SYNTESIS AND CRYSTALLINE STRUCTURE OF THE EXO-3,6-DIMETHYL-3,6-EPOXI-1,2,3,6-TETRAHYDROPHTLALIMIDE AND ITS N-BROMODECYL ANALOG: TWO THERMALLY LABILE DIELS-ALDER ADDUCTS

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ABSTRACT

The molecular structure of the *exo*-3,6-dimethyl-3,6-epoxi-1,2,3,6-tetrahydrophthalimide (**1**), determined by X-ray diffraction analysis, as well as, its complete spectroscopic characterization and the synthesis and complete spectroscopic characterization of its N-(10-bromodecyl) analog (**2**) are presented.

Keywords: Furan/Maleimide Diels-Alder adduct, thermally labile protecting group.

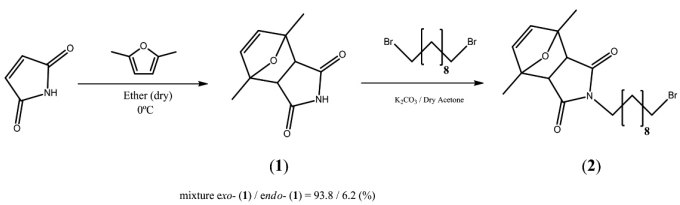
1. INTRODUCTION

The furan-maleimide (FM) Diels-Alder (DA) adduct has been used as a versatile tool in a broad spectrum of applications, among them, FM adduct has been used as thermal reversible coupling/decoupling moiety[1] and as a thermally labile protecting group, included in synthetic schemes[2]. These two applications are based on both, the ease of the adduct formation trough the DA reaction[3] and on the relatively low decoupling temperature through its retro DA reaction[4].

As a reversible coupling/decoupling moiety, the DA adduct has been included in oligonucleotide conjugates[5] and in reversible polymer network[6,7,8]. Also, Bakhtiari *et al.* used this DA adduct as a linker between gold nanoparticles and fluorescein dye, proving that the thermally labile adduct can release the dye under photothermal conditions (*i.e.* thermal or light irradiation)[9]. As a thermally labile protecting group has been included in synthetic schemes to provide for peptides, peptoids and peptide nucleic acids[10] and Maleimide functionalized gold nanoparticles[11,12].

From the structural point of view, the DA adducts between Furan and Maleimide, has been studied mainly for its N-substituted analogs, thus in this way the X-ray crystallography of the N-amino[13,14], N-acetoxyphenyl[15] and N-aryl[16] has been studied; Surprisingly, for the DA adduct of 2,5-dimethylfuran and Maleimide the molecular structure has not been determined using X-ray diffraction analysis.

We want to report here the molecular structure of the *exo*-3,6-dimethyl-3,6-epoxi-1,2,3,6-tetrahydrophthalimide (**1**), determined for first time by X-ray diffraction analysis, as well as its complete spectroscopic characterization. Additionally, we present here the synthesis and the complete spectroscopic characterization of its N-(10-bromodecyl) analog (**2**).



Scheme 1. Synthetic pathway to the *exo*-3,6-dimethyl-3,6-epoxi-1,2,3,6-tetrahydrophthalimide (**1**), and to its N-(10-bromodecyl) analog (**2**).

2. EXPERIMENTAL

2.1. General. Unless otherwise stated, all the chemicals were purchased from Sigma Aldrich and used without further purification. All manipulations were carried out under a nitrogen atmosphere. The solvents were dried and distilled according to standard procedures. Thin-layer chromatography (TLC) was performed on a glass plate pre-coated with silica gel with fluorescent indicator UV_{254}. TLC plates were visualized by exposure to ultraviolet light. Column chromatography was performed with silica gel 60 (40-63 µm, 230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer. All chemical shifts are reported in ppm (δ) relative to tetramethylsilane. Coupling constants (*J*) are reported in Hertz (Hz) and integrations are reported as numbers of protons. The following abbreviations are used to describe peak patterns: s, singlet; d, doublet; t, triplet; m, multiplet. IR spectra were obtained from KBr disks on a Perkin Elmer Spectrum BX FTIR spectrometer in the range of 4000-400 cm^{-1}. Elemental analysis was performed at Pontificia Universidad Católica de Chile, at the EA1108 CE instruments analyzer.

