



Diels-Alder reaction with cyclopentadiene and electronic structures of $(\eta^5\text{-cyclopentadienyl})\text{M}(\text{CO})_x(\eta^1\text{-N-maleimidato})$ ($\text{M} = \text{Fe}, \text{Mo}, \text{W}, x = 2 \text{ or } 3$)

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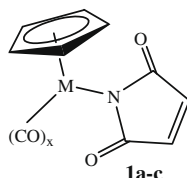
ABSTRACT

Diels-Alder reaction of $(\eta^5\text{-cyclopentadienyl})\text{M}(\text{CO})_x(\eta^1\text{-N-maleimidato})$ complexes ($\text{M} = \text{Fe}, \text{Mo}, \text{W}, x = 2$ or 3) with cyclopentadiene has been studied. The observed order of reactivity was: *N*-ethylmaleimide > W complex > Mo complex > Fe complex. The X-ray structures of the adducts have been determined for $\text{M} = \text{W}$ and Fe. DFT calculations on the starting complexes have been performed to explain the observed reactivity order.

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1. Introduction

Recently, the Diels-Alder reaction [1] using suitably *N*-substituted maleimides as dienophiles has been applied for the site-specific conjugation of biomolecules [1–6], because it is fast and efficient in aqueous media [7–9] in addition to being chemoselective. These applications prompted us to look at the Diels-Alder reactivity of metallo-carbonyl maleimides **1a–c** [10,11] with the purpose of using this reaction for the introduction of the IR-detectable or containing heavy metals [12,13] probes into diene-containing biomolecule conjugates. We have earlier studied the reaction of **1a–c** with thiol, amino and imidazole groups of biomolecules [10,11,14–16] and now we became interested in extension of the applicability of these complexes for biomolecules bearing attached diene moieties.



- a** $\text{M} = \text{Fe}; x = 2$
b $\text{M} = \text{Mo}; x = 3$
c $\text{M} = \text{W}; x = 3$

We have earlier reported that **1a** reacts with a very reactive diene, 1,3-diphenylisobenzofuran, to afford the Diels-Alder adduct [17]. This reaction was fast and to compare its rate with that of *N*-ethylmaleimide (NEM) the competitive reactions method had to be used. In this paper, we report the results of the study on the reaction of **1a–c** with a less reactive, ubiquitous diene, cyclopentadiene, which allowed us to determine the influence of organometallic moiety on the reaction rate. The structure of the products has been established by single crystal X-ray diffraction. We have also studied, using the DFT method the electronic structure of the complexes **1a–c**, with special emphasis on the nature of the frontier orbitals which play a primordial role in Diels-Alder reactions.

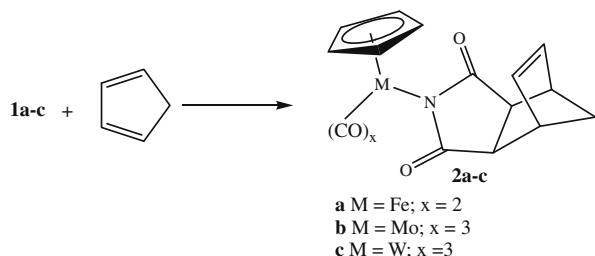
2. Results and discussion

2.1. Synthesis of **2a–c**

We have found that complexes **1a–c** react with cyclopentadiene in CH_2Cl_2 or under conditions mimicking biological labeling (water–methanol 9:1 to 3:1) at r.t. to give stable conjugates **2a–c** with 50–80% yield (Scheme 1). The reaction is slightly faster in aqueous solvent being completed in the case of **1a** after 30 min, whereas the same reaction in CH_2Cl_2 required 2 h. The products **2a–c** were purified by flash chromatography and their structure was confirmed by ^1H NMR and IR spectroscopic data and by elemental analyses. Moreover, the molecular structures of **2a** and **2c** have been determined by single crystal X-ray diffraction (*vide infra*).

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Scheme 1. Diels-Alder reaction of **1a-c** with cyclopentadiene.

2.2. The X-ray structures of **2a** and **2c**

The crystals of **2a** and **2c** suitable for X-ray diffraction were grown from layered CH_2Cl_2 -heptane. The molecular structures of these compounds are shown in Figs. 1 and 2.

The crystal and structure refinement data are gathered in Table 1, whereas Table 2 contains selected geometrical parameters. Interestingly, only one of two limit conformations resulting from the rotation around the M–N bond is observed in the crystals of both compounds, namely that having the cyclopentene ring of the bicyclic moiety and the cyclopentadienyl ligand on the same side of the imide ring plane. Since DFT calculations revealed practically the same stability of both conformers (*vide infra*) this preference may be due to crystal packing effect.

