Ring-Opening Polymerization of 1,4,8-Trioxaspiro-[4.6]-9-Undecanone: A Route to Novel Molecular Architectures for Biodegradable Aliphatic Polyesters

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Abstract : The ring-opening polymerization of 1,4,8-trioxaspiro-[4.6]-9-undecanone (TOSUO) initiated by aluminum isopropoxide, $Al(O^iPr)_3$, is typically "living" and allows random and block copolyesters of predictable molecular weight and composition to be prepared. Deacetalization of the polyester chains is complete, and reduction of the accordingly formed ketone groups into hydroxyl groups as well. No chain scission is observed when these two derivatization reactions are carried out. The potential of these novel functional aliphatic polyesters has been discussed as drug colloidal vectors and macroinitiators for the synthesis of biodegradable and biocompatible comb, graft and even hyperbranched polymers.

INTRODUCTION

Today macromolecular engineering is one of the most important targets for the polymer chemists in their search for new materials. It is thus essential to control in a predictable manner molecular weight, molecular weight distribution, molecular composition and architecture, since they control the macroscopic properties of the final materials. Several years ago, some of us reported that the living polymerization of ε-caprolactone (ε-CL) could be initiated by aluminum alkoxides, such as bimetallic (Zn, Al) μ-oxo alkoxides and derivatives (Refs. 1, 2). The ring-opening polymerization proceeds by a "coordination-insertion" mechanism, in such a way that one chain extremity is capped by an ester carrying the alkoxy radical of the initiator, whereas hydrolysis of the propagating active aluminum alkoxide leads to the formation of a hydroxyl end-group. The living polymerization of ε-CL has also been reported by Inoue (Ref. 3) and Penczek (Ref. 4) using α,β,γ,δ-tetraphenylporphinato aluminum ([TPP]AlX) derivatives and diethyl-aluminum methoxide, respectively, as initiators. More recently, our laboratory has launched a research

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 CCC 1022-1360/98/$ 10.00

program dealing with the macromolecular engineering of polylactones and polylactides. Aluminum alkoxides, such as $Al(O^iPr)_3$ and $Et_{3-p}Al(O(CH_2)_2X)_p$ with $3 \geq p \geq 1$, have proved to be very effective initiators for the polymerization of lactones, lactides, glycolide and cyclic anhydrides. Polymerization is typically "living" and allows block copolyesters of perfectly controlled molecular weight and composition to be prepared. Aluminum alkoxides carrying functional alkoxy groups (X = -Br, $-CH_2-NEt_2$, $-CH_2-CH=CH_2$, $-OC(O)-C(Me)=CH_2$, ...) are at the origin of asymmetric telechelic polyesters including polyester macromonomers(end-groups being -X and -OH, respectively) (Ref. 5). The coupling of the asymmetric telechelic chains via the hydroxyl end-group or better the Al alkoxide precursor is a straightforward way to symmetric telechelic polyesters and star-branched polyesters bearing the X functional end-group (Refs. 6, 7).

This paper aims are reporting new possibilities of macromolecular engineering based on the extension of the ring-opening (co)polymerization to 1,4,8-trioxaspiro [4.6]-9-undecanone (TOSUO). Synthesis of 1,4,8-trioxaspiro-[4.6]-9-undecanone was described elsewhere (Ref. 8). Homopolymerization of TOSUO initiated by the commercially available aluminum isopropoxide, $Al(O^iPr)_3$, will be first discussed. On the basis of these data, conditions have been defined for the tailoring of random and block copolyesters of TOSUO and ε-caprolactone. Finally, the discussion will focus on the synthesis of aliphatic polyesters bearing various functional pendent groups with predictable molecular weight and rather narrow polydispersity. Their contribution to novel molecular architectures will also be discussed.

