Synthesis of metallocarbonyl substituted 1,2,3-triazole complexes via copper(I)-catalyzed azide–alkyne cycloaddition

Bogna Rudolf

Abstract: (η^5-C_5H_5)M(CO)$_x$(η^1-*N*-maleimidato) (M = Fe, x = 2; M = W, x = 3) complexes react with propargylamine and propargyl alcohol giving products from the Michael addition to the η^1-*N*-maleimidato ligand. Metallocarbonyl compounds bearing a terminal alkyne group were reacted with organic azides affording corresponding 1,2,3-triazoles in high yields. One of these metallocarbonyl 1,2,3-triazoles (M = Fe, x = 2) was characterized by X-ray diffraction.

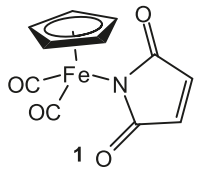
Key words: copper(I)-catalyzed azide–alkyne cycloaddition, click chemistry, metallocarbonyl complexes, X-ray structure.

Résumé : Les complexes (η^5-C_5H_5)M(CO)$_x$(η^1-*N*-maléimidato) (M = Fe, x = 2; M = W, x = 3) réagissent avec la propargylamine et l'alcool propargylique pour conduire à la formation de produits d'addition de Michael sur le ligand η^1-*N*-maléimidato. La réaction de composés métallocarbonyles portant un groupe alcyne terminal avec des azotures organiques conduit à la formation des 1,2,3-triazoles correspondants avec des rendements élevés. Faisant appel à la diffraction des rayons-X, on a caractérisé le métallocarbonyl-1,2,3-triazole dans lequel M = Fe et x = 2.

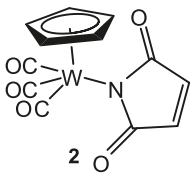
Mots-clés : cycloaddition azoture–alcyne catalysée par le cuivre(I), chimie de cliquage, complexes métallocarbonyles, structure, diffraction des rayons X.

Introduction

The copper(I) catalyzed, regioselective synthesis of 1,4-disubstitututed-1,2,3-triazoles, from azides and terminal alkynes, which was developed by Sharpless et al., has been shown to be amongst the most popular reactions recently studied, known as "click chemistry"[1–3]. There have been numerous applications of this reaction in the fields of bioconjugation, materials science, and drug discovery.[4–7] Copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) has been used to obtain conjugates which possess numerous functional subunits with fluorescent or electrochemical properties.[8,9] However, this methodology has not yet been applied to connecting metallocarbonyl complexes with organic ligands. In view of this situation, I became interested in exploring the CuAAC reaction as a synthetic method for preparating 1,4-disubstitututed-1,2,3-triazoles bearing IR-detectable metallocarbonyl complexes.[10] Over the past years we have explored the chemistry of the metallocarbonyl (η^5-C_5H_5)M(CO)$_x$(η^1-*N*-maleimidato) complexes of Fe, **1**, and W, **2**,[11,12] which were applied as labels of peptides and proteins, with potential applications in immunoassay analysis.[12–16]



1



2

It appeared of interest to introduce a terminal alkyne group to compounds **1** or **2** to form metallocarbonyl complexes that would be able to react with organic azides. Such a process could be an entry to new selective labeling of biomolecules, using the CuAAC reaction. In this paper, I report the synthesis of two new metallocarbonyl complexes bearing terminal alkyne ligands, **3** and **4**, and a preliminary study of their reactions with organic azide derivatives in the presence of a Cu(I) catalyst. The structure of the 1,3-cycloaddition product, **5**, has been established by a single crystal X-ray analysis.