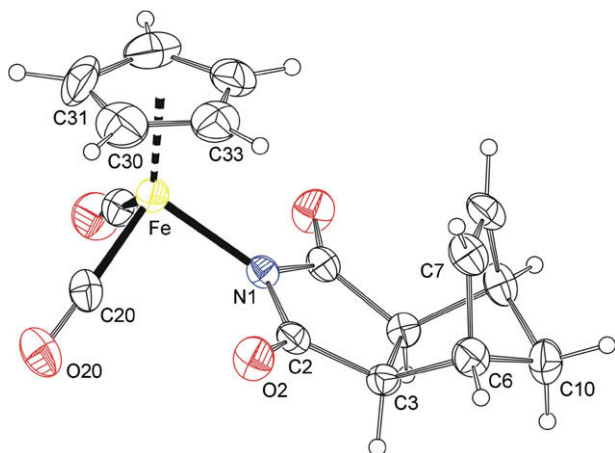


Fig. 1. Molecular structure of **2a** in the crystal. The thermal ellipsoids correspond to 50% probability.

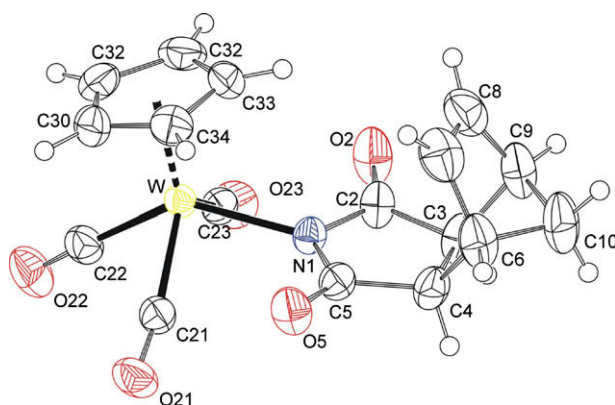


Fig. 2. Molecular structure of **2c** in the crystal. The thermal ellipsoids correspond to 50% probability.

Table 1

Crystallographic data and structure refinement for **2a** and **2c**.

Crystal data		
Formula	$\text{C}_{16}\text{H}_{13}\text{FeNO}_4$	$\text{C}_{17}\text{H}_{13}\text{WNO}_5$
Formula weight	339.12	495.13
Crystal system	Orthorhombic	Monoclinic
Space group	<i>Pnma</i> (no. 62)	<i>P2₁/n</i> (no. 14)
<i>a</i> (Å)	12.780(3)	6.4831(17)
<i>b</i> (Å)	11.402(10)	19.838(5)
<i>c</i> (Å)	9.878(2)	12.333(3)
β (°)	90.00	92.140(4)
<i>V</i> (Å ³)	1439.4(13)	1585.1(7)
<i>Z</i>	4	4
<i>D</i> _{calc} (g/cm ³)	2.147	2.075
Crystal size (mm)	0.18 × 0.10 × 0.10	0.18 × 0.15 × 0.05
Data collection		
Temperature (K)	293	293
Radiation (Å)	Cu K α 1.541780	Mo K α 0.71073
θ Minimum–Maximum (°)	5.7, 68.8	1.95, 31.4
Dataset	–14; 14; –13; 13; –11; 11	–9; 8; –29; 26; –16; 17
Total/Unique Data/ <i>R</i> _{int}	8147/944/0.0945	36548/4634/0.021
Observed data [<i>I</i> > 2.0 σ (<i>I</i>)]	1182	4220
μ (mm ^{–1})	8.569	7.315
Absorption correction <i>T</i> _{min} / <i>T</i> _{max}	0.4002/0.4173	0.2791/0.6932
Refinement		
Number of reflections	1182	4634
Number of parameters	107	217
<i>R</i> , <i>wR</i> ₂ , <i>S</i>	0.0462, 0.1339, 1.049	0.0189, 0.0489, 1.091
Minimum/maximum residual density (e Å ^{–3})	–0.56/0.41	–0.58/1.23

Table 2

Selected geometrical parameters estimated in X-ray experiment (distances in Å, angles in °). M denotes transition metal atom.

