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Synthesis and physical properties of methyl glycoside linked to triazole surfactants

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Abstracts

New heterocyclic compounds containing methyl glycoside were synthesized from available and renewable starting materials through click chemistry coupling. The row materials for this synthesis are methyl glycoside, both saturated (C12) and unsaturated (C18) fatty acids. The aim from this synthesis focus on synthesis of new water-in- oil emulsifier. Multi-step synthetic strategy was applied in this methodology, including activation of hydroxyl group at C6 of the methyl glycoside, functionalization of the activated atom and finally coupling with fatty acids derivatives by using click chemistry technique. The target compounds were identified and their purity confirmed by NMR type ^{1}H and ^{13}C in addition to high resolution mass spectroscopy. Lyotropic phases were investigated by Optical Polarizing Microscopy (OPM) contact penetration with water, Differential Scanning Calorimetry (DSC) was used to used to study the physical properties of the synthesized compounds . While the DuNouy ring approach measured the surface tension. The latter enables the determination of critical micelle concentrations

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Keywords: Triazole heterocyclic, surfactants, click chemistry, emulsifier, surface active agent

1.Introduction

A lot of natural raw materials available all over the world, the availability of these materials with the possibility of the chemical processes open the sky to develop many biodegradable products. Nowadays demands on biodegradable products increased in amounts due to the large number population and the excess of natural material resources, which driving forces for surfactants technology. Unfortunately recently most surfactants are depending on petrochemical material[1]. Environmental issues and availability of petrochemicals , which is expected to decrease by the years, cause continuous shift of chemical developments towards the utilization of renewable biological natural recourses in order to ensure sustainable raw materials. The development of bioactive products from available raw material such as carbohydrates and their derivatives with fatty acids is consider to be a good strategy for the exclusive utilization of natural renewable resources. Sugar surfactant may be synthesis based on the chemical linkage of the two starting materials to form the amphophilic structure of the surfactant. Surfactants of carbohydrate moiety with ester linkage exhibit surface active properties, biodegradable and expected to show low human toxicity based on the natural components and chemical linkages. The glycosides are the most chemical resistant but expensive compared to sugar esters, which are significantly less stable. Carbohydrate with amide surfactants are reasonable chemically stable and economic but unfortunately exhibit high krafft temperature. There is another accessible technique to connect the carbohydrates moiety with the long alkyl chain by 1,2,3 triazole ring which expects to keep the stability of the surfactants with reduce the krafft temperature. The synthesized carbohydrates surfactant based on click chemistry show reasonable physicochemical properties and expected to be good surfactants. Methyl glycoside was chosen as starting material for this surfactants for two reasons: first because of economy and accessibility and second based on its chemical stability as glycoside with reduce hydrophilicity compare to hexoses because of the lower number of the hydroxyl groups, which potentially increase the surfactant's solubility in an oil-based medium.

2. Experimental Part

2.1. General procedures

Melting points were measured by a manual melting point apparatus. Optical rotations were measured at 589 nm in 10 cm cells at room temperature. NMR spectra were recorded on Jeol and Bruker spectrometers at 400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively. Assignments of ^{13}C-signals are based on HMQC spectra. High-resolution mass spectra were recorded on an LC–MS system, applying MeOH/water eluents. Phase-transition temperatures were determined by DSC in replicated heating–cooling cycles at a heating/cooling rate of 10 °C min^{-1}. Lyotropic phases were investigated using the contact penetration technique under OPM observation[13,14]. The determination of Krafft points applied heating 20 mL samples of the surfactant in water at a concentration of about 10% above the CMC in an oil bath under moderate stirring until the mixture re cleared. Critical micelle concentrations were determined by surface tension measurements. Surface tension measurements were measured at room temperature in 5 replicates with a standard deviation below 0.1 mN m^{-1}.The intersection of the concentration dependent and the high concentration independent region in the plot of the surface tension versus the logarithmic concentration determines the CMC.

