

Account / Revue

Macrocyclic malonates. A new family of tethers for the regio- and diastereoselective functionalization of [60]fullerene

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Received 24 June 2005; accepted after revision 7 September 2005
Available online 19 January 2006

Abstract

The tether-directed remote functionalization of C₆₀ has been investigated by using cyclic bis- and tris-malonate tethers. The reactive malonate groups are connected with alkyl spacers and their synthesis was performed in one step by the condensation reaction of malonyl dichloride with an appropriate diol. Macrocycles containing identical alkyl spacers afforded bis- and triadducts of C₆₀ with rotational symmetry in a regioselective manner and in remarkable yields. In contrast, macrocycles bearing different alkyl spacers led to the formation of C_s-symmetrical bisadducts. Tuning of the spacer's length gave access to different addition patterns of C₆₀ while, the synthesis of enantiomerically pure trisadducts of C₆₀ with an *e,e,e*-addition pattern was achieved via cyclopropanation with chiral D₃-symmetrical *cyclo*-tris-malonate tethers. **To cite this article:** N. Chronakis et A. Hirsch. *C. R. Chimie* 8 (2005).

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Keywords: Macrocyclic malonates; Spacer; Regioselectivity; Functionalization; Addition pattern; Regioisomers; Inherently chiral

The three-dimensional structure of [60]fullerene and the 30 reactive double bonds of its carbon network have inspired chemists to design and synthesize novel building blocks with unique chemical and physical properties. The spherical, all-carbon soccer ball has attracted an enormous research activity since the birth of the third allotropic form of carbon with hundreds of literature reports dedicated to the derivatization of the fullerene C₆₀ [1]. A widely used method for the functiona-

lization of C₆₀ is the nucleophilic cyclopropanation of the [6,6] double bonds via the Bingel [2] reaction. For a single attack at a [6,6] bond one regioisomer is possible as the 30 double bond of the fullerene cage are equivalent. For a second attack, eight regioisomeric adducts (Fig. 1) are possible whereas, for trisadditions the number of the possible regioisomers increases to 46. The regioselective synthesis, isolation, and characterization of the different regioisomeric fullerene bisadducts and a limited number of trisadducts were firstly achieved by the stepwise cyclopropanation of C₆₀ with diethyl bromomalonate [3]. The multiple and tedious chromatographic separation and purification steps by means of preparative HPLC required a more sophisticated approach to access polyadducts of C₆₀ with well-defined

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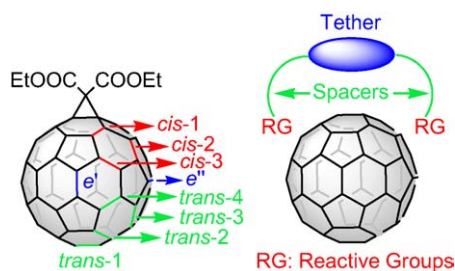


Fig. 1. Position notation for bisadducts of C_{60} and the 'tether-directed remote functionalization' concept.

three-dimensional structure. The tether-directed remote functionalization introduced by Icaacs et al. [4] was proved to be the method of choice and initiated a huge synthetic effort targeting a diversity of structurally different tethers in the first step and secondly, the facile access to fullerene addition patterns that had never been reported before. According to this concept (Fig. 1), the reactive malonate groups are connected with a more or less rigid organic moiety via spacers and thus, the tether directs the reactive groups to specific positions. The possibility of tuning the rigidity of the tether core as well as the spacer's length has enriched the literature with a plethora of tethered systems that showed in many cases excellent regioselectivity in the Bingel functionalization of C_{60} . However it should be mentioned that only opened-structure tethers were utilized for the regioselective remote functionalization of the C_{60} where, the malonate reactive groups are 'hanged' at the edges of the tethers. Furthermore, tethers designed for the synthesis of trisadducts of C_{60} required multiple synthetic steps or led to low yield functionalization reactions [5].