	2a	2c
M–C20	1.756(4)	–
M–C21	–	2.018(2)
M–C22	–	2.000(2)
M–C23	–	2.018(2)
M–N1	1.956(4)	2.1817(17)
N1–C2	1.375(4)	1.390(3)
N1–C5	–	1.403(3)
C5–O5	–	1.219(3)
C2–O2	1.212(4)	1.217(3)
C20–O20	1.147(5)	–
C21–O21	–	1.147(3)
C22–O22	–	1.151(3)
C23–O23	–	1.152(3)
M–C20–O20	178.1(4)	–
M–C21–O21	–	172.2(2)
M–C22–O22	–	176.8(2)
M–C23–O23	–	172.40(19)
C2–N1–C2	110.6(4)	–
C2–N1–C5	–	110.07(17)
O2–C2–N1	121.7(9)	124.7(2)
O5–C5–N1	–	124.4(2)
M–N1–C2–O2	–2.9(2)	–1.1(4)

2.3. Kinetic measurements

For kinetic studies the reaction of **1a-c** with cyclopentadiene was carried out directly in a NMR tube in CDCl_3 at 25 °C. The starting concentrations of **1a-c** and cyclopentadiene were 12 mM. The concentration of the adducts was determined by integration of their Cp signals, which were well separated from the Cp signals of the starting materials and did not overlapped with other signals. The calculated second-order rate constants are shown in Table 3. Under these conditions the reaction of NEM with cyclopentadiene was too fast for kinetic measurements.

Table 3

Second-order rate constants and half-lives of Diels-Alder reaction of **1a–c** with cyclopentadiene in chloroform.

	k_1 ($M^{-1} s^{-1}$)	$t_{1/2}$ (s)
1a	129 ± 10	843
1b	200 ± 22	543
1c	247 ± 23	440

Similarly as in the case of reaction with glutathione [11], the tungsten complex **1c** proved the most reactive and the least reactive was the iron complex **1a**. The ratio of the rate constants for these complexes ~1.9 is slightly lower than that observed for nucleophilic addition to the double bond, ~4.5.

2.4. Computational studies

2.4.1. Comparison of conformations of **2a**

A DFT study of two limit conformations of **2a** was carried out (see Section 3 for details). Atomic positions and total energies are collected in Table 1 of supporting material. The fully optimized geometries of both conformations are shown in Fig. 3. The conformations have practically the same energy (difference in total energies is equal to 0.75 kcal/mol). Hence, the presence of only conformation in the crystal of **2a** should be due to packing forces.

2.4.2. Analysis of MO's of **1a–c** and NEM

It is well known, that the energetic availability of the dienophile lowest unoccupied molecular orbital (LUMO) has a crucial influence on the Diels-Alder reaction process. Thus, MO analysis has been performed for **1a–c** and, for comparison, for a classical organic dienophile, NEM. The HOMO, LUMO and LUMO + 1 orbitals of **1a–c** and NEM and their energies are shown in Fig. 4.

As it can be seen, the LUMO's of **1a**, **1c**, and NEM are concentrated on the maleimidato ligand and have symmetry matching with that of the HOMO of a dienic system. Contrastingly, the LUMO of **1b** is concentrated mainly on the organometallic moiety and therefore can not take part in the Diels-Alder reaction. However, the LUMO + 1 of this complex adopt the same shape as the LUMO's of **1a**, **1c**, and NEM. Hence, we hypothesize that Diels-Alder reaction of **1b** involves the LUMO + 1 orbital. Nicely, the order of the calculated LUMO (or LUMO + 1 for **1b**) energies: NEM < **1c** < **1b** < **1a** (Fig. 4) is the same as the order of observed rate constants for reaction with cyclopentadiene. Additionally, the shape and spatial arrangement of HOMO's of **1b**, **1c** and NEM suggests that these

orbitals are not involved in reaction with cyclopentadiene. On the other hand, one can not exclude some participation of the HOMO of **1a** which is concentrated, to some extent, on the ethylenic bond and has a proper symmetry for overlapping with the LUMO of a diene.

3. Experimental

3.1. General remarks

The 1H NMR spectra were recorded in $CDCl_3$ on VARIAN GEMINI 200BB (200 MHz for 1H) and AVANCE TM DRX500 (500 MHz for 1H) spectrometers and referenced to internal tetramethylsilane. The IR spectra were recorded in $CHCl_3$ on a FT-IR NEXUS (Thermo Nicolet) spectrometer. All solvents were purified according to standard procedures. Chromatographic separations were performed on Silica gel Merck 60 (230–400 mesh ASTM). All reactions were carried out under argon.

3.2. Materials

Complexes **1a–c** were synthesized as previously described [10–11]. Cyclopentadiene was obtained by cracking of the dimer (Sigma–Aldrich) directly before use.