HOMOPOLYMERIZATION OF 1,4,8-TRIOXASPIRO-[4.6]-9-UNDECANONE INITIATED BY $Al(O^iPr)_3$

Consistently with a structure quite comparable to ε-CL, TOSUO is polymerized according to the same mechanism as ε-CL in toluene at 25°C. Indeed, the ^1H NMR analysis of the polymer recovered after purification confirms that the chains are end-capped by as many hydroxyl groups (δ=3.75ppm; H_f) as isopropyl ester groups (δ=5.01ppm; H_b) (Fig. 1). No carboxylic acid proton can be observed. On the basis of these observations and by analogy with the mechanism accepted for the ε-CL and LA polymerization initiated by aluminum alkoxides (Refs.1-9), the coordination of $Al(O^iPr)_3$ to the exocyclic carbonyl oxygen of TOSUO is followed by the acyl-oxygen cleavage of the monomer which accounts for the isopropyl ester end-group, (multiplet at 5.01 ppm (H_b) and a doublet at 1.24ppm (H_a) in a 1:6 ratio, Fig. 1) and the hydroxyl end-group issued from the hydrolysis of the propagating species (triplet at 3.75ppm (H_f), Fig. 1).

The TOSUO polymerization is perfectly "living" when initiated by $Al(O^iPr)_3$ in toluene at 25°C. Figure 2 shows indeed that the molecular weight of PTOSUO linearly increases with the monomer conversion. Furthermore, there is a close agreement between the mean degree of polymerization (D.P.) at total conversion (^1H-NMR and/or SEC) and the monomer/initiator

molar ratio (Fig. 2). Finally, the molecular weight distribution of PTOSUO is rather narrow (M_w/M_n=1.15 to 1.25) in agreement with a fast initiation compared to propagation, and a fast propagation compared to transfer or termination reaction if any.

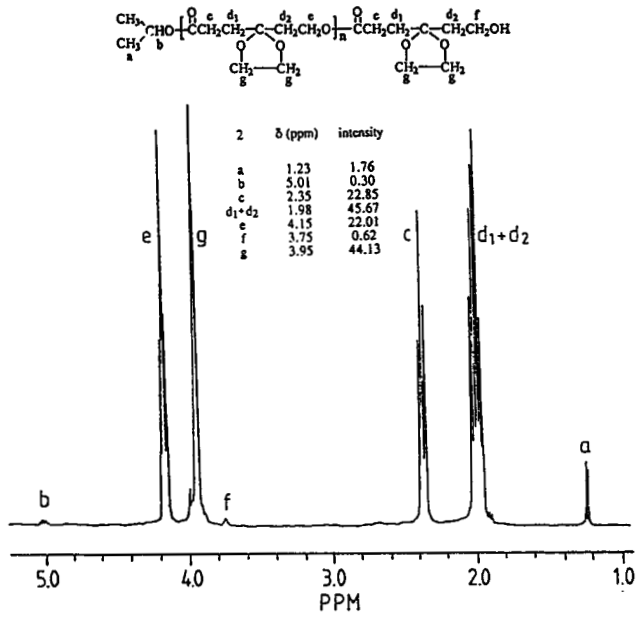


Figure 1. : ^{1}H-NMR spectrum of poly(TOSUO) in $CDCl_3$

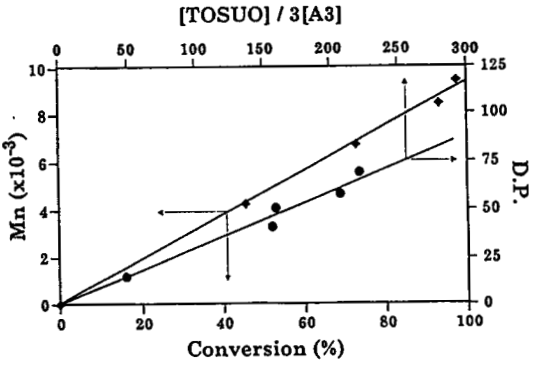


Figure 2. : Dependence of M_n on the monomer conversion and of the average degree of polymerization (DP) on the initial monomer/initiator molar ratio, for the TOSUO polymerization initiated by $Al(O^iPr)_3$ (A3) in toluene at 25°C.