2.2. Activation of methyl glycoside.

A solution of methyl α-D-glucopyranoside (1.0 eq.), triphenylphosphine (2.0 eq) and N-chlorosuccinimide (2.0 eq.) in dry *N*,*N*-dimethylformamide (20 mL per gram) was heated to 60 ^{o}C with stirring for about 2 hours. When the TLC (ethyl acetate:hexane 4:1) showed the consumption of the starting material the solution was cooled and 10

ml of methanol was added in order to decompose unreacted chlorinating agent (NCS). *N*,*N*-dimethylformamide was evaporated and triphenylphosphine oxide was removed by added water and extraction with dichloromethane. The filtrate was evaporated to yield methyl 6-chloro-6-deoxy-α-D- glucopyranoside, which subjected to azidation without further purification[15, 16]

2.3. Functionalization of C6.

A suspension of chloro deoxy sugar (1.0 eq.) And sodium azide NaN3 (6.0 eq) in N, N- dimethylformamide DMF (20 ml per gram) was heated to 80 ºC for 24 hours. The solution was cooled to room temperature, diluted with water and extracted with dichloromethane. Theorganic layer was washed with water, saturated $NaHCO_3$ solution and water, dried over $MgSO_4$ and concentrated under reduced pressure. After acetylation with acetic anhydride (2.0 eq.) in pyridine (20 mL per gram) and recrystallization with ethanol NMR pure white azide was obtained in very good yield[17, 18].

2.4. Esterification

Fatty acid (1.0 eq.) was refluxed with (1.2 eq.) of propargyl alcohol and catalytic amount of p-toluene sulfonic acid in toluene at about 100 °C for about 6h. The mixture was cooled down to room temperature and extracted two times with saturated $NaHCO_3$ solution and water to get NMR pure fatty acid ester in very good yield[19, 20.]

2.5. Coupling by Click chemistry

A solution of the sugar azide (1 equiv) was stirred with propargyl alcohol (1.1 equiv), (0.01equiv) and 1 copper chloride and sodium ascorbate (0.1 equiv) in methanol until TLC showed no traces of the starting sugar azide. Filtrate the reaction mixture through ciliate and concentrated under reduced pressure, the residue was purified through silica gel with 9:1 chloroform: methanol as eluent to result the final surfactant[21, 22,23].

2.5.1. Synthesis of [1-(Methyl 6-deoxy- α -D-glucopyranosid-6-yl)-1H-1,2,3- triazol-4-yl]-methyl dodecanoate [7]

Methyl glycoside 6-azide (2 g, 0.01 mmol) was reacted with propargyl dodecanoate according the general procedures (2.5) to furnished (2g, 78%) of surfactant **[6]** as NMR pure white crystals. mp 107 °C. [α]D25= + 65 (c 0.2, CH3OH). 1H NMR (400 MHz,CD3OD) , 8.0 (s. 1H, CH=C triazol), 5.20 (s, 1H, CH2-O) , 4.64 (d,1H, H-1), 4.55 (ddd,1H, H-6A), 3.85 (ddd, H-5), 3.62 (dd~t, H-3), 3.32 (s, 3H, Me), 3.32-3.33 (ddd~dt, H-6B), 3.11-3.16 (m,2H, H-4 and H-2), 2.31 (t, 2H, α-CH2), 1.60 (mc, 2H, β-CH2), 1.30 (mc, 16H, bulk-CH2), 0.91 (t, 3H, CH3; 3J1,2=3.5, 3J2,3=10.0, 3J3,4=9.5, 3J4,5=9.0, 3J5,6A=2.0, 3J5,6B=7.0, 2J6= 14.0, . 13C NMR (100 MHz , CD3OD) 173.62 (C=O) , 142.6 (*C*-quat triazol), 125.88 (N-*C*=C triazol), 100 (C-1), 73.56 (C-2), 72.02 (C-3), 71.62 (C-5), 70.40 (C-4), 56.70 (CH3), 54.20 (C-6),51.15 (C-O), 33.50 (α-CH2), 31.74 (ω -2), 29.93-28.80 (bulk-CH2), 24.62 (β-CH2), 22.40 (ω -1), 13.12 (ω). HRMS: [M+H]+ calcd for C22H40N3O7: 458,2860,459.2893 (26%), found: 458.2857 (100%), 459.2890 (30%).