Results and discussion

The Huisgen 1,3-cycloaddition of organic azides and alkynes has been shown to be the most direct route to obtaining 1,2,3-triazoles. The use of Cu(I) complexes in this process led to the formation of one regioisomer, a 1,4-disubstituted 1,2,3-triazole derivative. Cu(I) halide salts can also be used, or, alternatively, the Cu(I) complex could be generated in situ by the reduction of Cu(II) salts.[1–3] The reaction could be performed in various solvents or mixtures of organic solvents, or in water. Owing to the high regioselectivity, high yields, and an exceptional tolerance towards a wide range of functional groups and reaction conditions, the copper(I)-catalyzed azide–alkyne cycloaddition has been found to have numerous applications in biochemistry research, allowing the regioselective incorporation of various labels to biomolecules.[17–20]

Received 21 May 2010. Accepted 29 June 2010. Published on the NRC Research Press Web site at canjchem.nrc.ca on 8 September 2010.

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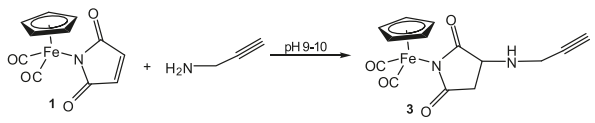
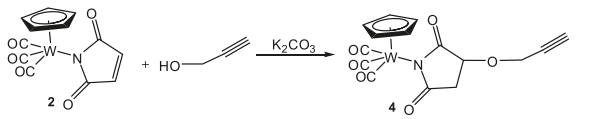
There has been no reported research concerning the Huisgen 1,3-cycloaddition of metallocarbonyl complexes in the literature, to my knowledge; however, there were several published examples of ferrocene compounds bearing azide or alkyne groups, which underwent the CuAAC reactions leading to the expected triazole products.[21–25] To investigate the CuAAC reaction of metallocarbonyl complexes with azides, it was first necessary to synthesize such complexes, bearing an alkyne group.

Because complex **1** reacted with primary amines at pH 9–10 providing aza-Michael addition products,[13] the reaction with propargylamine seemed a straightforward synthetic approach for the introduction of the terminal alkyne function to this complex (eq. [1])

[1] 

The reaction was carried out at room temperature in MeOH–H_2O, and afforded a yellow crystalline product. The ^{1}H NMR spectrum confirmed the structure of **3,** with the signal at 6.68 ppm, characteristic of the ethylenic protons in **1,** being absent, while the complex signals attributed to the succinimide ring and the propargyl protons were observed at 2.42, 3.33, and 3.83, including the acetylene proton signal, which appeared at 2.09 ppm, as a triplet.

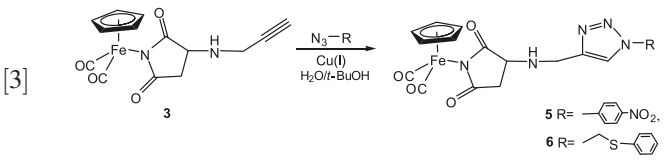
Since it was reported that maleimide derivatives undergo an oxa-Michael addition reaction with alcohols in the presence of K_2CO_3 under mild reaction conditions,[26] I decided to react **2** with propargyl alcohol, to give **4** (eq. [2]). This reaction resulted in the isolation of a yellow crystalline complex, whose ^{1}H NMR spectrum confirmed the structure as **4** (Yield 42%)

[2] 

The ^{1}H NMR spectrum showed a triplet at 2.48 ppm, which was expected for the alkyne proton, with an absence of the singlet at ~6.7 ppm, characteristic for the olefinic protons in the substrate, **2**. Further evidence of the oxa-Michael addition to the maleimide double bond were the signals of the succinimide protons at 2.66, 3.03, and 4.48 ppm.

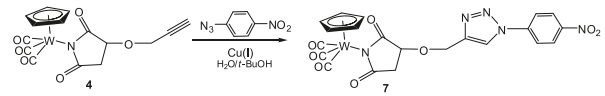
Metallocarbonyl complexes, **3** and **4**, displayed the characteristic strong absorption bands in their IR spectra, the $\nu_{C\equiv O}$ appearing in the 1950–2060 cm^{-1} spectral region, which is usually free of any absorption of biomolecules or biological matrices.

With the successful synthesis of complexes **3** and **4**, their reactivity towards organic azides in the presence of a CuCl–Cu catalyst were investigated. Both compounds were allowed to react with *p*-nitrophenyl azide, and complex **3** was also reacted with (phenylthio)methyl azide. In all cases, the cycloaddition reaction took place, and the expected triazoles, **5–7**, were isolated in 81%–88% yields (eqs. [3] and [4]).

