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Displacement of methoxy groups by thiol residues on the fullerene cage

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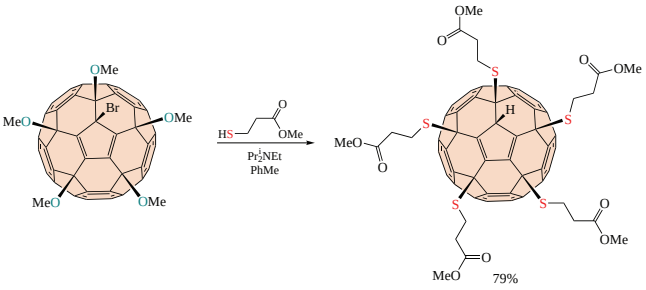
Methoxy groups on the fullerene cage in compound $C_{60}(OMe)_5Br$ were displaced by thiol residues of methyl 3-mercaptopropanoate thus leading to $C_{60}(SCH_2CH_2CO_2Me)_5H$ product. The structure of the product was established by NMR spectroscopy.



Keywords: alkoxy fullerene derivative, thiols, alcohols, substitution, sulfides, cyclopentadienyl-type addition pattern.

Functionalized fullerenes have found various applications in photovoltaics,[1,2] biomedical research[3,4] and cosmetics.[5] However, most of the utilized fullerene-based compounds are represented by the products of addition to one double bond, which can be easily obtained *via* the Prato or Bingel–Hirsch reactions.[6] Another type of actively utilized fullerene-based materials is represented by complex inseparable mixtures of multiadducts, such as fullerenols.[7,8] These compounds are typically utilized in biomedical studies due to their solubility in water, which is ensured by the presence of numerous hydrophilic groups. However, the examples of fullerene derivatives presented above do not always possess the desired physicochemical or biological properties. For example, photovoltaic properties can in some cases benefit from fullerene derivatives with a higher number of addends,[9,10] while biological experiments would rather utilize individual compounds, not complex mixtures. Taking these considerations into account, methods for the synthesis of individual fullerene multiadducts have to be developed. The main challenge on this way is a low regioselectivity of fullerene reactions. The higher the desired degree of functionalization, the greater the number of possible regioisomers.[11,12] For example, although the formation of fullerene monoadduct *via* the Bingel–Hirsch reaction leads to a single product, formation of bisadducts results in eight regioisomers.[13] For $C_{60}R_{24}$ compounds, the number of possible regioisomers reaches ~3×10^{14}.[14]

To avoid the formation of complex mixtures, several approaches for the regioselective synthesis of fullerene derivatives have been developed. They include, but are not limited to, electrosynthetic methods,[15,16] tether-directed functionalization,[17] Pd-catalyzed allylation,[18] addition of organocopper compounds,[19] *etc*. Among these approaches, a family of methods based on the reactions of chlorofullerenes, such as $C_{60}Cl_6$ or $C_{70}Cl_8$, and $C_{70}Cl_{10}$ with various nucleophiles stands out.[20] Their key advantages are: accessibility of the starting materials (pure chlorofullerenes $C_{60}Cl_6$ or $C_{70}Cl_8$, $C_{70}Cl_{10}$ can be obtained in hours is nearly quantitative yields), high yields, and the same addition pattern for the products as for the starting compounds. For example, the synthesis of fullerene derivatives with thiol-based addends allows one to obtain the compounds with the general formula $C_{60}(SR)_5H$ in one step from $C_{60}Cl_6$ without chromatographic purification.[21] This approach has been further utilized for the synthesis of compounds with antiviral activity against HIV, influenza and respiratory syncytial virus. Thermal decomposition of $C_{60}(SR)_5H$ compounds, leading to the formation of pure fullerene C_{60}, was used for environment-friendly aqueous processing of C_{60} semiconducting films for green organic electronics.[22] Another approach for the synthesis of fullerene derivatives $C_{60}(OR)_5Br$ with five functional addends has been developed based on the reaction of $C_{60}Cl_6$ with alcohols in the presence of tetrabutylammonium bromide.[23] This approach was also quite useful for the synthesis of water-soluble compound with pronounced anti-HIV activity *in vitro*.