2.5.2. Synthesis of [1-(Methyl 6-deoxy- α -D-glucopyranosid-6-yl)-1H-1,2,3-triazol-4-yl]-methyl oleate [8]

Methyl glycoside 6-azide (2 g, 0.01 mmol) was reacted with propargyl oleate according the general procedures (2.5) to furnished (4g, 74%) of surfactant [7] as NMR pure white crystals. mp 111 °C. [α]D25= + 90 (c 0.2,CH3OH). 1H NMR (400 MHz,CD3OD), 8.0 (s. 1H, CH=C triazol), 5.20 (s, 1H, CH2-O) ,4.85 (mc, 2H, C*H*=C*H*),4.62 (d,1H, H-1),4.50 (ddd,1H, H-6A), 3.82 (ddd, H-5), 3.61 (dd~t, H-3), 3.37 (ddd~dt, H-6B), 3.30 (m,2H, H-4 ,3.15 (ddd, 1H, H-2), 3.11 (s, 3H, Me), 2.30 (t, 2H, α-CH2), 1.89 (mc , 4H, C*H2*-CH=CHC*H2*), 1.60 (mc, 2H, β-CH2), 1.26 (mc, 16H, bulk-

CH2), 0.88 (t, 3H, CH3; 3J1,2=3.5, 3J2,3=10.5, 3J3,4=9.0, 3J4,5=9.0, 3J5,6A=3.0, 3J5,6B=6.5, 2J6= 14.5, . 13C NMR (100 MHz , CD3OD) 173.71 (C=O) , 143.13 (*C*-quat triazol),129.10 ,129.78 (C=C), 125.73 (N-*C*=C triazol), 100 (C-1), 74.26 (C-2), 72.10 (C-3), 70.68 (C-5), 69.90 (C-4), 57.43 (CH3), 55.60 (C-6),50.89 (C-O), 34.19 (α-CH2), 31.98 (ω -2), 29.84-27.30 (bulk-CH2), 24.90 (β-CH2), 22.76 (ω -1), 14.19 (ω). HRMS: [M+H]+ calcd for C28H50N3O7: 540,3643,541.3676 (33%), found: 540.3646 (100%), 541.3679 (29%).

3. Results and discussion

3.1. Synthesis

Figure 1 show the methodology used in this synthesis of methyl glycoside surfactant by multistep synthesis.