2.1. Synthesis of *exo*-3,6-dimethyl-3,6-epoxi-1,2,3,6-tetrahydrophthalimide (1): A solution of Maleimide (1,00 g; 10,3 mmol) in dry ether (20 mL) was treated with 2,5-dimethylfuran (3,79 g; 39,0 mmol) under Nitrogen. The mixture was stirred for 12 hours at room temperature. During this time, the *exo*-3,6-dimethyl-3,6-epoxi-1,2,3,6-tetrahydrophthalimide (**1**), precipitated as a white solid. This product was filtered, washed with 10 mL of cold ether, and then twice with 10 mL of hexane. Purification by column chromatography on silica gel (first with Ethyl acetate: Hexane = 1: 10 v/v, to remove any excess of 2,5-dimethylfuran, followed by Ethyl acetate: Hexane = 1: 3 v/v) afforded the product as a white solid, which was recrystallized by slow evaporation in a mixture of Methanol: Methylene Chloride = 1:1 (v/v). Yield = 1.90g (95.7 %); mp = decomposes at 120º C. **IR** (KBr) cm^{-1}: 1752, 1706 (C=O), 1579 (N-H). **^{1}H-NMR** (400 MHz., $CDCl_3$): δ = 1.73 (s, 6H, 2x CH_3), 2.88 (s, 2H, 2x CH), 6.31 (s, 2H, 2x =CH) 8.22 (broad s, 1H, NH). **^{13}C-NMR** (101 MHz., $CDCl_3$): δ = 175.0, 140.9, 87.7, 53.8, 15.8. Analysis calculated for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 63.02; H, 6.22; N, 7.88.

2.2. Synthesis of *exo*-N-(10-bromodecyl)-3,6-dimethyl-3,6-epoxi-1,2,3,6-tetrahydrophthalimide (2): A mixture of compound (**1**) (500mg, 2.60 mmol) and 1,10-dibromodecane (1.55g, 5.20 mmol), dissolved in dry acetone (12 mL), were treated portion wise with Potassium Carbonate (0.36g, 2.6 mmol). The reaction was allowed to react over 24 hours at 40º C in a thermo regulated bath. Then, the solvent was removed, in a rotatory evaporator; the remaining mixture was resuspended in water and extracted three times with 10 mL portions of dichloromethane. The combined organic layers were concentrated in *vacuo*, and submitted to flash chromatography: First n-hexane (11x 60 mL portions) were used to remove the unreacted 1,10-dibromodecane, and then, mixture of Ethyl acetate: Hexane = 1:10 (v/v; 6x 60 ml portions), were used to collect the title compound (**2**) as a pale yellow oil. Yield = 596 mg (55.6%). **IR** (KBr) cm^{-1}: 2929, 2854 (C-H), 1769, 1700 (C=O).). **^{1}H-NMR** (400 MHz., $CDCl_3$): δ = 1.27 (broad s, 10H, 5xCH_2), 1.40 (q, 2H, CH_2, *J* = 8.0 Hz.), 1.54 (q, 2H, *J* = 8.0 Hz.), 1.70 (s, 6H, 2x CH_3), 1.84 (q, 2H, CH_2, *J* = 8.0 Hz.), 2.80 (s, 2H, 2x CH), 3.40 (t, 2H, CH_2, *J* = 6.8 Hz.), 3.47 (t, 2H, CH_2, *J* = 7.3 Hz.), 6.30 (s, 2H, 2x =CH). **^{13}C-NMR** (101 MHz., $CDCl_3$): δ = 174.8, 140.9, 87.57, 52.39, 38.68, 34.01, 32.82, 29.30, 29.26, 28.97, 28.69, 28.14,

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27.58, 26.54, 15.89. Analysis calculated for $C_{20}H_{30}BrNO_3$: C, 58.25; H, 7.33; N, 3.40. Found: C, 55.62; H, 7.99; N, 3.22.

2.3. X-ray Crystal Structure Determination. An appropriate single crystal of compound (**1**) suitable for X-Ray diffraction analysis was obtained by recrystallization of (**1**) from a mixture of Methanol: Methylene Chloride = 1:1 (v/v). One of the cube-shaped single crystals obtained was mounted on top of a glass fiber in a random orientation. Compound (**1**) was studied at 223 K on a D8 Smart APEX II Bruker-AXS diffractometer employing X-ray source Mo *Kα* radiation (λ = 1.72 Å). Using Olex2[17], the structure was solved using direct methods (non-H atoms). All hydrogen atoms were inferred from neighbouring sites. The crystallographic data for Compound (**1**) were deposited at Cambridge Crystallographic Data Center (CCDC). Reference number 996959; these data can be obtained from free of charge from the CCDC via http://www. ccdc.cam.ac.uk/data request/cif. Crystal data, data collection, and refinement parameters are given in Table 1.