[3] 

The yellow products, **5** and **6**, were isolated by flash chromatography and crystallized from CH_2Cl_2–heptane. The identity and purity of these compounds were confirmed by spectroscopic methods and elemental analyses. The singlets in the ^{1}H NMR spectra of **5** and **6** (δ 8.06 and 7.51 ppm, respectively) were attributed to the triazole ring protons, and provided evidence of the formation of this heterocyclic ring. The structure of 1,2,3-triazole **5** was also confirmed by single crystal X-ray diffraction (vide infra).

The 1,2,3-triazole, **7**, was synthesized in the same manner from alkyne complex **4** and *p*-nitrophenyl azide in the presence of the CuCl–Cu catalyst (eq. [4]). The expected product was isolated in 81% yield, as an orange oil. The lack of an alkyne proton signal and the appearance of a singlet at δ 8.19 ppm in its ^{1}H NMR spectrum provided evidence of the formation of a 1,2,3-triazole derivative.

[4] 

The X-ray crystal structure of 5

Crystals of **5** suitable for X-ray structure determination were grown from CH_2Cl_2–heptane. Compound **5** crystallized in the triclinic *P*1 space group (see Fig. 1 for the graphical representation). The selected crystal data and structure refinement details are shown in Table 1. The triazole *p*-nitrophenyl substituent was shown to be attached to the succinimide ring in a position opposite to the Fp moiety. The best plane of the succimidato ring forms an angle of 44.02(19)° with the best plane of the Cp ring. The succinimidato ring was nearly coplanar with the triazole and *p*-nitrophenyl rings. This was shown by the relatively small values of the dihedral angles, being 9.00(19)° and 15.87(18)° for the triazole and phenyl rings, respectively. The triazole and phenyl rings were found to be coplanar, with the dihedral angle being 8.61(12)°. No classical hydrogen bonds were found for this compound; however, the crystal structure of **5** was stabilized by several weak intermolecular, non-covalent interactions of the C–H···O type.

Selected bond lengths (Å) and angles (°) are gathered in Table 2.

Conclusions

The metallocarbonyl complexes **3** and **4**, with terminal alkyne bonds, have been synthesized, and found to be effective CuAAC reaction substrates. Under the Sharpless conditions, the alkynes **3** and **4** effectively reacted with selected organic azides, affording the corresponding 1,2,3-triazoles in high yields. We plan to use this technique to develop new bioprobes for Carbonyl Metallo Immuno Assay (CMIA).

Fig. 1. ORTEP drawing of compound **5** with the atom-labelling scheme. Displacements ellipsoids are drawn at the 50% probability level. H atoms are omitted for clarity.

