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Kinetics of Diels-Alder Reaction Using Organic Molecular Models

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Abstract. To synthesize biopolymers with specific biodegradability and water solubility properties through the Diels-Alder and retro-Diels-Alder reactions, model molecules such as tri-(1-ethyl-pyrrole-2,5-dione) amine, exo-3,6-epoxy anhydride-1,2,3,6-tetrahydrophthalic, and bismaleimide were designed. The Diels-Alder cycloaddition was envisioned as a strategy to develop polymeric materials with potential self-healing, recyclability, and thermal reversibility properties. These polymers serve as carriers for active compounds.
NMR spectroscopy, including ^{1}H NMR and ^{13}C NMR**,** was employed to elucidate the structural characteristics of the synthesized compounds. The progress of the Diels-Alder reaction over time at room temperature and at 40°C between furan and 1,1'-(Methylenedi-4,1-phenylene)bismaleimide (commercial bismaleimide) was monitored using ^{1}H NMR spectroscopy. Conversion rates of 95% at 40°C and 87% at 25°C were achieved after 16 hours.

Keywords. Cyclodehydration; Furan; Kinetic; Retro-Diels-Alder reaction; Synthesis.

INTRODUCTION

Polymers with reactive sites represent particularly interesting materials in the medical field for anchoring active molecules. The use of polymer-based drug carriers not only reduces toxic side effects and improves targeting but also optimizes release control. These polymers, which serve as vectors for biologically active molecules, must meet specific criteria. However, for these polymeric carriers to be effective, they must not be prematurely degraded by the body's natural defense mechanisms before fulfilling their function. To mitigate this issue, one strategy involves adsorbing or grafting polymers with stealth properties (Owens

and Peppas, 2006). Among the tested polymers, poly(ethylene oxide)s have proven to be the most effective.

This study was conducted in this context. To develop polymers structurally resembling nucleic and teichoic acids, chemical modifications were necessary, notably by introducing specific molecular functionalities. The Atherton-Todd reaction was employed to convert the P-H bond of diethyl hydrogen phosphonate into a more stable P-N bond (Oussadi et al., 2011).

Click chemistry refers to a set of highly efficient reactions that proceed rapidly under simple experimental conditions (Fig. 1). In recent years, this approach has been widely used to synthesize complex macromolecular architectures and introduce novel functionalities onto polymers. Click chemistry offers several advantages:

- High reproducibility;
- Quantitative yields;
- Broad tolerance to various functional groups;
- Mild reaction conditions requiring minimal synthetic effort (N'Guyen et al., 2013).

A key innovation in this field is the transition from the purely thermal Huisgen 1,3-dipolar cycloaddition to a Cu(I)-catalyzed 1,3-dipolar cycloaddition, which induces regioselectivity. Unlike the Huisgen thermal process, which produces a mixture of regioisomers, the Cu(I)-catalyzed reaction leads exclusively to the 1,4-regioisomer (Allock and Wood, 2006; Rostovtsev et al., 2002; Meldal and Tornoe, 2008).

The Kabachnik-Fields reaction plays a crucial role in drug discovery for synthesizing peptidomimetic compounds (Fig. 1). Functionalizing poly(ethylene oxide) (PEO) with a phosphonic acid group via the Kabachnik-Fields reaction, combined with click chemistry, allows for the replacement of the P-H bond, which is sensitive to dealkylation, with a more resistant P-C bond. Additionally, this modification introduces a functional group that serves as a potential anchoring site for biomolecules (N'Guyen et al., 2013).

Furan chemistry offers a versatile approach for designing novel materials from renewable resources (Gandini et al., 2008). Furan and maleimide derivatives can undergo Diels-Alder cycloaddition above 60°C, and this reaction can be reversed at temperatures exceeding 100°C. As a result, furan-maleimide Diels-Alder cycloaddition has emerged as a strategy for developing polymeric materials with self-healing, recyclability, and thermal reversibility (Gandini et al., 2008; Briou et al., 2021; Ionita et al., 2023).

Similarly, furfural, a widely produced furan derivative from renewable sources, offers promising applications in polymer chemistry. Its furan moiety can be linked to maleimide derivatives, enabling the synthesis of diverse polymeric architectures with the benefits of furan chemistry. Additionally, furfural can undergo imine formation via amine reduction, further expanding its synthetic potential.

The Diels-Alder reaction, a [4+2] cycloaddition between an electron-rich conjugated diene and an electron-poor dienophile, forms a six-membered ring (Diels and Alder, 1928; Carruthers, 1990). Notably, this reaction involves functional groups absent from biomolecules, enabling chemoselective transformations without the need for prior protection. Moreover, it occurs without catalysts or initiators (Wei et al., 2011), operates under mild physiological conditions, and benefits from increased reaction rates in the presence of water (Nandivada et al., 2007; Graziano, 2004; Sun et al., 2008). Importantly, the Diels-Alder reaction is thermally reversible, allowing controlled ring decomposition via temperature modulation (Murphy and Wudl, 2010; Bergman and Wudl, 2008; Gandini and Belgacem, 2007; Syrett et al., 2010; Ripoll et al., 1978; McElhanon et al., 2002; Chen et al., 2002).

The objective of this study is summarized in figure 1, which illustrates the different model molecules synthesized using classical organic chemistry reactions. These reactions will be adapted to polymer systems to generate a biocompatible and water-soluble biopolymer. This

article specifically presents our results on the Diels-Alder reaction, as our previous work on the Atherton-Todd and Kabachnik-Fields reactions has already been published (Fig. 1).

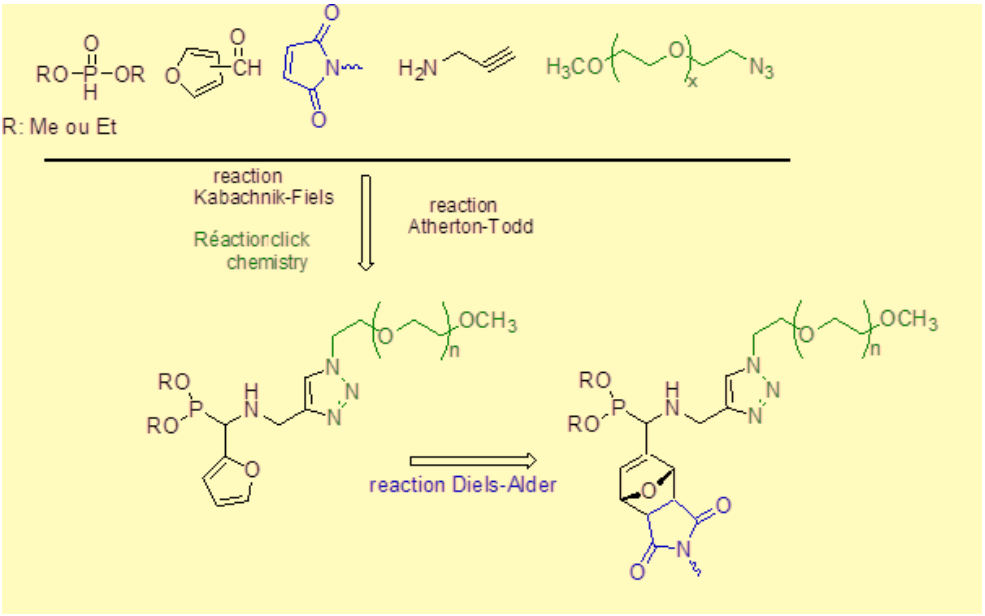


Fig.1. Multistep Synthesis Combining Kabachnik-Fields, Click Chemistry, Atherton-Todd, and Diels-Alder Reactions.