In toluene, $Al(O^iPr)_3$ forms tetrameric (A4) and/or trimeric (A3) aggregates, which can be dissociated upon the addition of the cyclic monomer (Refs. 10-12). Whatever the monomer (ε-CL or LA), three chains are initiated by the dissociated A_1 species (Ref. 11). In this study, the A3 content of the initiator solution has been measured by ^1H NMR. Similarly to ε-CL, TOSUO also dissociates preferentially the A3 aggregates of $Al(O^iPr)_3$ in toluene, so that three PTOSUO chains are initiated per $Al(O^iPr)_3$ molecule and the molecular weight (M_n) can be predicted by equ. 1, where M_T is the molecular mass of TOSUO (172g/mol), α is the monomer conversion, and [A3] is the initial concentration of $Al(O^iPr)_3$ trimers.

$$M_{n(theoretical)}=([TOSUO] \times M_T \times \alpha)/(9[A3]) \quad (1)$$

A kinetic study has shown that except for the induction period, the ring opening polymerization fits the following overall kinetic law:

$$-d[TOSUO]/dt = k[TOSUO][Al(O^iPr)_3] \quad (2)$$

where the kinetic constant k = 21 $L \cdot mol^{-1} \cdot min^{-1}$. This equation is exactly the same as for polymerization of ε-CL and LA in toluene at 0°C and 70°C, respectively. k values are then 36.6 $L \cdot mol^{-1} \cdot min^{-1}$ for ε-CL (Ref. 3) and 0.6 $L \cdot mol^{-1} \cdot min^{-1}$ for LA (Ref. 12).

RANDOM COPOLYMERIZATION OF 1,4,8-TRIOXASPIRO-[4.6]-9-UNDECANONE AND ε-CAPROLACTONE INITIATED BY $Al(O^iPr)_3$

Random copolymerization of ε-CL and TOSUO has been initiated by $Al(O^iPr)_3$ in toluene at 25°C. The molar fraction of TOSUO in mixture with ε-CL has been changed from 0.13 to 0.91. Copolymerization conditions and results have been detailed elsewhere (Ref. 13). In all the conducted experiments, the comonomer conversion was quantitative, and the number average degree of polymerization (D.P.) was directly controlled by the $([\varepsilon\text{-CL}]_o + [TOSUO]_o)/3[Al(O^iPr)_3]_o$ molar ratio, as assessed by the good agreement between values calculated from equation (3) which holds for a living system at complete comonomer conversion, and the experimental values measured by ^1H-NMR.

$$Mn = (114 \times [\varepsilon\text{-CL}]_o + 172 \times [TOSUO]_o)/3[Al(O^iPr)_3]_o + 60 \quad (3)$$

Mn measured by size exclusion chromatography with the universal calibration curve valid to PCL is as less consistent with values calculated from ^1H-NMR data as the TOSUO content is high

(Ref. 13). Actually, the elution volume in THF tends to decrease with respect to PCL of the same molecular weight as the TOSUO content of the copolymer is higher.

Since the application of equ. 3 accounts for the experimental D.P., three chains are growing per $Al(O^iPr)_3$ molecule, as it is the case for the ε-CL and TOSUO homopolymerization. Molecular weight distribution of the copolymers remains narrow when the chains are deactivated as soon as the monomer conversion is complete (Mw/Mn : 1.15-1.25). When the molar fraction of TOSUO in the comonomer feed is increased, the time for a 100 % copolymerization reaction becomes longer.

The average lengths of the ε-CL sequences (L_C) and TOSUO sequences (L_T) in the random copolymers have been calculated from quantitative ^{13}C-NMR. From the average lengths of the ε-CL sequences and TOSUO sequences, the reactivity ratios have been calculated.

A relationship between the reactivity ratio (r) and the average length of the sequence (L) for each comonomer (1 and 2) in a binary copolymerization is given by eqs. 4 and 5, (Ref. 13) where $A=[M_C]_o/[M_T]_o$:

$$L_1 = A \cdot r_1 + 1 \qquad (4)$$

$$L_2 = \frac{r_2}{A} + 1 \qquad (5)$$

Indeed, a linear relationship is observed when the sequence length (L_C or L_T) is plotted against A ($[M_C]_o/[M_T]_o$) or A^{-1} ($[M_T]_o/[M_C]_o$) (Figure 3). Thus, from the slope of the straight line, r_C and r_T are easily calculated as 1.3 and 1.0, respectively. The reliability of the r_C and r_T values is of course basically dependent on the accuracy of L_C and L_T, which depends on the possible occurrence of transesterification reactions.