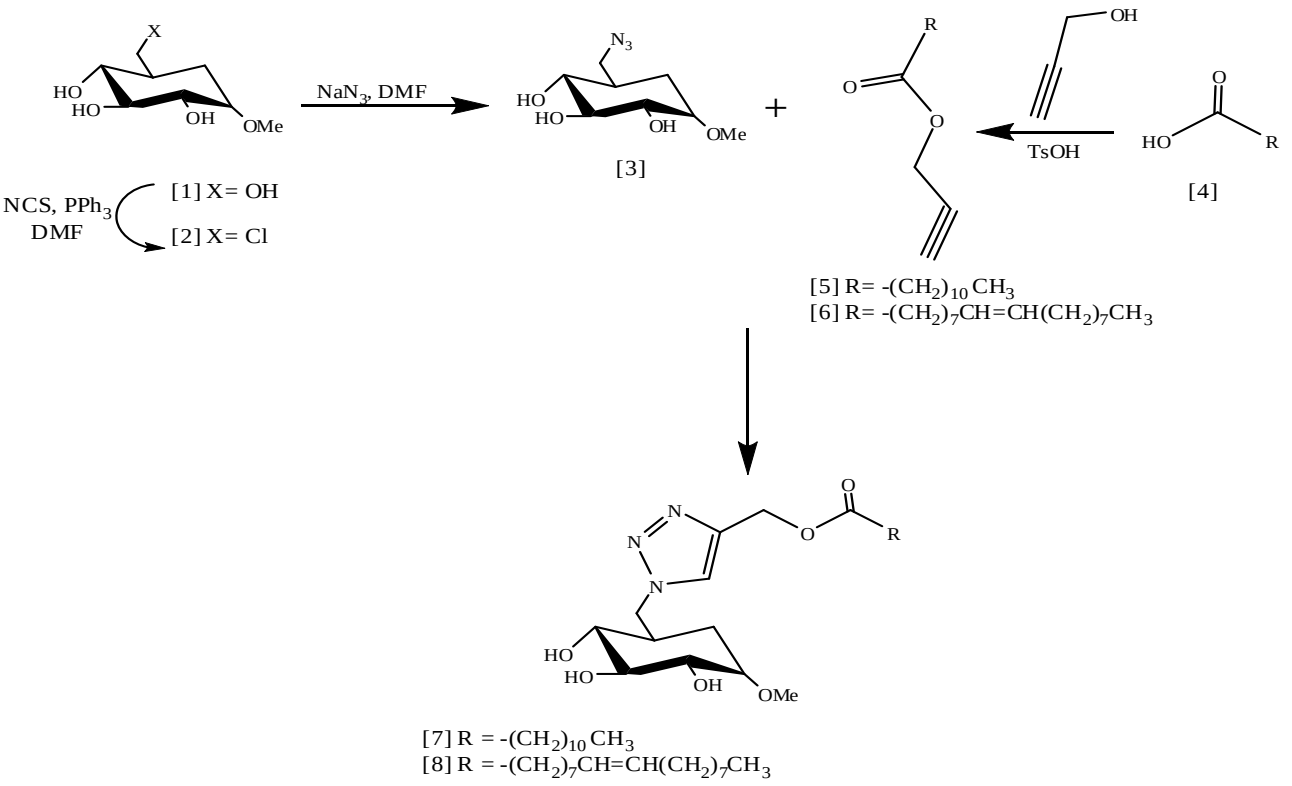

Figure 1: General scheme of methyl glycoside tiazole derivatives synthesis

The synthesis scheme of the target derivatives is started with methyl 6-azido-6-deoxy–α-D-glucopyranoside [3], which had been reported previously by Hanssian et al in a one flask reaction[2]. The methyl glucoside **[1]** has only a unique primary hydroxyl group which easily and directly chlorinated with *N*-chlorosccuinimde in DMF in the presence of triphenylphosphine. This reaction need anhydrous conditions and furnishes methyl-6-deoxy-6-chloro-α-D-glucopyranoside [**2]** in good yield [3-5]. The halogen was replaced by sodium azide after the excess of chlorination reagent was damaged by addition of methanol. As long as the reaction medium still the same there is no need for solvent exchange to get compound **[3]**[6,7].Click coupling chemistry based on azide **[3]** with two fatty acid propargyl C12 and C18 was performed[8,9]. Saturated propargyl laurate **[5]** and Unsaturated propargyl oleate **[6**] was applied. The latter is easily accessible by simple treatment of lauric acid and oleic acid with propagyl alcohol under acidic conditions respectively. The click chemistry coupling used copper acetate Cu(OAc)2 and sodium ascorbate C6H7NaO6 in methanol to offer compounds **[7]** and **[8][10].** The final target compounds were spectroscopically

analyzed, the chemical structural and purity identities are based on NMR spectra (H1 & C13) and high resolution mass spectrometry. ^{1}H NMR for compound **[7]** (figure.2) shows the proton signal of the triazol ring at δ 8.04, singlet of (CH2-O) at δ 5.20, the anomeric signal (H-1) appears around δ 4.64, while the sugar protons (H-2 to H-5) are located between δ 3.85 and δ 3.14. The primary CH2 (H-6a/b) appears between δ 4.53 and δ 3.34 and the methyl group at about δ 3.24. The protons of the alkyl chain appear between δ 2.31 (α-CH2) and δ 0.91 (terminal CH3).

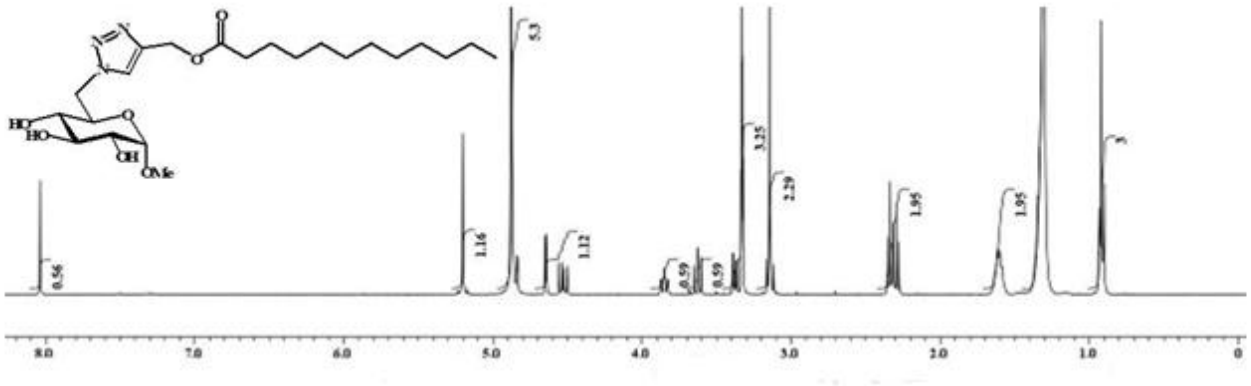

Figure 2: H[1] NMR for [1-(Methyl 6-deoxy- α -D-glucopyranosid-6-yl)-1H-1,2,3- triazol-4-yl]-methyl dodecanoate [7]

The 13C NMR (figure.3) for compound [7] show the signal of the carbon of (C=O) at δ 173.62, (C-N) at about δ 142.64, (C=C) of the triazol ring at about δ125.88, the carbon of (C-O) at δ51.15, the anomeric carbon at around δ 100. Other sugar carbons appear between δ 72 and δ 70.50. The position of the primary carbon (C-6) is around δ40, while the methyl group is found at δ 54. The alkyl chain carbons appear in between δ 35 (α-CH2) and δ 14 (CH3).