EXPERIMENTAL

General characterization

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 spectrometer, operating at 200 MHz for ^{1}H NMR and 400 MHz for ^{13}C NMR. Deuterated chloroform ($CDCl_3$) was used as the solvent, with tetramethylsilane (TMS) or 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as the internal reference. Chemical shifts are reported in parts per million (ppm).

Materials

Maleic anhydride (99%), furan (≥99%), tri(2-aminoethyl)amine (96%), triethylamine, and 4,7,10-trioxa-1,13-tridecanediamine (97%) were purchased from commercial sources and used without further purification. Tri-(1-ethyl-pyrrole-2,5-dione)amine (2) and **bismaleimide** were synthesized according to literature procedures (Gandini et al., 2008; Chen et al., 2002**).** These molecules were selected for their ability to contribute to the synthesis of macromolecules structurally similar to natural biopolymers. All reagents were handled in a chemical hood under safe conditions.

Synthesis of exo-3.6 epoxy anhydride-1.2.3.6 tetrahydrophthalic.

In a 100 mL round-bottom flask, 5 g (0.0508 moles) of maleic anhydride and 30 mL of toluene were introduced. The solution was stirred for one hour to ensure complete dissolution of the maleic anhydride. Then, 5 mL of furan was added to the solution. The reaction was carried out under a nitrogen atmosphere, stirred at room temperature, and stopped after seven days.

A white solid was obtained. After filtration and washing with toluene, the product was vacuum-dried and analyzed by ^{1}H NMR and ^{13}C NMR spectroscopy. The spectra confirmed the absence of side products (Fig. 8-9).

- Mass obtained: 7.6032 g (Yield: 90.2%).

- ^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 6.59 (s, 2H, HC=), 5.46 (s, 2H, CHOCH), 3.18 (s, 2H, CHC-O)
- ^{13}C NMR ($CDCl_3$, 400 MHz), δ (ppm): 169.95 (C=O), 137.01 (C=C), 82.25 (CHOCH), 48.74 (CHC-O)

Synthesis of tri-(1-éthyl-pyrrole-2.5-dione)amine

In a 100 mL round-bottom flask, 0.25 mL of tri(2-aminoethyl)amine and 1 mL of DMF are added. The flask is placed under magnetic stirring at 75°C for one hour. Then, a solution of 1 g of exo-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride in 2.5 mL of DMF is added dropwise. The reaction mixture is stirred at room temperature for two hours.

Next, 2 mL of acetic anhydride, 0.1 mL of freshly distilled triethylamine, and 0.01 g of $Ni(OAc)_2 \cdot H_2O$ are introduced. The reaction mixture is then refluxed at 75°C under magnetic stirring for three hours. After cooling to room temperature, 1 mL of ultrapure water is added. The solvent is removed under vacuum using a rotary evaporator at 60°C.

Afterward, 15 mL of CH_2Cl_2 and 30 mL of ultrapure water are added. The mixture is decanted, and the organic phase is collected and concentrated using a rotary evaporator. To purify the resulting product, a chromatography column is prepared with 4 g of silica gel impregnated with triethylamine. The product is then loaded onto the column and eluted with CH_2Cl_2. The fraction containing the product is concentrated using a rotary evaporator, yielding a yellow liquid.

To further refine the product, 6 mL of toluene is added, and the reaction mixture is refluxed overnight at 110°C under mechanical stirring. The next day, the mixture is placed under a nitrogen atmosphere, then filtered. The solvent is removed using a rotary evaporator. The final product is stored in the freezer and subsequently vacuum-dried.

The structure of the obtained product was confirmed by NMR spectroscopy (Fig. 11-12).

Mass obtained: 0.1678 g (7.24%)

^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 6.61 (s, 6H, HC=): 3.45 (t, 6H, NCH, J_C-H = 21.62 Hz) ; 2.65 (t, 6H, CHNCH, J_C-H = 21.62 Hz)

^{13}C NMR ($CDCl_3$, 400 MHz), δ (ppm): 169.5 (C=O), 133.3 (C-C) , 50.6 (CNC-O), 34.5 (CNC)

Synthesis of bismaleimide

A maleic anhydride solution (0.02 moles, 1.961 g, two equivalents) dissolved in 15 mL of ether was added dropwise to 4,7,10-trioxa-1,13-tridecanediamine (0.01 moles, 2.2031 g, one equivalent). The reaction mixture was stirred magnetically at 25°C for 3 hours, and then heated under reflux at 50°C for an additional 3 hours, until a white solid was formed.

^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 8.52 (s, 2H, HN-CO, J_C-H = 22.67 Hz); 6.6 (d, 2H, CHCON, J_C-H = 22.27 Hz); 6.3 (d, 2H, $=CHCO_2H$, J_C-H = 22.27 Hz); 3.51-3.8 (t, 2H, $NHCH_2CH_2$, J_C-H = 28.73 Hz; t, CH_2-O; t, O-CH_2); m ($NCH_2CH_2CH_2$-O).

Step 2: Cyclization of the Amic Acid End-Groups

The product obtained in the first step was subjected to cyclization. Anhydrous sodium acetate and 15 mL of acetic anhydride were added to the reaction mixture, which was then kept under magnetic stirring and reflux at 100°C for 5 hours. After cooling to room temperature, the mixture was left for 15 minutes under an inert nitrogen atmosphere. Ice water was then added, and the solvents were evaporated using a rotary evaporator.

To purify the product, it was passed through a chromatographic column of SiO_2 impregnated with a petroleum ether/ethyl acetate (1:2) mixture. The solvents were then removed under vacuum, and the product was washed with dichloromethane, filtered, and dried under vacuum. The final product was obtained as a yellowish paste.

The cyclization was achieved with a conversion rate of 55%, as determined by ^{1}H NMR spectroscopy.