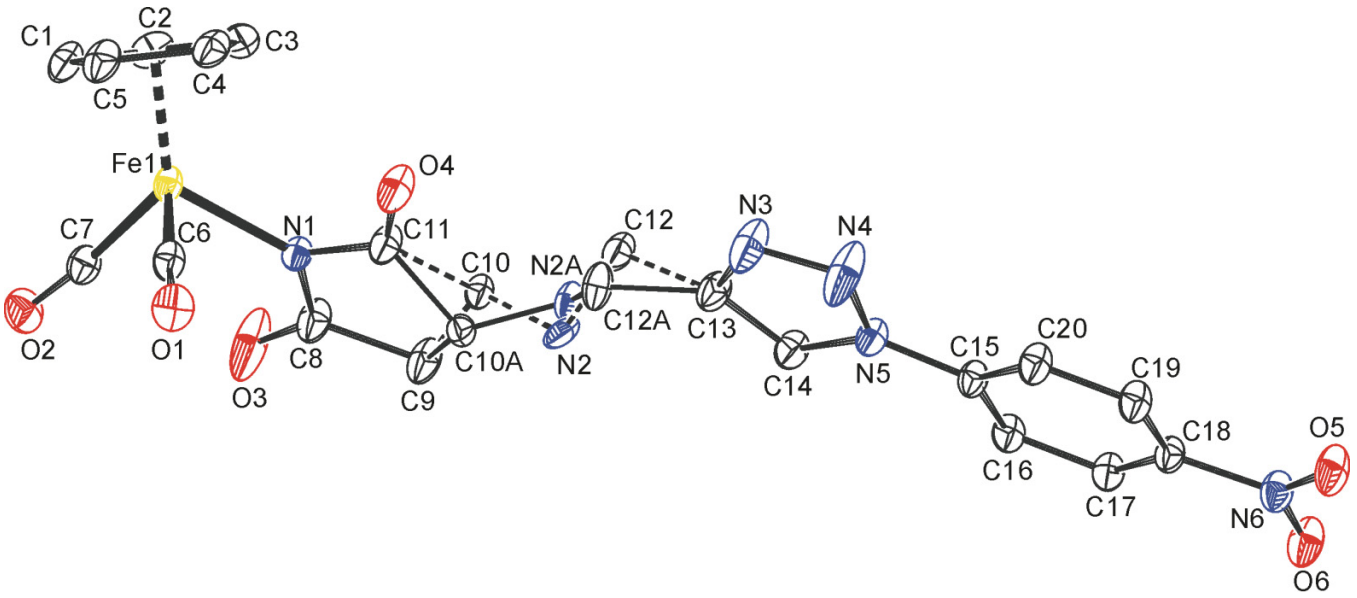


Table 1. Crystallographic data and structure refinement of **5**.

Chemical formula	C_{20} $H_{16}FeN_6O_6$
Measurement temperature	293 K
Beam length λ (Å)	0.71073
Space group	*P*1
a (Å)	6.6833(3)
b (Å)	11.9347(7)
c (Å)	12.4586(6)
α (Å)	79.417(3)
β (Å)	84.442(3)
γ (Å)	85.386(3)
V (Å^3)	970.25(9)
Z	2
Absorption coefficient (mm^{-1})	0.83
Independent reflections	5794, 4644
T_{min}, T_{max}	0.6914, 0.7461
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.70
$R_{(int)}$, $R_{(sigma)}$	0.0000, 0.0362
R_1 [$I > 2\sigma$ (I)], R_1 all	0.0426, 0.0568
wR_2 all	0.1122
Goodness-of-fit	1.060

Table 2. Bond lengths (Å) and angles (°) for **5**.

Bond lengths (Å)	
Fe(1)—C(6)	1.781(2)
Fe(1)—C(7)	1.783 (2)
Fe(1)—N(1)	1.9773(15)
Fe(1)—C(1)	2.083(2)
C(8)—O(3)	1.212(3)
C(10)—N(2)	1.450(12)
C(10a)—N(2a)	1.451(9)
C(11)—O(4)	1.209(2)
C(12A—N(2A)	1.450(9)
C(12A)—(C13)	1.523(5)
N(1)—C(8)	1.363(2)
N(3)—N(4)	1.302(3)
N(4)—N(5)	1.349(2)
N(5)—C(15)	1.417(2)
O(2)—C(7)	1.134(3)
Bond angles (°)	
C(7)–Fe(1)–C(1)	88.96(9)
C(7)–Fe(1)–N(1)	95.55(8)
C(11)–N(1)–Fe(1)	120.72(13)
C(20)–C(15)–N(5)	118.31(17)
N(2)–C(12)–C(13)	112.5(6)
N(2A)–C(10A)–C(11)	113.3(5)
N(4)–N(5)–C(15)	118.88(16)
O(2)–C(7)–Fe(1)	174.19(18)
O(4)–C(11)–C(10)	123.6(2)
O(5)–N(6)–C(18)	118.28(17)
O(5)–N(6)–O(6)	123.84(17)

Experimental section

General remarks

The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200BB (200 MHz for ^{1}H) spectrometer and referenced to internal tetramethylsilane. The IR spectra were recorded in $CHCl_3$ on a FTIR NEXUS (Thermo Nicolet) spectrometer. Elemental analyses were performed by the Analytical Services of the Center of Molecular and Macromolecular Studies of the Polish Academy of the Sciences (Łódź). 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.