Table 1. Crystal data, data collection and structure refinement parameters for (**1**).

Empirical formula	$C_{80}H_{88}N_8O_{24}$
Formula weight	1545.63
Temperature/K	296.15
Crystal system	orthorhombic
Space group	$Pc2_1b$
a/Å	5.6786(2)
b/Å	11.9269(5)
c/Å	27.3892(10)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1855.02(12)
Z	8
ρ_{calc}mg/mm^3	1.3835
m/mm^{-1}	0.103
F(000)	816.5
Crystal size/mm^3	0.898 × 0.348 × 0.236
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection	4.52 to 57.1°
Index ranges	-7 ≤ h ≤ 7, -16 ≤ k ≤ 14, -36 ≤ l ≤ 36
Reflections collected	18161
Independent reflections	4621 [R_{int} = 0.0423, R_{sigma} = 0.0400]
Data/restraints/parameters	4621/0/256
Goodness-of-fit on F^2	1.054
Final R indexes [I>=2σ (I)]	R_1 = 0.0439, wR_2 = 0.1174
Final R indexes [all data]	R_1 = 0.0684, wR_2 = 0.1511
Largest diff. peak/hole / e Å^{-3}	0.44/-0.7

3. RESULTS AND DISCUSSION

3.1. Chemistry. *exo*-3,6-dimethyl-3,6-epoxi-1,2,3,6-tetrahydrophthalimide (**1**) was prepared following the previous report of Elduque, X. *et al.*[10], introducing slightly modifications; the more remarkable feature of the ^{1}H NMR spectrum for (**1**) reported by Elduque is the assignation done to the double bond protons (*i.e.* the CH protons located at positions 4 and 5) they were assigned at 6.31 ppm for both the *exo* and the *endo* isomers. In our hands, the ^{1}H NMR spectrum for (**1**) recorded at room temperature in deuterated chloroform showed the presence of a mixture of *exo* and *endo* isomers, in a ratio of 93.8 % for the thermodynamic stable *exo* isomer, and 6.2 % for the *endo* isomer (percentages based on the signals integration at the ^{1}H NMR spectrum). In our case, the CH protons for the *exo* isomer appeared also at 6.31 ppm, mean while, the CH protons for the *endo* isomer appeared at 6.70 ppm. For the bridgeheads CH protons (*i.e.* the CH protons located at positions 1 and 2), we found for the *exo* isomer a chemical shift of 2.88 ppm and 3.27 ppm for *endo* isomer, in accordance with the chemical shifts and multiplicities previously reported.

An analog of the *exo*-N-(10-bromodecyl)-3,6-dimethyl-3,6-epoxi-1,2,3,6-tetrahydrophthalimide (**2**), the N-(10-bromodecyl)-3,6-epoxi-1,2,3,6-tetrahydrophthalimide has been described by Bakhtiari, A. B. S.*et al.*[9]. Our ^{1}H NMR data are in accordance with the chemical shifts and multiplicities previously reported for that analog compound. The more remarkable features of our ^{1}H NMR spectrum for (**2**) are again the bridgeheads CH protons, appearing at 2.80 ppm and the double bond protons, appearing at 6.30 ppm, confirming the *exo* isomerism of compound (**2**). Other remarkable features are the chemical shifts and multiplicities of the twenty methylene groups of the N-(10- bromodecyl) side chain. Those directly attached to the C9 show a triplet multiplicity appearing at 3.40ppm (J = 6.8 Hz.), and those of the C1 appear at 3.47 ppm (J = 7.3 Hz.), meanwhile those corresponding to C2 and C9, are represented by quintuplets, appearing at, 1.84 ppm (C2, J = 8.0 Hz.) and 1.54 ppm (C9, J = 8.0 Hz.), respectively. Also protons at C3 appear as a quintet appearing at 1.40 ppm. (J = 8.0 Hz.). The other ten protons appear collected together in one broad singlet signal appearing at 1.27 ppm.