^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 6.7 (s, H, CH=CHC); 3.3-3.8 (m, CH_2N, CH_2O-OCH_2CH_2O); 2.2 (m, 2H, $OCH_2CH_2CH_2N$).

The structure of the obtained product was confirmed by NMR spectroscopy (Fig. 14, Fig. 16).

KineticProcedure

Study of the Evolution of the Diels-Alder Reaction Over Time at Room Temperature

The progress of the Diels-Alder reaction at room temperature was studied between furan (^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): **7.5** (s, 1H, CH=CH-O); **6.5** (s, 1H, CH=CH-O)) and 1,1'-(Methylenedi-4,1-phenylene) bismaleimide (^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 7.5 (s, 4H, phenyl); 6.9 (s, 2H, CH=CH-CO); **4.0** (s, 2H, phenyl-CH_2-phenyl)) (Fig. 2).

In an NMR tube, a solution was prepared by dissolving two equivalents of furan (0.0037 g, 5.58×10^{-5} moles) and one equivalent of 1,1'-(Methylenedi-4,1-phenylene) bismaleimide (0.01 g, 2.79×10^{-5} moles) in 2 mL of $CDCl_3$. The tube was maintained at room temperature, and ^{1}H NMR analyses were performed immediately after preparation, followed by a series of measurements every 4 hours to monitor the reaction's progression.

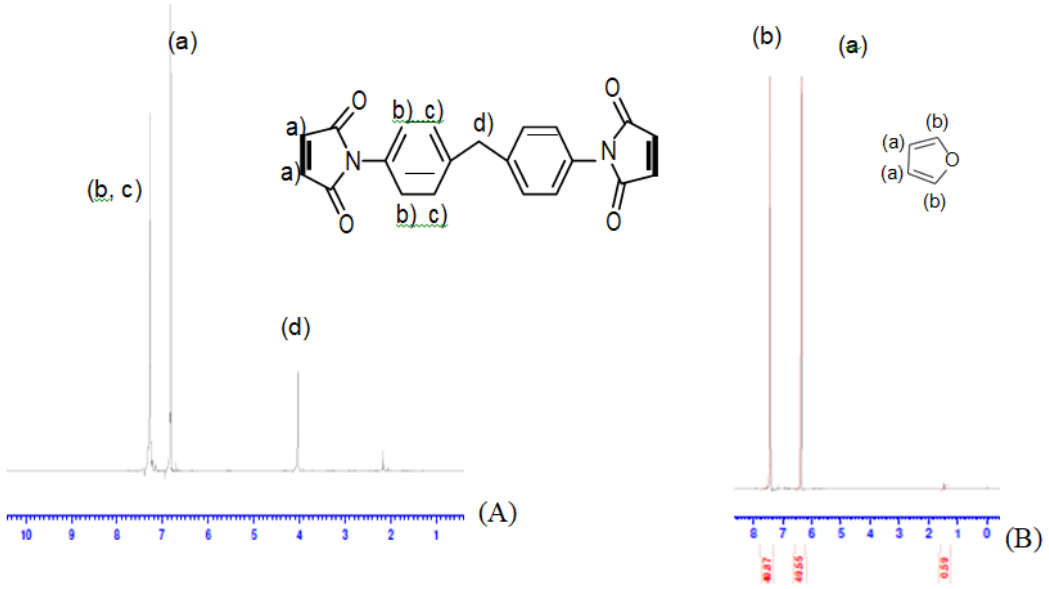


Fig.2. ^{1}HNM Rspectrao f1.1′- (Méthylènedi-4.1-phénylène) bismaleimide (A) and Furan (B) in $CDCl_3$.

The kinetics of the Diels-Alder reaction between commercial bismaleimide and furan in deuterated chloroform are summarized in Table 1. The graphs illustrate the evolution of the reaction conversion over time (Table 1, run 7), showing a final conversion of 95%.

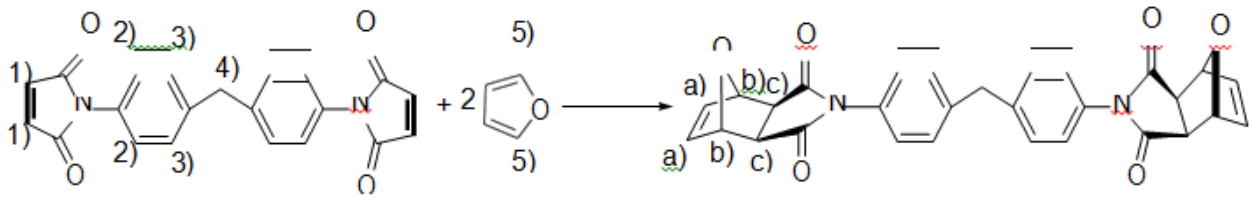
^{1}H NMR ($CDCl_3$, 400 MHz, δ in ppm): 7.4 (s, 4H, phenyl), 6.6 (d, 2H, CH=C), 5.4 (m, 1H, CH-O), 3.5–3.8 (m, 2H, CHC=O)

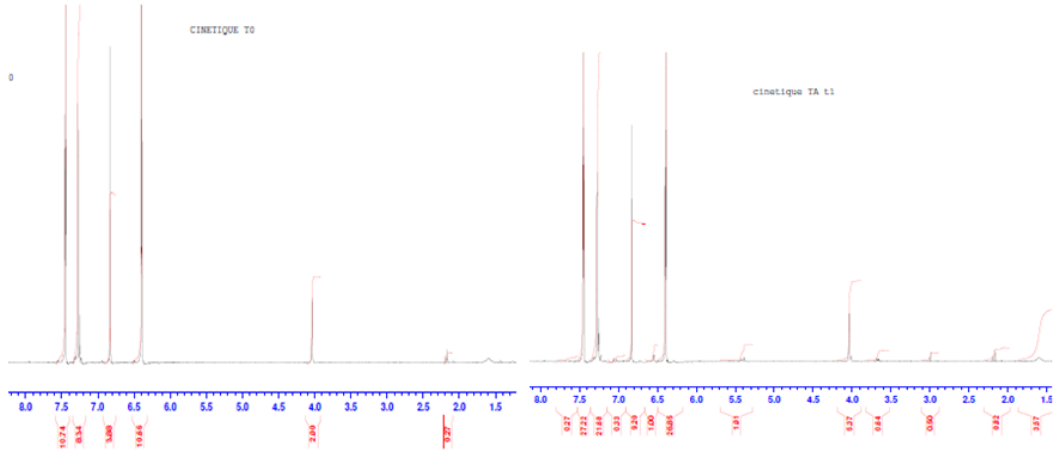
After 16 hours at 40°C, a 95% conversion was achieved. The conversion was determined using ^{1}H NMR spectroscopy, by comparing the peak area of the CH-O groups of oxanorbornene at δ = 5.4 ppm (which increases) with the peak characteristic of methylene protons at δ = 4 ppm (which decreases) (Fig. 3–4).