BLOCK COPOLYMERIZATION OF 1,4,8-TRIOXASPIRO [4.6]-9-UNDECANONE WITH ε-CAPROLACTONE INITIATED BY $Al(O^iPr)_3$

When two or more monomers are polymerized in a living manner according to the same mechanism, their sequential polymerization is a unique way to prepare block copolymers. As shown in the previous section, TOSUO comply to the same "coordination-insertion" polymerization as ε-CL, which is the prerequisite for the straightforward synthesis of diblock and even triblock copolymers of TOSUO and ε-CL.

Diblock copolymers have been prepared from either living PCL or living PTOSUO chains as macroinitiators. Synthesis of triblock copolymers of ε-CL and TOSUO has also been

successfully achieved. The typical SEC chromatograms for block copolymers are shown in Figure 4. The molecular weight distribution for the first block is narrow and does not change significantly upon the second and the third block formation, whereas no homopolymer formation can be detected by SEC. As expected, the molecular weight of the macroinitiator is systematically shifted toward higher values, in agreement with the theoretical values. Results and conditions for the block copolymerization have been reported elsewhere (Ref. 14).

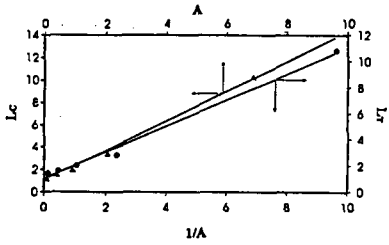


Figure 3. : Relationship between sequence lengths (Lc or L_T) and initial comonomer ratio A = $[M_C]_o/[M_T]_o$ or A^{-1} = $([M_T]_o/[M_C]_o$.

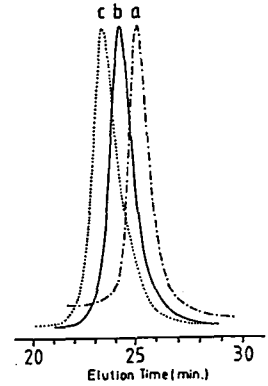


Figure 4. : SEC chromatograms of block copolymers. (A) the first block, PCL, Mn = 16.0K; (B) poly(ε-CL-b-TOSUO), Mn = 16.0K/14.5K; (C) poly (ε-CL-b-TOSUO-b-ε-CL), Mn = 16.0K/14.5K/19.0K.

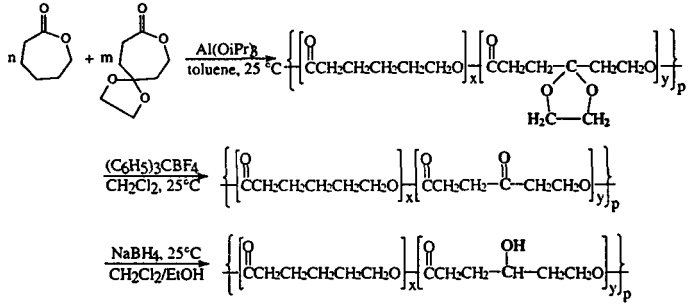
In all the cases, the molecular weight of each block is in good agreement with the value expected from the monomer/initiator molar ratio and the number of active sites per Al. Furthermore, ^{13}C-NMR analysis indicates that no detectable transesterification reactions occur under the experimental conditions used.

ALIPHATIC POLYESTERS BEARING FUNCTIONAL PENDENT GROUPS

The shortage of polyester chains bearing functional pendent groups is a severe limitation to further progress. Indeed, the availability of functional pendent groups is highly desirable for attachment of drugs, improved surface hydrophilicity, regulation of cell activity, etc. The typical pathway to functional polyesters is based on functional monomers, which are prone to polymerization or copolymerization with lactones or lactides. The functional groups must be selected or previously protected in such a way that they do not interfere with the polymerization mechanism.

A novel and efficient way to synthesize aliphatic polyesters bearing functional pendent groups is shown in Scheme 1. The first step, i.e. synthesis of chains bearing acetal pendent groups, has

proved the inertness of the acetal groups towards the active initiating and propagating species, at least under the experimental conditions used. As discussed above, both random and block copolymerization of TOSUO and ε-CL is typically living and allows copolyesters of well-controlled molecular weight and composition to be prepared. Deprotection of the ketone groups has been carried out with triphenylcarbenium tetrafluoroborate (Ref. 15), within a 100 % yield. Finally, the ketone groups can be completely reduced to hydroxyl groups by sodium borohydride. Furthermore, polyester chains are not degraded during the deacetalization and reduction processes. Therefore, the molar fraction of TOSUO allows the content of ketone and hydroxyl pendent groups to be accurately controlled.