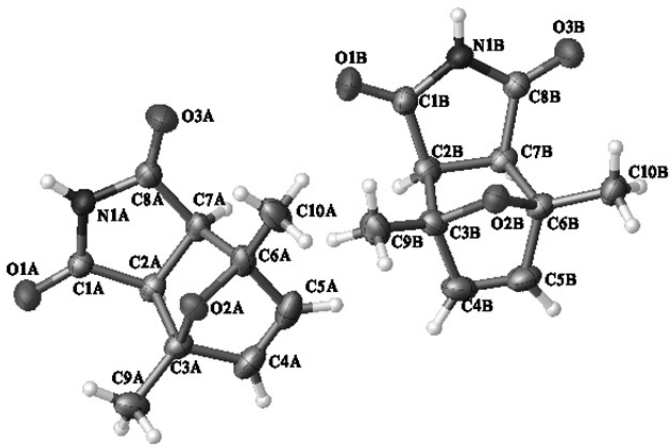

Figure 1. Molecular structure of two non- superimposable independent molecules (1A, left; 1B right) in the asymmetric unit of adduct (**1**), showing the atom-numbering scheme and displacement ellipsoids at the 50 % probability level.

3.2. X-ray crystallographic analysis. Crystal data, data collection and structure refinement parameters for (**1**) are presented in Table 1. Selected bond distances and angles are reported in Table 2, likewise, Figure 1**,** present an ORTEP drawing for (**1**), along with the atom numbering scheme. As shown in this figure, the molecular structure of the compound, confirms the *exo* isomerism of (**1**). Additionally, compound (**1**) crystallizes in orthorhombic space group $Pc2_1b$, with two independents entities present in the asymmetric unit, labeled (**1**A) and (**1**B). The common geometric features of both molecules (Table 3) are in agreement with those reported in the literature[18,19] for homologous compounds. When comparing bond lengths of **1**A and **1**B (Figure 1), it is shown that they are not identical (*i.e.* a non-superimposable pair), differences in bond lengths can be found, for example, at the carbonyl moiety (Table 2, entry 9 and 10), the carbonyl bonds of **1**A is found to measure 1.205(3) Å (O3A-C8A) meanwhile for **1**B the same bond (O3B-C8B) is found to be longer (1.226(3) Å). The other two carbonyls, in contrast, are ranging in the same values (*i. e.* 1.219(3) Å for O1A-C1A, and 1.217(3) Å for O1B-C1B). Other differences in bond lengths can be found along the molecules, in the following pairs of bond lengths, N1A-C1A = 1.356(3) Å and 1.373(3) Å; N1A-C8A = 1.385(3) Å and N1B-C8B = 1.357(3) Å; C10A-C6A = 1.494(4) Å and C10B-C6B = 1.501(3) Å; C1A-C2A = 1.521(3) Å and C1B-C2B = 1.508(3) Å; C5A-C6A = 1.516(4) and C5B-C6B = 1.509(3) Å; C4A-C5A = 1.317(5) Å and C4B-C5B = 1.306(4); C7A-C8A = 1.516(3) and C7B-C8B = 1.507(3), this making **1**A and **1**B virtually a non-superimposable pair.

When the supramolecular structure of (**1**) is analyzed (Figure 2), the more remarkable feature is the racemic nature of the crystal. The intermolecular hydrogen-bonds observed are formed only by interaction of the imide moiety of one molecule and the longest carbonyl moiety of the other (*i.e.* the shorter carbonyl moiety is not involved in the hydrogen bonds interactions).

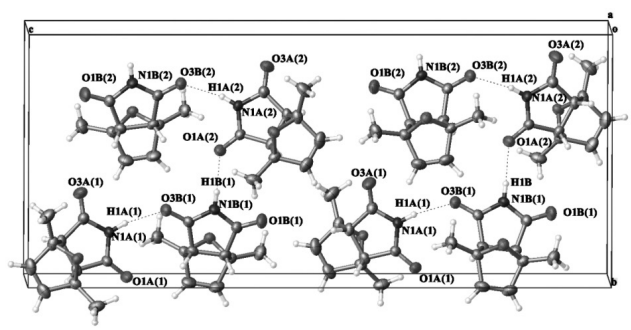

Figure 2. The supramolecular structure of (**1**), viewed along the *a* axis.