Table 1.Kinetics of Diels-Alder reaction between commercial bismaleimide and furan in deuterated chloroform.

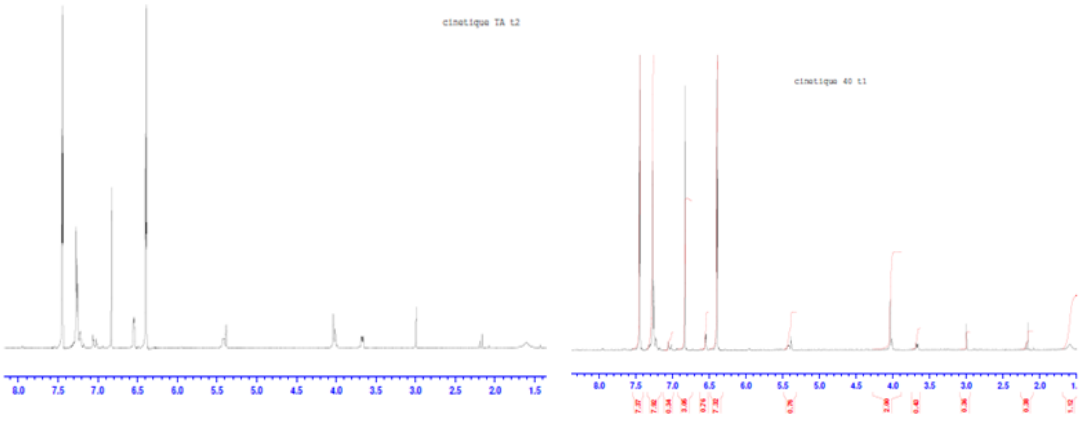
Run	Time(h)	Temperature(°C)	Cov.[a](%)
1	0	25	0
2	4	25	18.5
3	8	25	78
4	16	25	87
5	4	40	39
6	8	40	85.5
7	16	40	95

[a]determinedby[1]HNMRspectroscopycomparingthepeakareasoftheC*H*-Ogroupsofoxanorbornene atδ=5,4ppmandthemethylene protonsatδ= 4ppm.

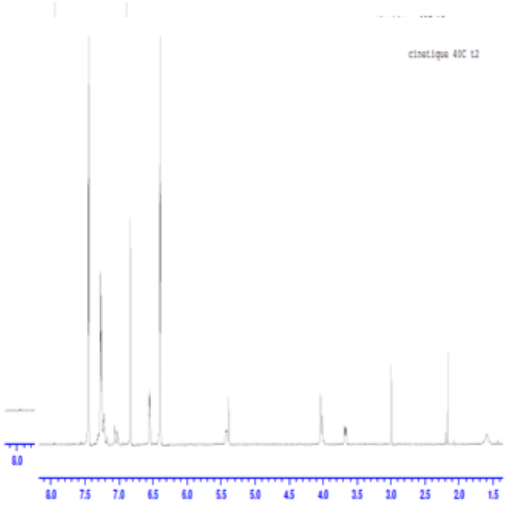




a) t0 = 0 at 25°C. b) t1 = 4h, at 25°C.

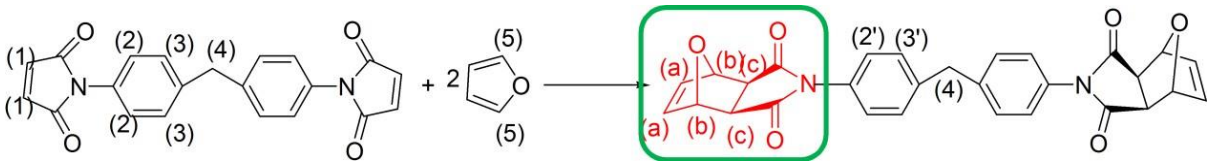


a') t1 = 4h, at 40oC. c) t2 = 8h, at 25°C.



b') t_2=8h,at40°C.

Fig.3. Overlay of ^{1}H NMR spectra of the reaction mixture of commercial bismaleimide withFuraninCDCl$_3$at25°Cand40°Cversustime.



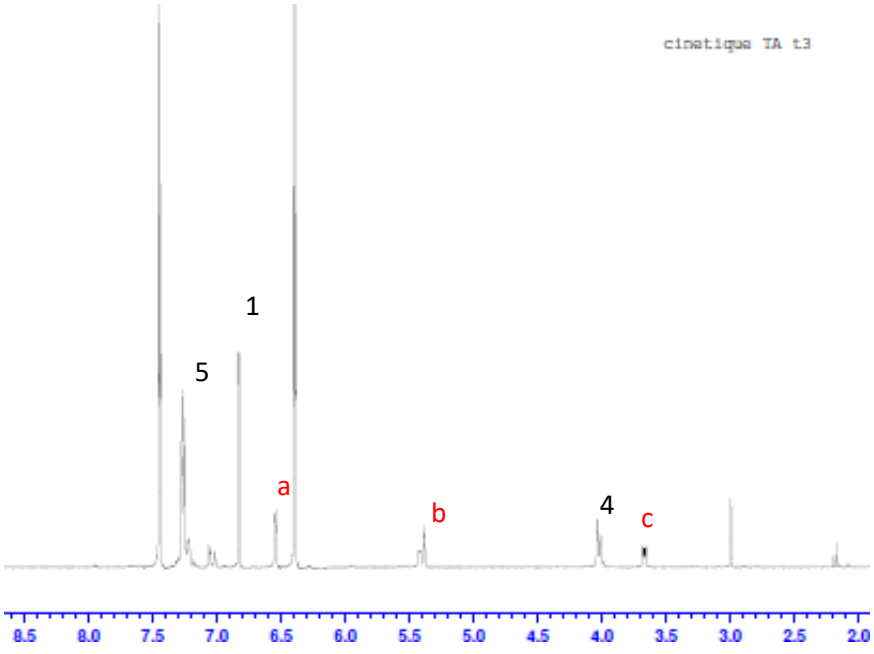


Fig.4. ^{1}H NMR Spectra of the Diels-Alder reaction between commercial maleimidebis and furanin CDCl$_3$ at the time t_3=16h, at25°C.

Study of the Evolution of the Diels-Alder Reaction Over Time at 40°C

The evolution of the Diels-Alder reaction between furan and 1,1'-(Methylenedi-4,1-phenylene) bismaleimide was monitored over time at 40°C. In an NMR tube, a solution containing two equivalents of furan (0.0037 g, 5.58×10^{-5} moles) and one equivalent of 1,1'-(Methylenedi-4,1-phenylene) bismaleimide (0.01 g, 2.79×10^{-5} moles) was prepared in 2 mL of $CDCl_3$. The NMR tube was placed in an oil bath maintained at 40°C.

