Comparing the experimental and calculated values of the infrared spectrum absorption frequencies of compound **III** shows a good agreement as displayed in Table 2.

Table 2: Wave number (cm^{-1}) of the functional groups of Compound III

Wave number (cm^{-1})		Functional group
Computational	Experimental	
3267	3249	C=O (Harmonic)
3021	3007	C-H (Stretch aromatic)
1647	1655	C=O (Stretch)
1580	1598	C=C
1433	1452	N=N
1370	1369	CH_3
1237	1218	C-N
1070	1058	C-O-C
748	755	C-H (Bend)

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