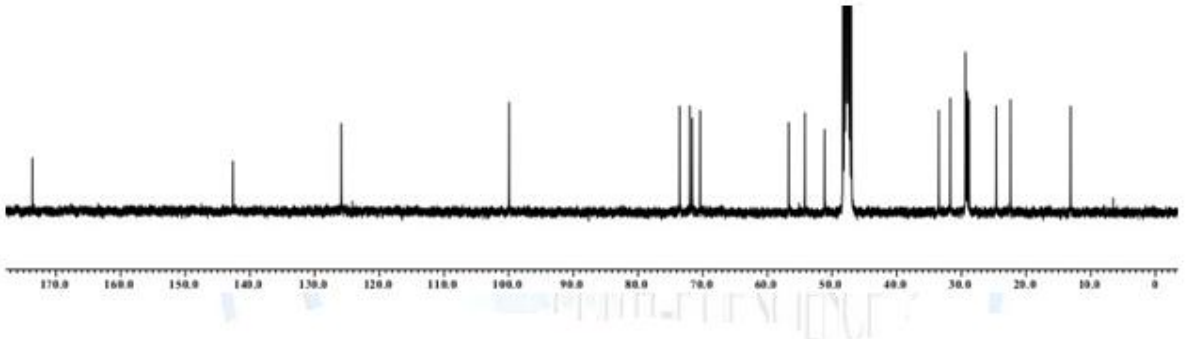

Figure 3: C[13] NMR for [1-(Methyl 6-deoxy- α -D-glucopyranosid-6-yl)-1H-1,2,3- triazol-4-yl]-methyl dodecanoate [7]

Both H1 NMR and C13 NMR for surfactants **[8**] show approximately the same chemical shift in addition to the signal of (CH=CH) at δ 5.35 and the signal of (C*H2*-CH) at δ 2.0. The structures of the synthesized surfactants were confirmed by the high resolution mass spectrum, which shows [M+H] + fractions and their isotopes for details see the experimental data.

3.2. Physical properties

The methyl glycoside containing triazol surfactants exhibit low solubility in water at room temperature, the kraffit temperature for surfactant **[7]** is (45 °C), which is consider be reasonable compare to the high krafft temperature of compound **[8]** which is reach to (100 °C) **.** No liquid crystals phase shown in the Optical Polarizing Microscopy OPM

investigation for both surfactants. Non surfactants show a liquid crystals phase in OPM investigations, while but both surfactants exhibit a crystalline phase (figure 4) and isotropic liquid. In contact with water myelin figure were found (figure 5).

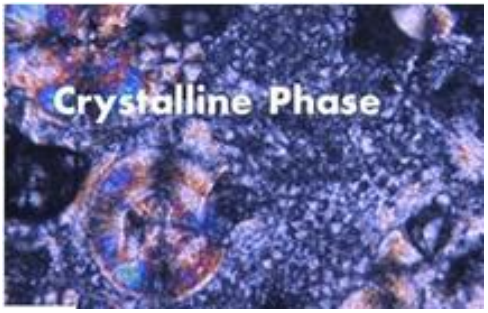

Figure 4: Isotropic phase for [1-(Methyl 6-deoxy- α -D-glucopyranosid-6-yl)-1H-1,2,3-triazol-4-yl]-methyl oleate [8]

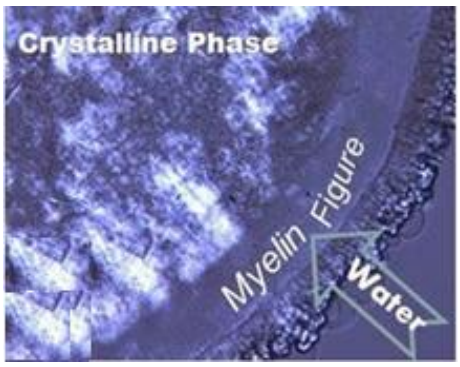

Figure 5: Compound [8] in contact with water

The differential scanning calorimetry (DSC) confirm the absence of thermotropic liquid crystalline of methyl glycoside triazol surfactants Which show only single phase with an enthalpy that is outside the range of liquid crystalline phase termination (28 kg/mol for C12 and 38 kg/mol for C18). The DSC spectrum of **[8] (**figure 4) shows only one phase transition at 110 ºC for both heating and cooling cycle, which is refers to the melting and recrystallization of a crystalline phase.