3.3. Diels-Alder reaction of **1a–c** with cyclopentadiene

3.3.1. Reactions carried out in CH_2Cl_2

To argon-saturated solutions of complexes **1a–c** (0.07 mmol) in CH_2Cl_2 (4 ml) 4 equiv. of cyclopentadiene were added and the reaction mixtures were stirred 2 h at r.t. Column chromatography (chloroform–MeOH 9:1 as eluent) afforded an yellow (**2a**) or orange (**2b–c**) solids. After evaporation of the solvent the solids were dissolved in chloroform and washed three times with 2.5% aq. NaOH solution. Crystallization from CH_2Cl_2 /heptane (3:1) afforded analytically pure samples.

Compound 2a: Yield: 80%, M.p. 150 °C, 1H NMR (δ , ppm): 1.43 (d, $J = 7.5$ Hz, H, CH_2) 1.61 (d, $J = 7.8$ Hz, H, CH_2) 3.17 (s, 2H, CH), 3.23 (s, 2H, CH), 4.97 (s, 5H, Cp) 5.97 (s, 2H olefin), IR (cm^{-1}): 2042, 1975 ($C\equiv O$), 1647 (CO imide). Anal. Calc. for $C_{16}H_{13}FeNO_4$ C, 56.63; H, 3.83; N, 4.12. Found: C, 56.62; H, 3.79; N, 4.21.

Compound 2b: Yield: 65%, M.p. 142 °C, 1H NMR (δ , ppm): 1.65 (d, $J = 8.4$ Hz, H, CH_2) 1.26 (d, $J = 8.4$ Hz, H, CH_2) 3.25 (s, 2H, CH), 3.28 (s, 2H, CH), 5.48 (s, 5H, Cp) 6.01 (s, 2H olefin), IR (cm^{-1}): 2050,

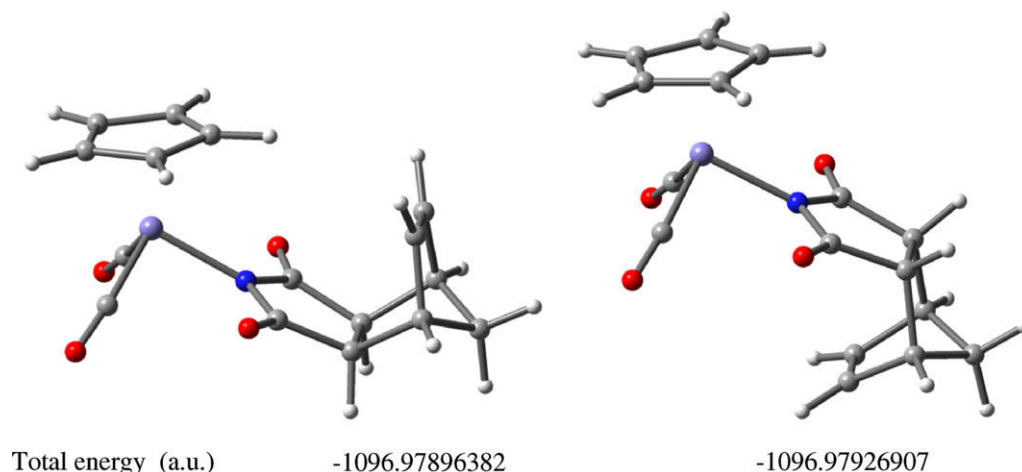


Fig. 3. Graphical representation of the fully optimized molecular geometries of two limit conformations of **2a**.

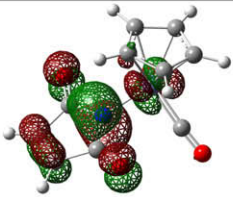
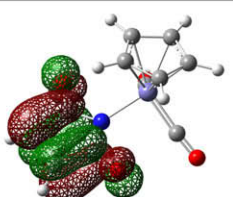
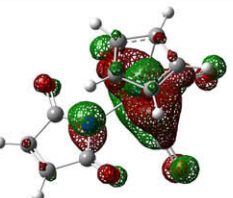
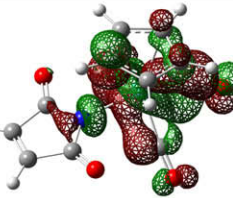
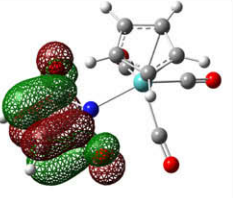
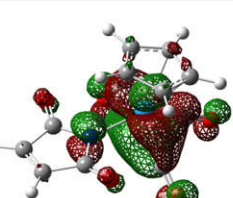
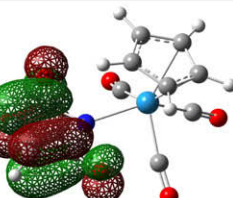
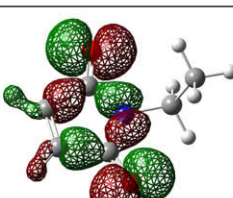
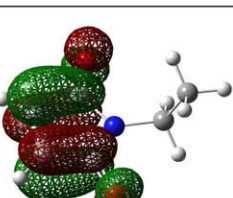
	HOMO	LUMO	LUMO+1
1a	 -0.249 a.u.	 -0.083 a.u.	
1b	 -0.234 a.u.	 -0.096 a.u.	 -0.091 a.u.
1c	 -0.230 a.u.	 -0.094 a.u.	
NEM	 -0.286 a.u.	 -0.109 a.u.	