Recently, we reported [6] a new concept of the tether approach which was proved to be advantageous from different points of view. The rigid spacers were replaced by flexible alkyl chains and the malonate groups were incorporated in a macrocyclic ring. This way, the regioselectivity is not based on steric preorganization, but on the avoidance of unequal strain in the alkyl chains. The consequence for the symmetry of the addition pattern of the fullerene adducts is that macrocycles with two or three malonate units are forced to form adducts with rotational symmetry, that is C_2 for bisadducts and C_3 for trisadducts. All other regioisomers are excluded since they would result in different distances between the ester groups and thus, introduce strain. Fig. 2 shows the addition patterns of bis- and trisadducts that fulfill these restrictions. It becomes obvious that the regioselectivity of the Bingel functionalization can be adjusted by varying the length of the alkyl

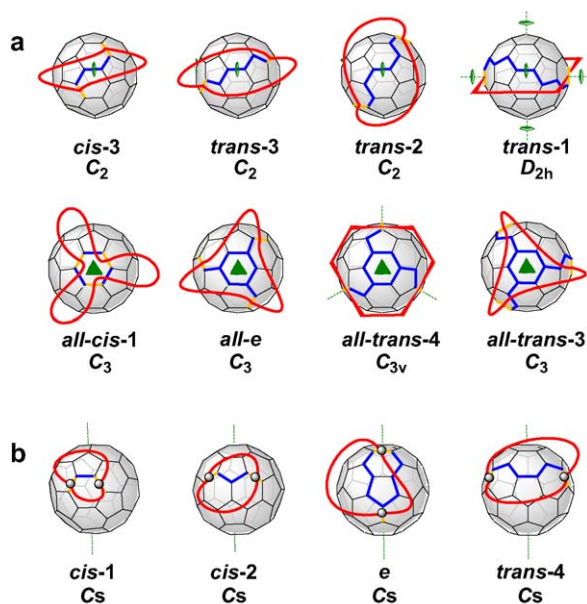
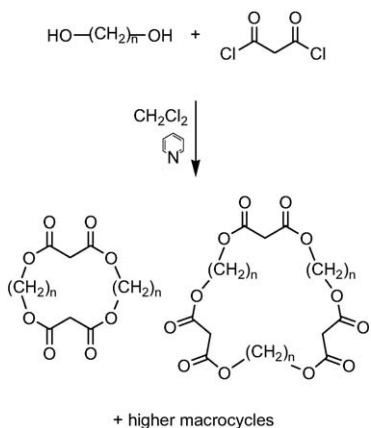


Fig. 2. (a) Possible bis- and trisadducts of C_{60} containing rotational axes. All distances between adjacent addend positions are identical. (b) Bisadducts of C_{60} with C_s symmetry. The possible distances between adjacent addend positions are different. The yellow bonds denote the positions of addends, such as malonates.

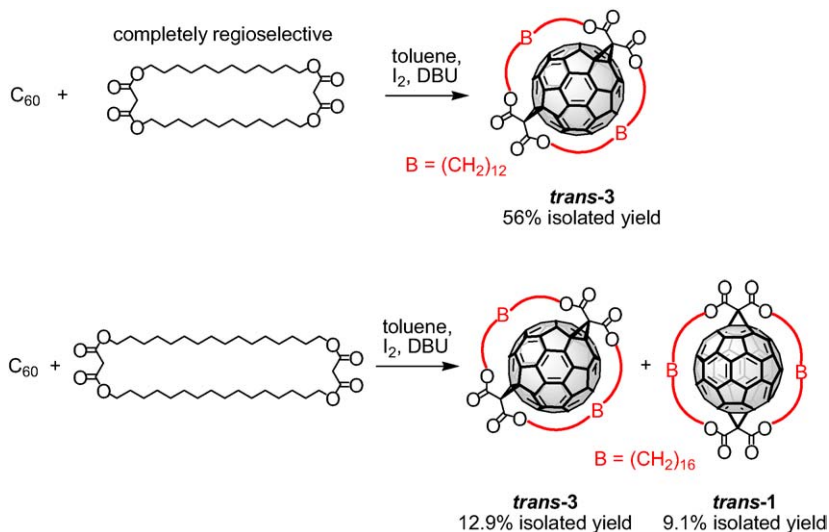
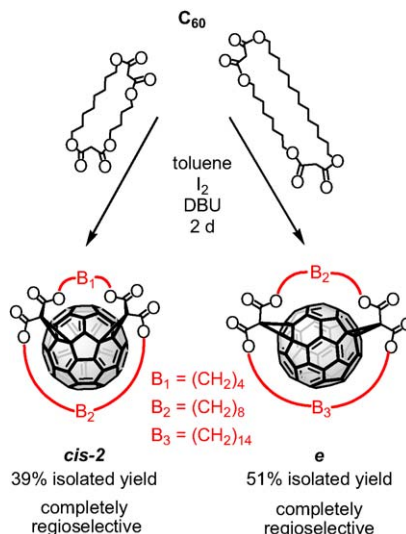
chains, a fact that accounts for the high versatility of this method. The concept of the *cyclo* alkylmalonates is not limited only for the synthesis of fullerene multiadducts containing rotational axes. If mixed macrocycles with two alkyl spacers of different length are used, bisadducts with C_s -symmetrical addition pattern are expected to form as outlined in Fig. 2.