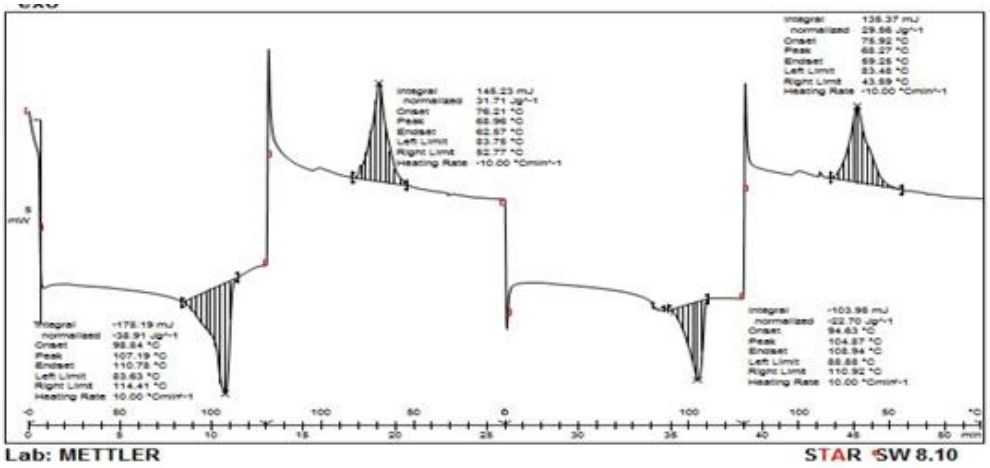

Figure 6: DSC spectrum for [1-(Methyl 6-deoxy- α -D-glucopyranosid-6-yl)-1H-1,2,3-triazol-4-yl]-methyl oleate [8]

The critical micelle concentrations (CMC) were determined based the DuNouy ring approach measurements of the surface tension which was carried out for the series of surfactant [7] solutions with different concentrations[11]. The

critical micelle concentrations CMC investigation was limited to the C12 surfactants as the longer surfactant [8] is extremely difficult to measure, due to the high Krafft temperature. The surface tensions and CMC for C12 surfactants are 30 mN/m at CMC 0.5 mmol/L (figure 5), which is in good agreement with previously reported monosaccharide linked to the same number of carbon atoms chain12.

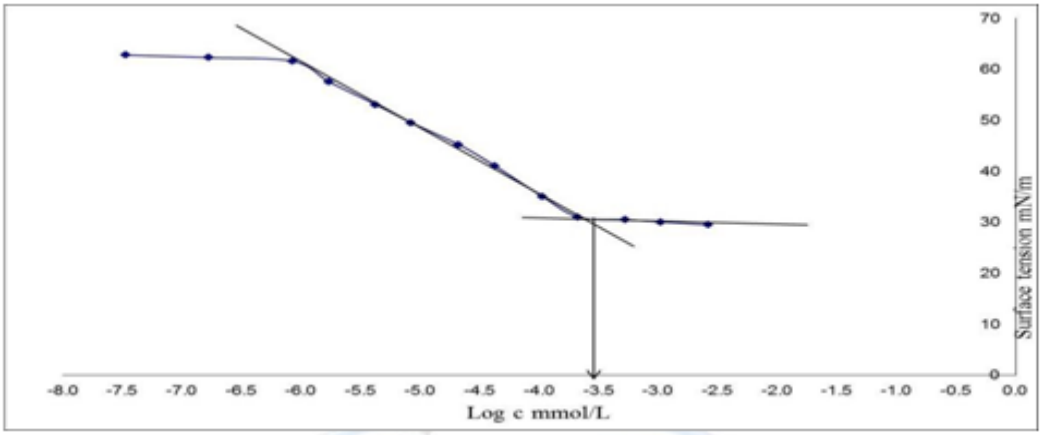

Figure 5: CMC investigation NMR for [1-(Methyl 6-deoxy- α -D-glucopyranosid-6-yl)-1H-1,2,3- triazol-4-yl]-methyl dodecanoate [7]

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