To monitor the reaction progress, samples were taken every 4 hours, and ^1H NMR spectroscopy was used to track the conversion. The reaction was assessed by comparing the characteristic peaks of the CH–O groups of oxanorbornene at $\delta = 5.4$ ppm and the methylene protons at $\delta = 4$ ppm.

For in situ monitoring, the same formulation was used:

- Furan: 0.0037 g, 5.58×10^{-5} moles,
- 1,1'-(Methylenedi-4,1-phenylene) bismaleimide: 0.01 g, 2.79×10^{-5} moles,
- Deuterated solvent: $CDCl_3$.

The NMR tube was immersed in an oil bath set at 25°C or 40°C, marking the initial reaction time (t = 0). NMR spectra were recorded periodically to monitor the conversion of the Diels-Alder reaction over time (Fig. 5-6).

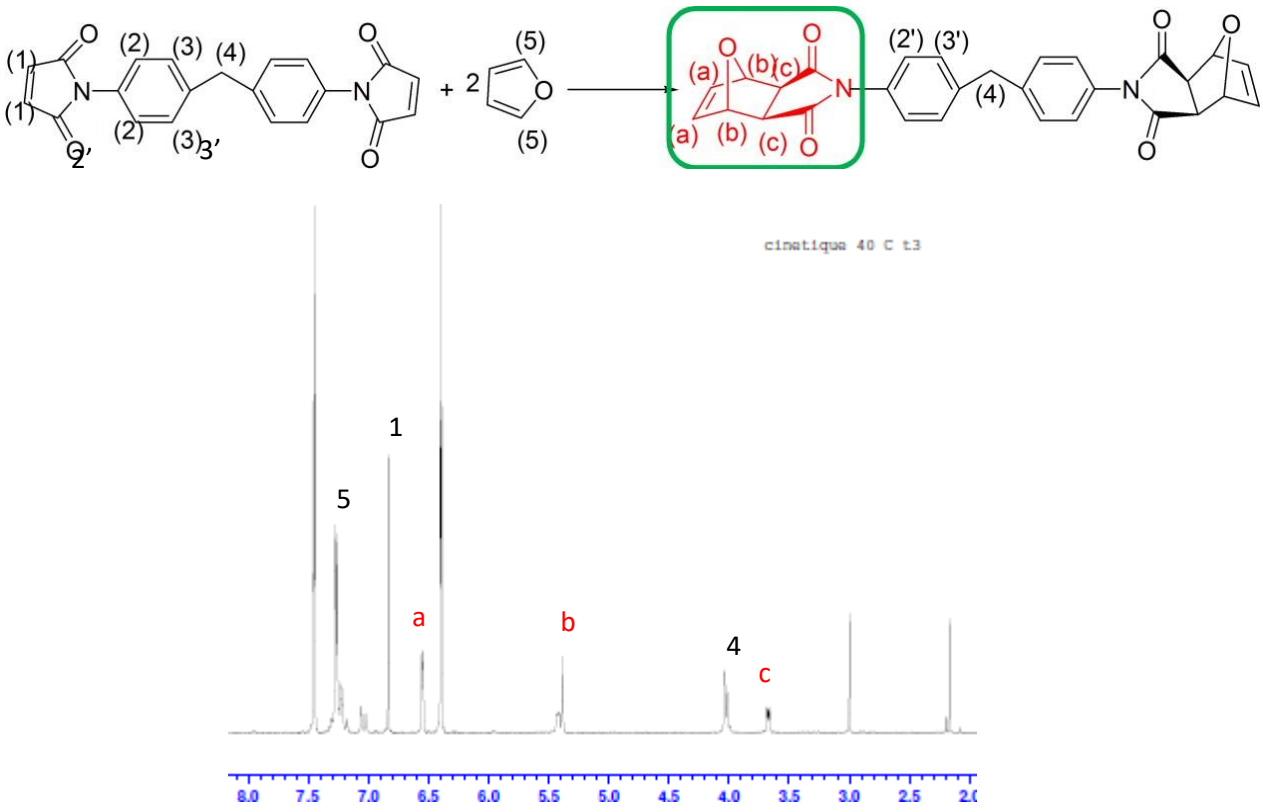


Fig.5. ^1H NMR Spectra of the Diels-Alder's reaction between commercial bismaleimide and furan in $CDCl_3$ at the time t_3=16h, at 40°C.

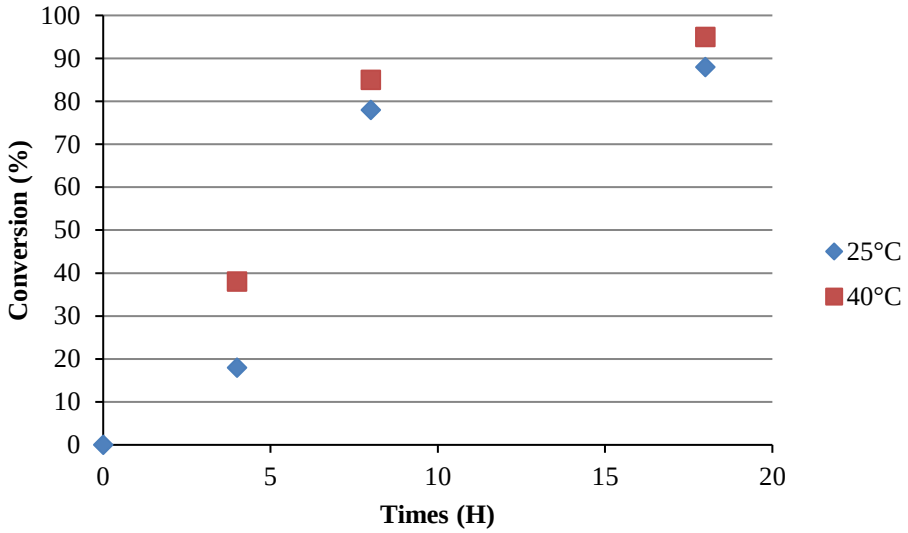


Fig. 6. Conversion of the Kinetics of Diels-Alder reaction between commercial maleimidebisis and furan in deuterated chloro format 25˚C and 40˚C versus time.

RESULTS AND DISCUSSION

Synthesis of exo-3.6 epoxy anhydride-1.2.3.6 tetrahydrophthalic (1) (Fig.7-9)

The exo-3,6-epoxy-anhydride-1,2,3,6-tetrahydrophthalic acid (1) was synthesized with a yield of 90.2%. The Diels-Alder reaction between maleic anhydride and furan was conducted at ambient temperature. ^{1}H NMR and ^{13}C NMR spectroscopy confirmed the successful synthesis of compound (1). The ^{1}H NMR spectrum revealed the appearance of the $–CH_2–$ peak of oxanorbornene at $\delta = 3.18$ ppm, along with the almost complete disappearance of the peak at $\delta = 7.5$ ppm corresponding to furan, which accounts for the 90.2% yield.