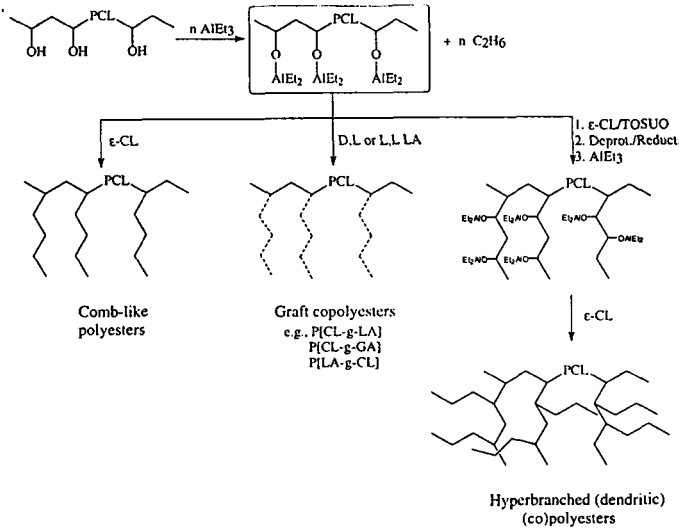
Scheme 1

Compared to PCL that precipitates in water both TOSUO homopolymers and copolymers with ε-caprolactone form stable dispersions in water of an average size below 100 nm. The average size of 0.10 wt % dispersions of poly(ε-caprolactone) containing, e.g. 12mol% functional comonomer in a 10/90 v/v DMSO/water mixture, depends on the functional pendent groups. The size of the colloidal dispersion decreases from 213 nm in case of ethylene acetal pendent groups to 72 nm and 74 nm upon deacetalization into more polar ketone and hydroxyl groups, respectively. A decrease in the dispersion concentration from 0.10% to 0.01% results in smaller colloidal particles (from 213 nm to 72 nm). In all the cases, these suspensions are stable for more than 48 hours at room temperature as checked by photon correlation spectrometry (PCS). This novel family of copolymers has potential for biomedical applications, particularly as tailored drug colloidal vectors with a core-shell like structure. Reactive groups on the surface of these nanoparticules are indeed available to the binding of species selected for molecular recognition and drug targeting.

SYNTHESIS OF FULLY BIODEGRADABLE COMB AND GRAFT ALIPHATIC POLYESTERS

The availability of pendent hydroxyl groups onto poly(ε-caprolactone) paves the way to novel molecular architectures and materials. For instance, reaction of the pendent hydroxyl groups with

an excess of triethylaluminum provides a macroinitiator for the ring-opening polymerization of lactones and lactides with formation of comb like polymers and graft copolymers. If the grafts also contain TOSUO units, the release of the hydroxyl groups and their reaction with $AlEt_3$, allows an additional grafting reaction to be performed, leading to hyperbranched structures (see Scheme 2).



Scheme 2.

The first two entries of Table 1 show that comb-shaped polyesters and graft copolyesters can be successfully prepared according to this synthesis procedure. However, the molecular weight distribution is rather broad and not all the hydroxyl pendent groups of the macroinitiator are active. This observation might reflect the partial aggregation of aluminum alkoxide groups attached to the polymer backbone. According to S. Penczek et al., the aggregation degree of growing Al alkoxide species depends on several parameters, such as the structure of the alkyl substituents of Al and the solvent polarity (Refs. 16,17). For instance, $C_2H_5OAl(C_2H_5)_2$ is aggregated in benzene, but non-aggregated in acetonitrile. Nevertheless, when diisobutylaluminum alkoxide is used as initiator in acetonitrile, the graft efficiency is low and the molecular weight distribution still broader than before (entry 3, Table 1). According to the entry 4, the graft efficiency is more than twofold increased, the molecular weight distribution is much narrower (1.25) and the polymerization rate is much faster (complete conversion within 1.3 hours) when toluene is substituted for acetonitrile. The average sequence length of ε-CL and functional ε-CL units in the macroinitiator used in experiments 1 to 4 (Table 1) is 10.30 and 1.40, respectively, as measured by quantitative ^{13}C-NMR. The average distance between the near neighbor hydroxyl, and thus alkoxide groups might be too short for them being independent of each other. A PCL macroinitiator containing less hydroxyl pendent groups (8 per chain of a