The first advantage of the new concept presented was the synthesis of the proposed macrocyclic malonates which was proved to be quite simple. The desired *cyclo* alkylmalonates were obtained by the condensation reaction of malonyl dichloride with the appropriate diol in CH_2Cl_2 solvent and using pyridine as a base (Scheme 1). The reaction was performed under high dilution conditions to give a facile access to a great number of *cyclo*-[n]-alkylmalonates varying in the length of the alkyl chains and the ring size. The mixed macrocycles with two alkyl spacers of different length were prepared by the same method, using two different diols in the condensation reaction. The purification of the macrocycles could be accomplished by flash column chromatography on silica gel and the newly synthesized cyclic compounds were studied for the regioselective remote functionalization of [60]fullerene.

The Bingel functionalization of C_{60} with the bis-malonate tether bearing C_8 alkyl spacers was unsuccessful leading to the formation of polymeric material.

Scheme 1. Synthesis of the *cyclo*-[*n*]-alkylmalonates.

Obviously, this macrocycle is not suitable for the formation of strain-free bisadduct with rotational symmetry because of the short length of the spacer units. The bis-malonate macrocycles with C_{12} and C_{16} alkyl spacers were treated with C_{60} in separate experiments under the Bingel conditions and the formed fullerene bisadducts were separated and characterized. The *cyclo*-[2]-dodecylmalonate afforded cleanly bisadduct *trans*-3 in a completely regioselective manner and in a remarkable 56% isolated yield (Scheme 2). Similarly, the *cyclo*-[2]-hexadecylmalonate bearing longer alkyl spacers reacted successfully with C_{60} leading to the formation of the *trans*-3 and *trans*-1 bisadducts, in a 55:45 ratio. The two regioisomers were isolated by flash column chromatography on SiO_2 in 12.9% and 9.1% yields, respectively (Scheme 2). These results con-

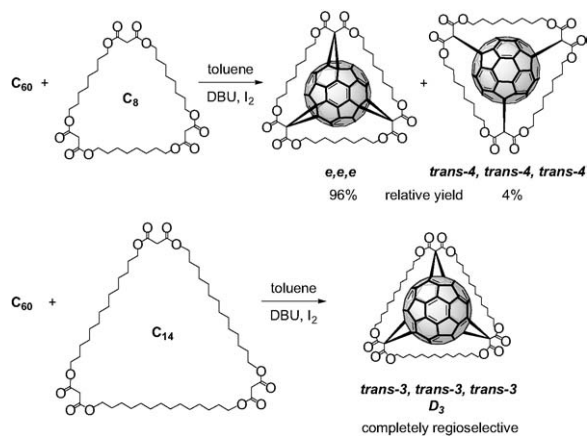
Scheme 2. Tether-directed remote functionalization of C_{60} with the bis-malonates bearing C_{12} and C_{16} alkyl spacers.Scheme 3. Tether-directed remote functionalization of C_{60} with the bis-malonates bearing C_4 – C_8 and C_8 – C_{14} alkyl spacers.

firmed that the remote functionalization of C_{60} utilizing cyclic malonates proceeds with high degree of selectivity and more interestingly, this approach allows the access of different addition patterns by simple variation of the alkyl spacers.