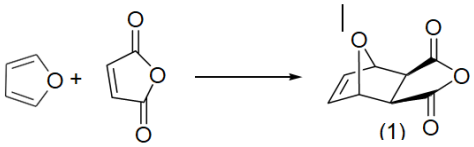


Fig. 7.Synthesis of exo-3.6 epoxy anhydride-1.2.3.6 tetrahydrophthalic (1).

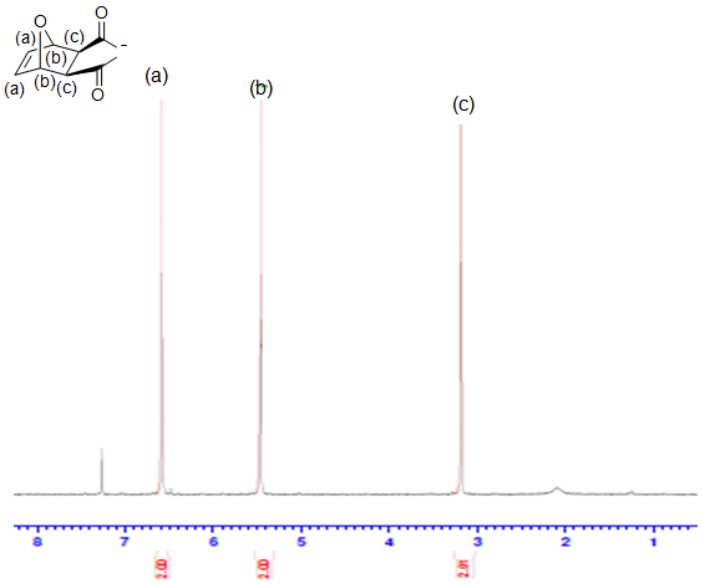


Fig.8.[1]H NMR Spectra of exo-3.6 epoxy anhydride- 1.2.3.6 tetra hydrophthalic (1); solvent: $CDCl_3$.

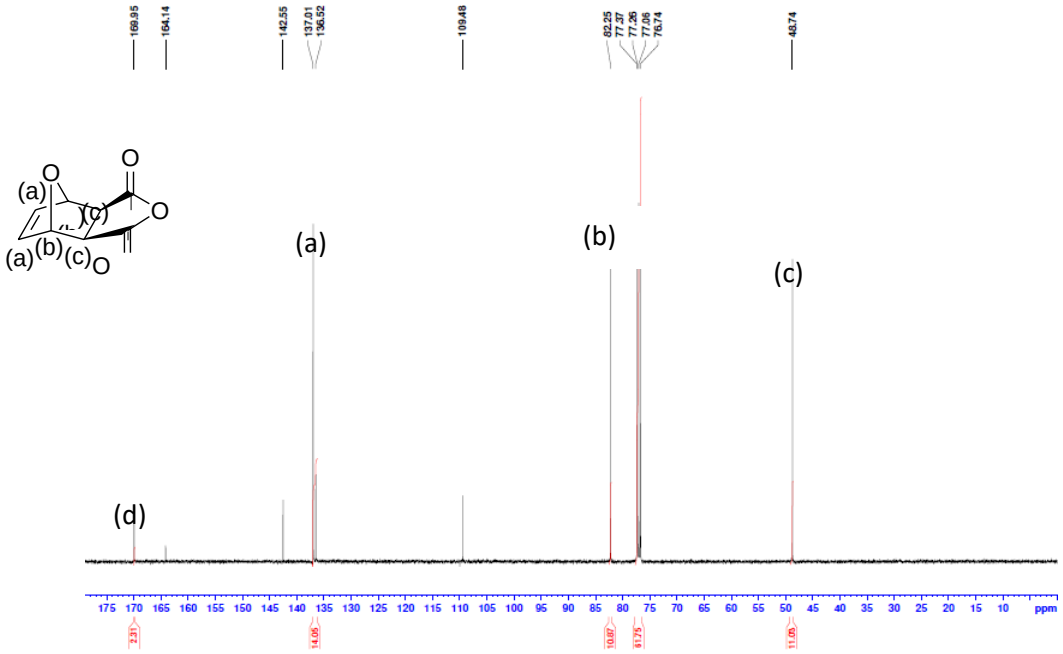


Fig.9.[13]C NMR Spectra of exo-3.6 epoxy anhydride-1.2.3.6 tetra hydrophthalic(1).

Synthesis of tri-(1-ethyl-pyrrole-2.5-dione) amine (2)

In the second step, compound (1) reacts with tris (2-aminoethyl)amine following a literature procedure, resulting in compound (2) with a yield of 7.24%, as shown in figure 10 (Searle, 1948).

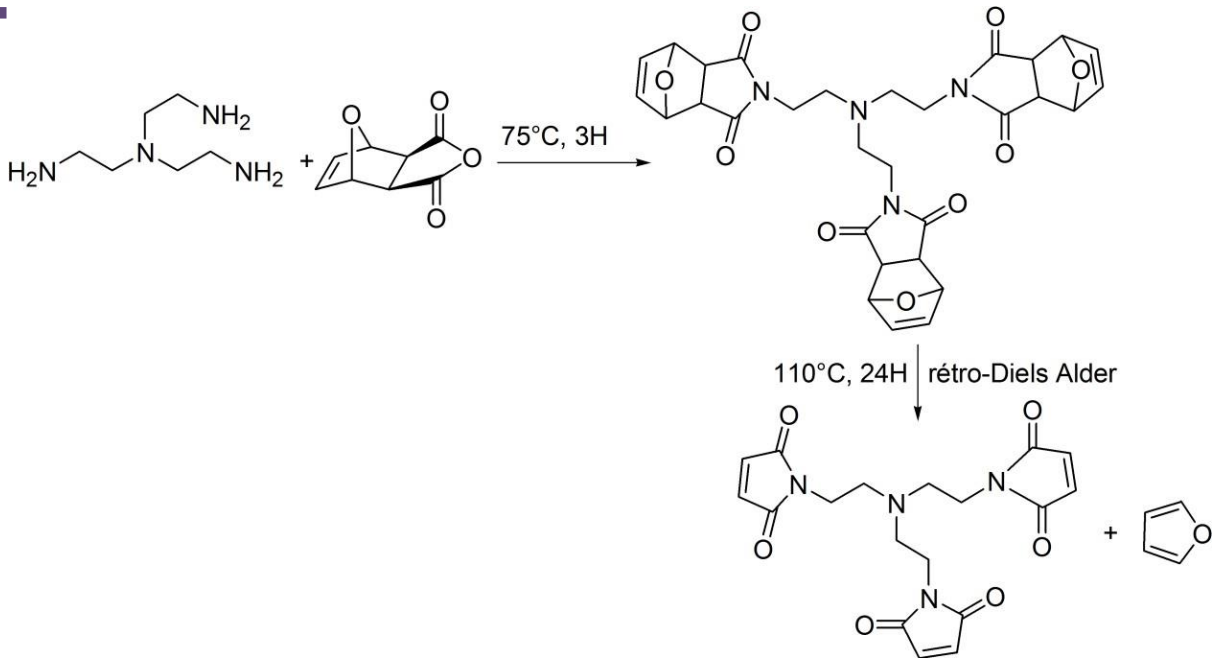


Fig.10.Synthesis of tri-(1-ethyl-pyrrole-2.5-dione) amine (2).