Materials

Complexes **1 and 2** were synthesized as previously described.[11,12] Propargylamine, propargyl alcohol, and (phenylthio)methyl azide were purchased from Sigma-Aldrich. Propargyl alcohol and propargylamine were distilled before

use. *p*-Nitrophenyl azide was synthesized according to Meudtner and al.[27]

Synthesis of 3

Propargylamine (20 μl, 0.37 mmol) and aqueous solution of K_2CO_3 pH 9–10 (2 mL) were added to an argon-saturated solution of complex **1** (100 mg, 0.37 mmol) in MeOH (3 mL) and the reaction mixture was stirred overnight at rt. After this time the mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to column chromatography; a yellow band containing the starting material **1** was eluted with dichloromethane, followed by a yellow band containing product **3** eluted with chloroform–MeOH (9:1). Crystallization from CH_2Cl_2–heptane (3:1) gave an analytically pure sample;.yield: 57 mg (47%). IR ν (cm^{-1}): 3290 (CH alkyne), 2103 (C≡C), 2056, 2009 (C≡O), 1639 (CO imide). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.09 (t, *J* = 1.4 Hz, H,CH, alkyne), 2.42 (dd, *J* = 5.1 Hz, *J* = 16 Hz, H, succinimide), 2.83 (dd, *J* = 7.9 Hz, *J* = 16 Hz, H, succinimide), 3.33 (d, *J* = 17 Hz, H, CH_2), 3.58 (d, *J* = 17 Hz, H, CH_2), 3.83 (dd, *J* = 5.1 Hz, *J*= 16 Hz, H, succinimide), 5.04 (s, 5H, Cp). Anal. calcd. for $C_{14}H_{12}FeN_2O_4$:C 54.24, H 3.66, N 8.54; found C 51.42, H 3.61, N 8.49.

Synthesis of 4

Tungsten complex **2** (120 mg, 0.29 mmol) was dissolved in propargyl alcohol (3 mL) and a saturated aqueous solution of K_2CO_3 (2 mL) was added. Then the reaction mixture was stirred overnight at rt. After this time, the mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated at reduced pressure. The residue was subjected to column chromatography; an orange band containing the starting material **2** was eluted with hexane–dichloromethane (1:4), followed by a yellow band containing product **4** eluted by the mixture of dichloromethane–MeOH 19:1. Crystallization from CH_2Cl_2–heptane (3:1) gave in analytically pure sample; yield: 59 mg (42%). IR ν (cm^{-1}): 3307 (CH alkyne), 2100 (C≡C), 2056, 2046, 1959 (C≡O), 1655 (CO imide). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.48 (t, *J* = 2.4 Hz, H, CH alkyne), 2.66 (dd, *J* = 4.6 Hz, *J* = 20 Hz, H, succinimide), 3.03 (dd, *J* = 9.2 Hz, *J* = 16 Hz, H, succinimide), 4.48 (dd, *J* = 4.6 Hz, *J* = 20 Hz, H, succinimide), 4.53 (t, 2H, CH_2, *J* = 4 Hz, H, CH_2), 5.64 (s, 5H, Cp). Anal. calcd. for $C_{15}H_{11}NO_6W$:C 37.14, H 2.29, N 2.89; found C 37.25,H 2.47, N 2.89.

Synthesis of metallocarbonyl 1,2,3 -triazoles 5–7

A typical procedure for the 1,3-dipolar cycloaddition of organic azides to metallocarbonyl alkynes was as follows: azide (0.11 mmol), CuCl (2 mg), and Cu (50 mg as thin wire) were added to a solution of **3** or **4** (0.11 mmol) in the mixture of H_2O–*tert*-butanol (1:1). Then the reaction mixture was stirred overnight. The resulting solution was filtered and concentrated under reduced pressure. The residue was diluted in CH_2Cl_2 and crude product was chromatographed on silica gel, using the mixture of MeOH–CH_2Cl_2 (1:19) as eluent to obtain compounds **5–7**. Crystallization from CH_2Cl_2–heptane (2:1) gave an analytically pure sample.