Table 2. Selected geometric parameters (Å, º) for (**1**A and **1**B)

C3A-O2A-C6A	97.83(17)	**C3B-O2B-C6B**	97.57(16)
C1A-N1A-C8A	114.00 (19)	**C1B-N1B-C8A**	113.6(2)
C5A-C6A-C7A	104.4(2)	**C5B-C6B-C7B**	104.45(19)
C2A-C3A-C4A	104.22(18)	**C2B-C3B-C4B**	105.2 (2)
N1A-C1A-C2A	109.07(19)	**N1B-C1B-C2B**	108.77(19)
N1A-C7A-C8A	107.71(19)	**N1B-C7B-C8B**	108.67(19)
N1A-C1A	1.356(3)	**N1B-C1B**	1.373(3)
N1A-C8A	1.385(3)	**N1B-C8B**	1.357(3)
O1A-C1A	1.219(3)	**O1B-C1B**	1.217(3)
O3A-C8A	1.205(3)	**O3B-C8B**	1.226(3)
O2A-C3A	1.440(3)	**O2B-C3B**	1.448(3)
O2A-C6A	1.447(3)	**O2B-C6B**	1.444(3)
C4A-C5A	1.317(5)	**C4B-C5B**	1.306(4)

It is also remarkable that in the supramolecular structure (Figure 2) and due to the noncrystallographic inversion center, four kinds of molecules can be found, those already described (*i.e.* **1**A and **1**B, Figure 1) and its enantiomers (pairs of enantiomers named as 1A(1) and 1A(2), 1B(1) and 1B(2), respectively, Figure 2). Here the 1A (1) molecule is not superimposable with 1B(1), due the bond lengths differences, as previously described, but also is not superimposable with 1A(2), since they are mirror images (Figure 2 and Table 3).

Table 3. Hydrogen-bond geometry (Å, º) for (**1**)

D—H ···A	D—H	H···A	D···A	D—H···A
$N_{1A(1)}$-$H_{1A(1)}$···$O_{3B(1)}$ *(1)	0.86(3)	2.036(3)	2.881(3)	171.2(6)
$N_{1B(1)}$-$H_{1B(1)}$···$O_{1A(2)}$ *(2)	0.86(3)	1.998(3)	2.851(3)	173.6(5)
$N_{1A(2)}$-$H_{1A(2)}$···O_{3B} *(3)	0.86(3)	2.036(3)	2.881(3)	171.2(6)
$N_{1A(1)}$-$H_{1A(1)}$···$O_{3B(1)}$ *(4)	0.86(3)	2.036(3)	2.881(3)	167.5(8)
$N_{1B(1)}$-$H_{1B(1)}$···$O_{1A(2)}$ *(5)	0.86(3)	1.998(3)	2.851(3)	170.8(8)
$N_{1A(2)}$-$H_{1A(2)}$···$O_{3B(2)}$ *(6)	0.86(3)	2.036(3)	2.881(3)	167.5(8)

Symmetry code: *(1) 2-x, y, ½+z; *(2) 1-x, -1/2+y, 1-z; *(3) -1+x, ½ +y, ½-z; *(4) 1-x, ½+y, 1-z; *(5) x, -1/2+y, 3/2-z; *(6) -1+x, y, z.

4. CONCLUSION

In summary a modified strategy to the synthesis of: *exo*-3,6-dimethyl-3,6-epoxi-1,2,3,6-tetrahydrophthalimide (**1**) and *exo*-N-(10-bromodecyl)-3,6-dimethyl-3,6-epoxi-1,2,3,6-tetrahydrophthalimide (**2**) was presented. The ^{1}H-NMR confirmed the chemical shifts and multiplicities previously reported for (**1**), and those reported for (**2**) were corrected in this work. The X ray crystal structure of (**1**) confirmed the *exo* isomerism of the DA adduct and showed the racemic nature of the crystal. Also it was found that the intermolecular hydrogen-bonds observed in the supramolecular structure of (**1**) are formed only by interaction of the imide moiety of one molecule and the longest carbonyl moiety of the other, and also that due to the noncrystallographic inversion center, four kinds of not superimposable entities can be found in the supramolecular structure. Further studies will be conducted to explore structural modifications to introduce a terminal SH group in (**2**) with the aim to link it to gold nanoparticles.

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