The obtained product is characterized using ^{1}H NMR and ^{13}C NMR spectroscopy. Specifically, the ^{1}H NMR spectrum (Fig. 8) shows the disappearance of the characteristic peak of the amine group present in tris (2-aminoethyl)amine, which typically appears as a singlet at $\delta = 2$ ppm. The ^{13}C NMR spectrum (Fig. 9) reveals the disappearance of the C-O peak from oxanorbornene (exo-3,6-epoxy anhydride-1,2,3,6-tetrahydrophthalic) at $\delta = 82.25$ ppm, accompanied by the appearance of peaks at $\delta = 169.5$ ppm and $\delta = 133.3$ ppm, which are indicative of the maleimide ring. These peaks correspond to peaks (c) and (d) in the **^{13}C** NMR spectra (Fig. 11-12).

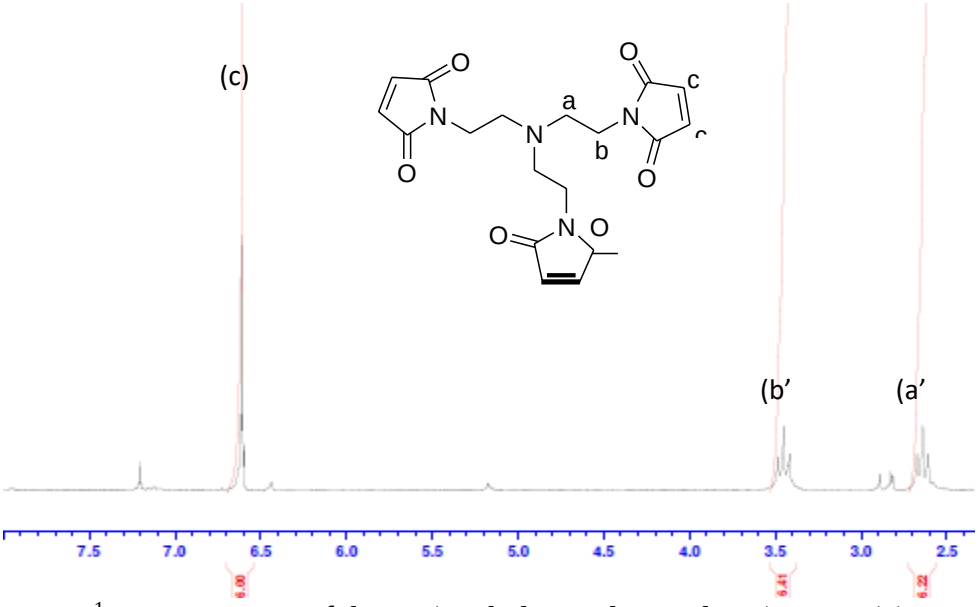


Fig.11.^{1}HNMR spectra of the tri-(1-ethyl-pyrrole-2.5-dione) amine (2).

Fig. 12.^{13}CNMR spectra of the tri-(1-ethyl-pyrrole-2.5-dione) amine(2).

Synthesis of bismaleimide

The synthesis of bismaleimide is carried out according to the procedure described in the literature. The first step involves the synthesis of di(1-(3-ethoxypropyl)-pyrrole-2,5-dione) oxide (Gandini et al., 2008). This compound was obtained by reacting maleic anhydride with 4,7,10-trioxa-1,13-tridecanediamine (Fig. 13). The successful synthesis of di(1-(3-ethoxypropyl)-pyrrole-2,5-dione) oxide was confirmed by ^{1}H NMR spectroscopy. Specifically, the ^{1}H NMR spectrum (Fig. 10) shows a peak at δ = 8.52 ppm (Fig. 14, peak (1)), which is characteristic of the amide proton. No issues were encountered during the execution of these reactions.

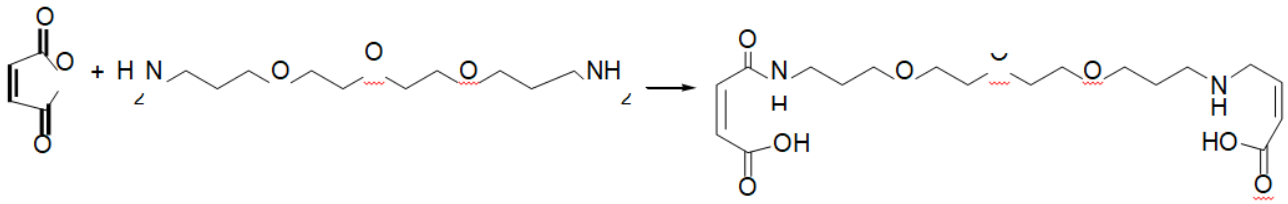


Fig. 13.Synthesis of di(1-(3-éthoxy-propyl)-pyrrole-2,5-dione) oxide.

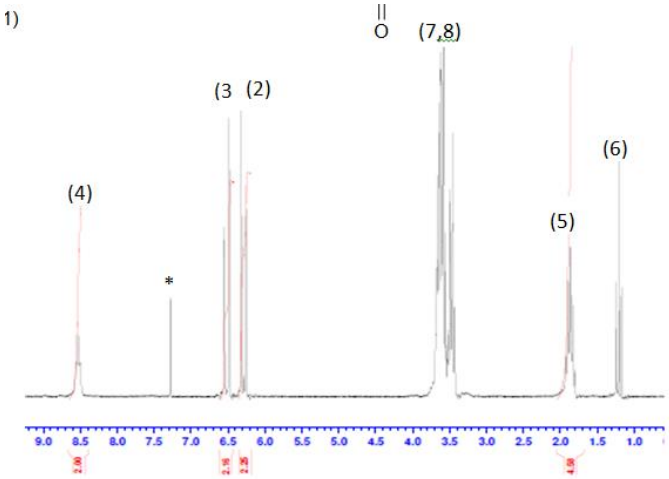


Fig.14.[1]HNMR spectra of the di(1-(3-éthoxy-propyl)-pyrrole-2.5-dione)oxide.