Targeting the regioselective synthesis of C_s -symmetrical bisadducts of C_{60} we investigated the Bingel functionalization of the mixed bis-malonates that bear two alkyl spacers of different length. The results are demonstrated in Scheme 3. Both macrocycles gave a complete regioselective reaction with C_{60} and high yields of the formed bisadducts. Specifically, the bis-

malonate tether bearing C_4 and C_8 alkyl spacers favored exclusively the *cis-2* addition pattern while, the mixed macrocycle with C_8 and C_{14} alkyl spacers showed complete regioselectivity for the equatorial fullerene bis-adduct. In both cases the isolated yields were remarkably high.

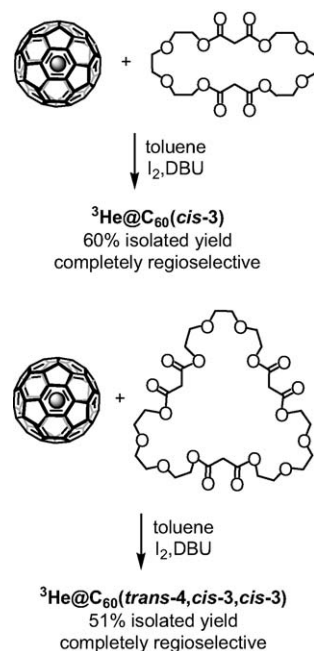
As the regiochemistry of trisadditions on C_{60} is more complicated because of the large number of the possible regioisomers we applied the concept of the *cyclo*-malonates targeting trisadducts with well-defined structure. It was mentioned before that the symmetry of the tris-malonates synthesized is expected to favor the formation of trisadducts of C_{60} possessing threefold rotational symmetry, namely *cis-1,cis-1,cis-1*, *e,e,e*, *trans-3,trans-3,trans-3* and *trans-4,trans-4,trans-4*. The formation of *cis-1,cis-1,cis-1* is expected to be energetically disfavored because of the steric crowding of the malonate addends. In order to confirm our theoretical predictions we firstly investigated the Bingel functionalization of C_{60} with the trimeric macrocycle bearing C_8 alkyl spacers (Scheme 4). The reaction afforded the *e,e,e* trisadduct as the major product in 96% relative yield and the *trans-4,trans-4,trans-4* as the minor in 4%. The separation of the adducts was accomplished by preparative HPLC and the two regioisomers were isolated in 40.2% and 2% yields, respectively. It should be highlighted that the *trans-4,trans-4,trans-4* addition pattern was synthesized and characterized for the first time. Obviously, the C_8 -tris-malonate tether fulfilled the expectation for the regioselective synthesis of trisadducts and prompted us to target a more remote addition pattern than the *e,e,e*. Thus, we subjected the macrocyclic tris-malonate bearing C_{14} alkyl spacers in a threefold Bingel cyclopropanation with the fullerene carbon sphere. The remote functionalization functioned in an



Scheme 4. Tether-directed remote functionalization of C_{60} with the tris-malonates bearing C_8 and C_{14} alkyl spacers.

excellent way and delivered the *trans-3,trans-3,trans-3* regioisomer in a complete regioselective manner (Scheme 4).