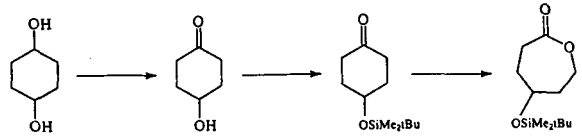
14.5 10^3 molecular weight has been used in the fifth experiment (entry 5, Table 1). The average sequence length of ε-CL and functional ε-CL units is now 14.7 and 1.0, respectively. As a result, the molecular weight distribution of the graft copolymer is rather narrow (1.25) and the graft efficiency is 100%.

Table 1. Preparation of Comb-shaped and Graft Aliphatic Copolyesters

Entries	Monomer	Alkyl aluminum	Solvent	Time (h)	Conversion (%)	Graft[c] efficiency (%)	M_w/M_n
1[a]	ε-CL	$AlEt_3$	toluene	25	94.5	80.0	1.50
2[a]	(L,L)LA	$AlEt_3$	toluene	113	82.0	50.0	1.40
3[a]	ε-CL	$HAl(^iBu)_2$	CH_3CN	43.5	46.0	30.2	1.65
4[a]	ε-CL	$HAl(^iBu)_2$	toluene	1.3	100	77.1	1.25
5[b]	ε-CL	$HAl(^iBu)_2$	toluene	0.5	94	100	1.25

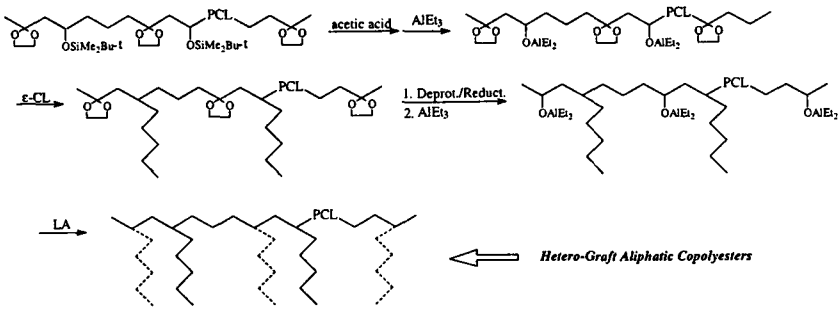
A PCL macroinitiator was used (a) $M_n = 8.5 \times 10^3$ and $N_{OH} = 9$ (hydroxy groups per chain); (b) $M_n = 14.5 \times 10^3$ and $N_{OH} = 8$. Temperature was 25°C, except for the entry 2 (70°C); (c) The percentage of hydroxyl pendent groups that initiated the second polymerization step was determined by ^1H NMR (proton in α-position of the hydroxyl group).

Scheme 3 shows the reaction pathway for the synthesis of an alternative functional ε-caprolactone, i.e. 5-(t-butyldimethylsilyloxy)-ε-caprolactone (SCL) (Ref. 18). Pitt et al. reported that SCL could be copolymerized with ε-CL, δ-valerolactone and various molar amounts of 2,2-bis(ε-caprolactone-4-yl)propane at 140°C in the presence of stannous octoate with formation of elastomers of different crosslink density. We have confirmed that SCL can also be copolymerized with ε-CL in toluene at 25°C using $Al(O^iPr)_3$ as initiator. So, a terpolymer of TOSUO, ε-CL and SCL has been prepared, which has the unique characteristic of containing two types of hydroxyl precursors, i.e. silanolate groups that can be selectively hydrolyzed in the presence of the acetal groups. This characteristic feature paves the way for the synthesis of hetero-graft aliphatic copolyesters as schematized below (Scheme 4). This synthetic strategy will be detailed in a forthcoming paper.



(SCL)

Scheme 3



Scheme 4

ACKNOWLEDGEMENT

The authors are very much indebted to the "Services Fédéraux des Affaires Scientifiques, Techniques et Culturelles" for general support to CERM in the frame of the "Pôles d'Attraction Interuniversitaires : Polymères". Ph. D. is a research associate by the Belgian National Fund For Scientific Research (FNRS).

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