5 Yield: 45 mg (84%). IR ν (cm^{-1}): 2045, 1999 (C≡O), 1636 (CO imide), 1525, 1343 (NO_2). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.45 (dd, *J* = 5 Hz, *J* = 16 Hz, H, succinimide), 2.85 (dd, *J* = 8.2 Hz, *J* = 16 Hz, H, succinimide), 3.72 (dd, *J* = 5 Hz, *J* = 8 Hz, H, succinimide), 4.06 (s, 2H, CH_2), 5.04 (s, 5H, Cp), 7.97 (d, *J* = 9.1 Hz, 2H), 8.06 (s, triazole H), 8.41 (d, *J* = 9.1 Hz, 2H). Anal. calcd. for $C_{20}H_{16}FeN_6O_6$: C 48.80, H 3.28, N 17.07; found: C 48.69, H 3.41, N 16.89.

6 Yield: 47 mg (88%).IR ν (cm^{-1}): 2044, 1993 (C≡O), 1636 (CO imide). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.38 (dd, *J* = 5 Hz, *J* = 18 Hz, H, succinimide), 2.79 (dd, *J* = 8 Hz, *J* = 16 Hz, H, succinimide), 3.60 (dd, *J* = 5 Hz, *J* = 8 Hz, H, succinimide), 3.91 (s, 2H, CH_2), 5.03 (s, 5H, Cp), 5.61 (s, CH_2, H), 7.31 (s, 5H), 7.51 (s, triazole H). Anal. calcd. for $C_{21}H_{19}FeN_5O_4$: C 51.13, H 3.88, N14.20; found C 50.98, H 4.17, N 14.23.

7 Yield: 58 mg 81%.IR ν (cm^{-1}): 2037, 1932 (C≡O), 1636 (CO imide). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.66 (dd, *J* = 4.8 Hz, *J* = 18 Hz, H, succinimide), 3.04 (dd, *J* = 8.3 Hz, *J* = 20 Hz, H, succinimide), 4.44 (dd, *J* = 4.8 Hz, *J* = 8 Hz, H, succinimide), 5.07 (dd, *J* = 12.5 Hz, 2H, CH_2), 5.64 (s, 5H, Cp), 7.98 (d, *J* = 9 Hz, 2H), 8.19 (s, H, =CH), 8.43 (d, *J* = 9 Hz, 2H), 8.06 (s, triazole H). ESI–MS (M+Na) *m*/*z* = 672. Anal. calcd. for $C_{21}H_{15}N_5O_8W$: C 38.85, H 2.33, N 10.79; found C39.05, H 2.28 .

X-ray structure determination of 5

Single-crystal X-ray measurement of **5** was performed on a BRUKER APEX II ULTRAκ-axis diffractometer with a TXS rotating anode using MoKα radiation at 293 K. The data were collected using the omega scan measurement method, with 0.5 degrees scan width and 30s maximal counting time. The θ angle for data collection was varied in the range of 5.00–20.00°. The data were corrected with respect to Lorentz and polarization effects. An analytical absorption correction was applied using SADABS.[28] Indexing, integration, and scaling were performed with original Bruker Apex II software.[29] The structure was solved using direct methods and refined using SHELXL.[30] The refinement was based on F^2 for all reflections. Weighted *R* factors *wR* and all goodness-of-fit *S* values were based on F^2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined on idealized positions using a riding model.

Supplementary data

Supplementary data for this article are available on the journal Web site (canjchem.nrc.ca). CCDC 763118 contains the X-ray data in CIF format for this manuscript. These data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Acknowledgements

Dr. Damian Plażuk is gratefully acknowledged for the synthesis of *p*-nitrophenylazide. The Polish Ministry of Sci-

ence and Education is gratefully acknowledged for financial support (Grant PBZ-KBN 118/T09/12).

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