The concept of the macrocyclic malonates in the tether-directed remote functionalization of C_{60} was proved to be a powerful method to access fullerene polyadducts in a regioselective manner and in very satisfying isolated yields. The facile synthesis of the poly-malonates, their ability to show excellent regioselectivity, and the control of the regioselectivity by tuning the alkyl spacer's length offered a new and effective method in this area of fullerene chemistry. In 2003, Zhou et al. [7] modified this approach by replacing the alkyl chains with polyether linkers and by using $^3\text{He}@C_{60}$ instead of pristine C_{60} . In an elegant way, the specific formation of C_{60} multiple adducts was monitored by ^3He NMR. The bis-malonate macrocycle with tri-ethylene glycol spacers (Scheme 5) afforded regioselectively the *cis-3* bis-adduct of C_{60} in 60% yield. ^3He NMR analysis of the crude reaction mixture confirmed the formation of a single bis-adduct showing only one sharp peak at -10.236 ppm which is the precise chemical shift for the *cis-3* fullerene bis-adduct of diethyl malonate. Similarly, the tris-malonate tether reacted with C_{60} to afford only one trisadduct isomer as confirmed by the ^3He NMR spectra that showed one sharp peak at -12.040 ppm (Scheme 5). Its addition pattern was assigned as *trans-4,cis-3,cis-3*.



Scheme 5. Functionalization of $^3\text{He}@C_{60}$ with polyether malonates.

The successful synthesis of bis- and trisadducts of C_{60} utilizing the macrocyclic polymalonates prompted us to extend this study towards the preparation of enantiomerically pure polyadducts with an inherently chiral addition pattern. An addition pattern of a C_{60} adduct is inherently chiral when it belongs to one of the D_3 , C_3 , C_2 , or C_1 point groups [3,8]. Fig. 3 shows the inherently chiral bisadducts with C_2 symmetry and the inherently chiral trisadducts of C_{60} with C_3 and D_3 symmetry, as pairs of enantiomers. The chiroptical properties of fullerene derivatives with an inherently chiral addition pattern depend on the structure of the conjugated π system since, the whole chromophore itself is responsible for the chirality. Thus, such bulky building blocks represent attractive candidates for the construction of chiral macromolecular architectures such as dendrimers and spherical amphiphiles [9]. The utilization of opened-structure chiral bis-malonate tethers for the synthesis of enantiomerically pure bisadducts with an inherently chiral addition pattern was firstly reported by Nierengarten et al. [10]. In contrast, pure enantiomers of inherently chiral trisadducts of C_{60} have been synthesized by stepwise nucleophilic cyclopropanation of the [6,6] double bonds with diethyl bromomalonate and enantiomeric separation of the racemic mixture of the inherently chiral trisadducts by means of preparative chromatography (HPLC) on chiral stationary phases [11]. In addition, enantiomerically pure trisadducts of C_{60} were obtained by cyclopropanation of [6,6] bonds of the fullerene cage with C_2 -symmetrical bisoxazolines and subsequent HPLC chromatographic

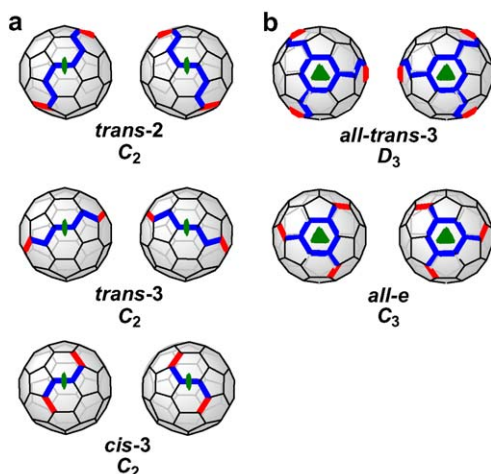
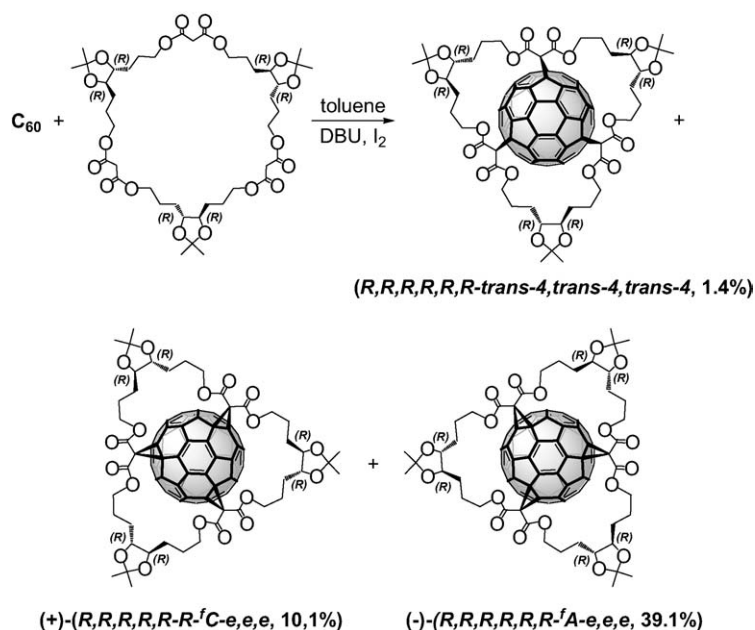