Fig. 4. Frontier MO's and their energies of **1a–c** and NEM.

1975(C≡O), 1639 (CO imide). Anal. Calc. for $C_{17}H_{13}MoNO_5$: C, 50.14; H, 3.22; N, 3.44. Found: C, 50.52; H, 3.70; N, 3.42.

Compound 2c: Yield: 51%, M.p. 160 °C, 1H NMR (δ , ppm): 1.26; 1.68 (m, 2H, CH₂) 3.23 (s, 2H, CH), 3.28 (s, 2H, CH), 5.63 (s, 5H, Cp) 6.02 (s, 2H olefin), IR (cm⁻¹): 2049, 1997 (C≡O), 1632 (CO imide). Anal. Calc. for $C_{17}H_{13}NO_5W$: C, 41.24; H, 2.65; N, 2.83. Found C, 41.49; H, 2.88; N, 2.78.

3.3.2. Reaction carried out in water–methanol

To argon-saturated solutions of complexes **1a–c** (0.07 mmol) in water–methanol (4 ml, 9:1 for **1a** and 3:1 for **1b–c**) 4 equivalents of cyclopentadiene were added and reaction mixtures were stirred 30 min at r.t. The solvent was evaporated and the residues dissolved in chloroform and chromatographed. Yellow (**2a**) or orange (**2b–c**) bands containing products were eluted with chloroform–MeOH 9:1. After evaporation of the solvent the solids were

dissolved in chloroform and washed three times with 2.5% aq. NaOH solution. Crystallization from CH₂Cl₂/heptane (3:1) afforded analytically pure samples. Complexes **2a**, **2b** and **2c** were isolated in 75%, 58% and 40% yield, respectively.

3.4. Computational details

Geometries of the molecular systems investigated by means of MO theory were taken from our previous studies [18]. MO analysis was performed using DFT-B3LYP functional [19–21] in combination with the 6-311+G(d) basis set [22–23] for C, N, O and H atoms and the LanL2DZ basis set [24–26] for the transition metals, both basis implemented in GAUSSIAN 03 set of codes [27]. ECP corrections were applied for the latter using LanL2DZ pseudopotentials for core electrons. This level of theory corresponds to that one which was applied for geometry optimization process. It is worth to men-

tion, that the obtained geometries are generally in agreement with the previously reported geometries from crystal structures [11,18].

Geometries of the systems corresponding to the Diels-Alder reaction products were optimized without any restraints using the same DFT-functional, however with the basis function for C, N, O and H atoms augmented by additional polarization functions (6-311+G(3df) basis set for C, N, O and H atoms). Starting geometry of *syn* conformation was taken directly from crystal structure. Starting geometry of *anti* conformation was obtained from optimized *syn* conformation geometry after 180° rotation of the ligand around the Fe–N bond.

3.5. X-ray structure determination of **2a** and **2c**

Single crystals mounted on glass fibers were used for measurements at room temperature on Enraf-Nonius and Rigaku AFC5S diffractometers for **2a** and **2c** compounds, respectively, in both cases using Mo K α X-ray source. Structures were solved by direct methods using SHELXS-97 [28] and refined by full-matrix least square method on F^2 using SHELXL-97 [29]. An analytical correction for absorption has been applied [30]. For both structures, after the refinement with isotropic displacement parameters, refinement was continued with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were located geometrically using AFIX in SHELXL-97. In the final step of refinement all the non-hydrogen atoms were refined with anisotropic thermal parameters. A summary of crystallographic relevant data is given in Table 1.

The molecular geometry was calculated by PLATON [31]. Selected bond distances, angles are summarized in Tables 1 and 2. The drawings were made by PLATON [31].

Appendix A. Supplementary material

CCDC 674034 and 674035 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2008.12.031.

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