The cyclization was carried out with a conversion of **55%** (calculated by NMR), as determined by ¹H NM**R** spectroscopy. This was assessed by comparing the peak areas of the double bond (d, 2H, =CHCO₂H at 6.3 ppm (peak (2), Fig. 14)) and the residual di(1-(3-ethoxypropyl)-pyrrole-2,5-dione) oxide (Fig. 16, peak (*) at 6.3 ppm), which remained unreacted.

The synthesis of the bismaleimide follows a procedure involving the conversion of primary amines into maleimides through the cyclodehydration of maleamic acid, using a chemical dehydrating agent such as acetic anhydride in the presence of sodium acetate (Searle, 1948) (Fig. 15).

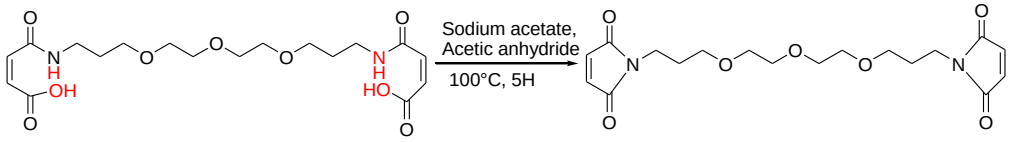


Fig.15. Synthesis of maleimidebis.

¹H NMR (CDCl₃, 200 MHz), δ (ppm): 6.7 (s, H, CH=CHC), 3.3-3.8 (m, CH₂N, CH₂O-, OCH₂CH₂O); 2.2 (m, 2H, OCH₂CH₂CH₂N).

The results obtained are in good agreement with those reported in the literature. Indeed, Garandini et al. (2008) observed a chemical shift at 6.68 ppm, which was attributed to the double bond in the cycle.

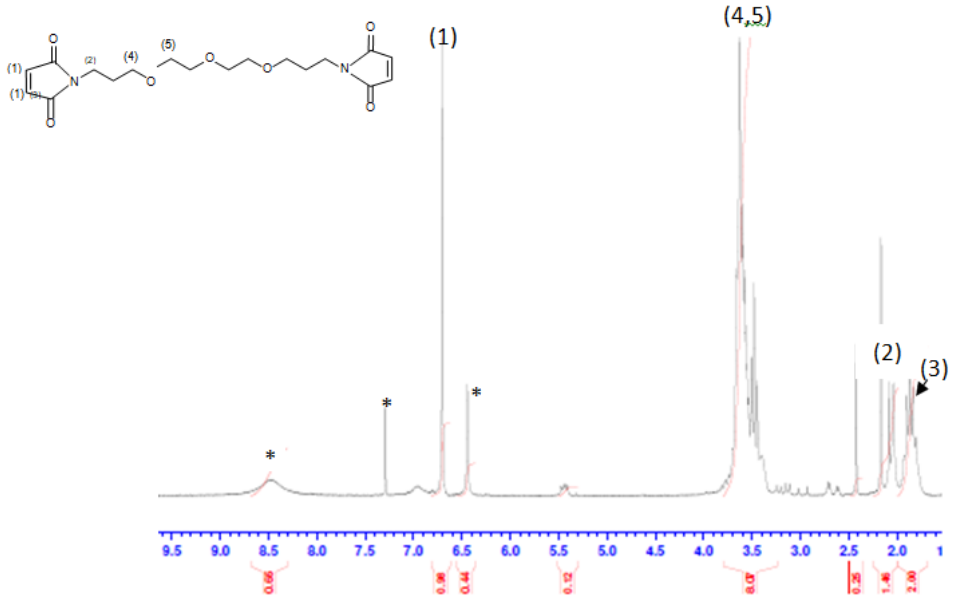


Fig. 16.[1]HNMR spectra of bismaleimide.

Diels-Alder reaction

The Diels-Alder reaction was investigated using commercial 1,1′-(Methylenedi-4,1-phenylene) bismaleimide (Fig. 17).

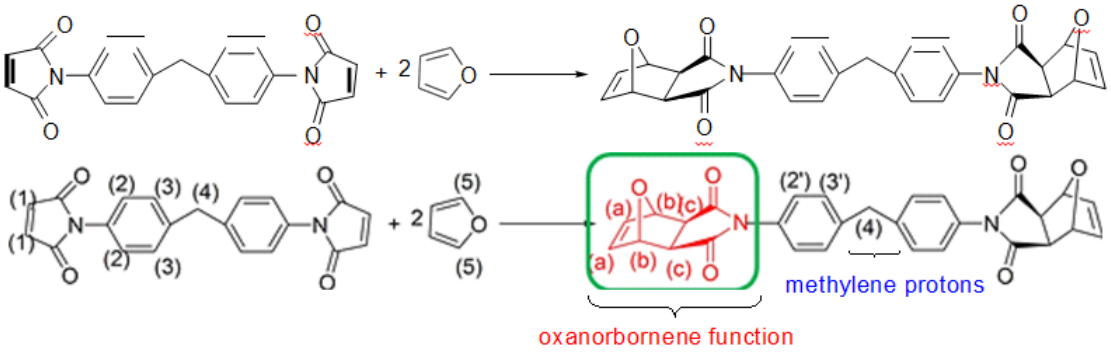


Fig. 17. Synthesis of maleimide bis-terminated oxanorbornene-function.

The appearance of peaks at δ = 6.6 ppm (d, 2H, CH=C)**,** δ = 5.4 ppm (m, 1H, CH-O)**,** and **δ** = 3.5-3.8 ppm (m, 2H, CH-C=O) indicates that the Diels-Alder reaction has occurred. After four hours at 25°C, a conversion of 18.5% was recorded. This conversion improved significantly after eight hours and further increased after sixteen hours, reaching 87% at 25°C and 95% at 40°C**.** Conversion rates were calculated using ¹H NMR spectroscopy by comparing the proton peak of the oxanorbornene, specifically the CH-O group **at** δ = 5.4 ppm and the methylene protons at δ = 4 ppm, as shown in figure 5.

CONCLUSION

In this work, model molecules were synthesized under mild conditions, primarily utilizing the Diels-Alder reaction. The Diels-Alder cycloaddition has proven to be particularly well-suited for synthesizing molecules with structural similarities to biomolecules. This is due to its rapid reaction time (a few hours), excellent yields, and the mild reaction conditions—such as room temperature—without side reactions and in the absence of a catalyst, and it proceeds reversibly. This study will be extended to include a polymer, specifically

polyethylene oxide monomethyl ether, known for its stealth properties, to develop biopolymers intended for biological advancement and medical applications.

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