Fig. 3. Schematic representation of inherently chiral bis- (a) and trisadducts (b) of C_{60} as pairs of enantiomers. The bold red lines denote the [6,6] bonds carrying the addends and the blue motifs represent C_2 - or C_3 -symmetrical substructures with the C_2 and C_3 axes as symmetry elements.

separation of the corresponding diastereomers on achiral stationary phases [12]. In these cases, only poor regio- and diastereoselectivities were observed, while tedious preparative HPLC chromatographic separations were required. To overcome these problems we addressed the concept of the *cyclo*-malonates targeting enantiomerically pure trisadducts of C_{60} and in a first step we performed the synthesis of an enantiomerically pure D_3 -symmetrical tris-malonate tether (Scheme 6). The macrocycle reacted cleanly with C_{60} in the presence of I_2 and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene solvent, to afford three fullerene trisadducts (Scheme 6) [13]. The crude mixture was separated successfully by flash column chromatography on SiO_2 followed by the spectroscopic characterization of the formed trisadducts. The minor adduct (1.4% isolated yield) was assigned as the *trans-4,trans-4,trans-4* isomer which is inherently achiral. The two other trisadducts is a pair of diastereomers whose inherently chiral *e,e,e* addition pattern has an enantiomeric relationship. Their circular dichroism (CD) spectra showed almost perfect mirror-image behavior and pronounced Cotton effects. By direct comparison of the CD spectroscopic data, with those of enantiomerically pure [60]fullerene adducts with an *e,e,e* addition pattern, synthesized previously by non-tethered methods, the absolute configuration was unambiguously determined. Thus, the minor *e,e,e* trisadduct formed in 10.1% was assigned as the (+)-(*R,R,R,R,R,R*)- $\int C$ isomer, while the major (39.1%) as the (-)-(*R,R,R,R,R,R*)- $\int A$. The formation of the *e,e,e* trisadducts is diastereoselective with a *de* value of 55% (HPLC) favoring the $\int A$ enantiomer.

The new approach applied for the tether-directed functionalization of C_{60} by the use of tethers containing the reactive malonate groups in a closed structure fulfilled our initial predictions and offers now a relatively simple way to access regioisomeric fullerene bis- and trisadducts with excellent selectivity. The regioselectivity can be controlled by tuning the length of the spacers connecting the malonate moieties, making this method highly flexible. The one step synthesis of the macrocyclic malonates via the condensation reaction of malonyl dichloride with an appropriate diol, combined with the high yield synthesis of fullerene multiadducts facilitates the wide applicability of the method. That was demonstrated by the synthesis of enantiomerically pure trisadducts of C_{60} having an inherently chiral addition pattern. Finally, the introduction of functional groups in the spacers will give the opportunity to synthesize novel fullerene architectures with promising properties as functional materials.



Scheme 6. Synthesis of the *trans-4,trans-4,trans-4* and the enantiomerically pure (+)-(*R,R,R,R,R,R*)-*f*-*C-e,e,e* and (-)-(*R,R,R,R,R,R*)-*f*-*A-e,e,e* trisadducts.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (Hi 468/14-1) for financial support.

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