In this work, we explored the possibility of utilizing alkoxy fullerene derivatives $C_{60}(OR)_5Br$ as precursors for the synthesis of compounds $C_{60}(SR)_5H$ (Figure 1). This would provide new information on the chemical properties of alkoxy fullerene derivatives and reveal the connections between the different classes of fullerene-based compounds. Chemical properties of alkoxy fullerenes have been investigated by Deng[24] (the reaction of $C_{60}(OMe)_4$ with azides and tosylhydrazones leading to cyclopropanation and the completion of a cyclopentadienyl-type

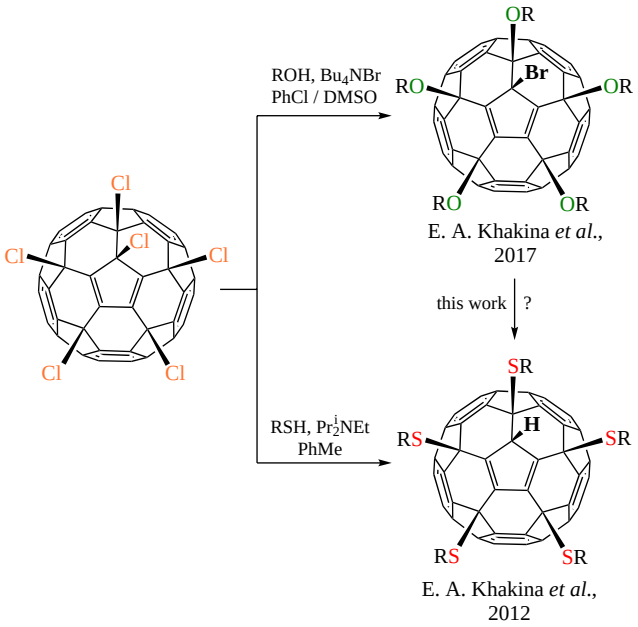


Figure 1 Reactions of chlorofullerene $C_{60}Cl_6$ with alcohols and thiols.

pattern) and Gan[25] (very interesting examples on fullerene peroxide chemistry). However, examples of the complete replacement of alkoxy addends attached to the fullerene cage have not been reported.

The synthetic procedure performed in this work has been rather simple (Scheme 1). Known[23] fullerene derivative $C_{60}(OMe)_5Br$ **1** was treated with methyl 3-mercaptopropanoate in toluene in the presence of the Hünig's base for 10 min. During this time, the HPLC control showed the full conversion of the starting compound **1** to the product (see Online Supplementary Materials, Figure S1) which was isolated by column chromatography in 79% yield. Product **2** appeared as a red powder, which is typical for the fullerene derivatives with cyclopentadienyl-type addition pattern.

Compound **2** has been characterized by ^{1}H NMR spectroscopy (Figure S2). The spectrum was similar to that reported previously[21] for the known compound with five attached residues of methyl 3-mercaptopropanoate $C_{60}(SCH_2CH_2CO_2Me)_5H$. In particular, in the range of 2.7–2.9 and 3.4–3.6 ppm, the signals for the methylene groups of the addends were observed; at 3.7 ppm, three singlets with integral intensities of 6 : 3 : 6 corresponding to CO_2Me groups appeared. The singlet for the hydrogen atom attached directly to the fullerene cage appeared at 5.14 ppm. It should be noted that the bromine atom attached to the fullerene cage was also displaced by a hydrogen atom. This type of substitution also takes place during the reaction of $C_{60}Cl_6$ with various thiols.[21]

The observed substitution reaction allowed us to conclude that the alkoxy addends attached to the fullerene cage can serve as good leaving groups. Alkoxy fullerene derivatives, similarly to chlorofullerenes, can be utilized as precursors for the synthesis of other functional compounds.

To simulate the structures of the reaction products and calculate the energy effects of individual stages, quantum-chemical calculations were carried out using the PBE density functional method[26] and the PRIRODA software package[27] at the Joint Supercomputer Center of the Russian Academy of Sciences. SBK pseudopotential[26] and extended basis set: H [5s 1p/3s 1p] C, O [5s 5p 2d/3s 3p 2d] for valence shells were used to optimize the geometry. The Hirshfeld method[28] was utilized to calculate atomic charges.

To calculate the thermal effects of the reaction, the values of the standard enthalpy (T = 298.3 K) were used, taking into account the vibrational contribution to the partition function since reactions occur in a condensed medium. Substitution of the alkoxy addends occurs *via* the following reaction:

$$C_{60}(OMe)_5Br + 5\,HSR \rightarrow C_{60}(SR)_5Br + 5\,MeOH,$$

$$\Delta H_{298} = -15.9 \text{ kcal mol}^{-1},$$

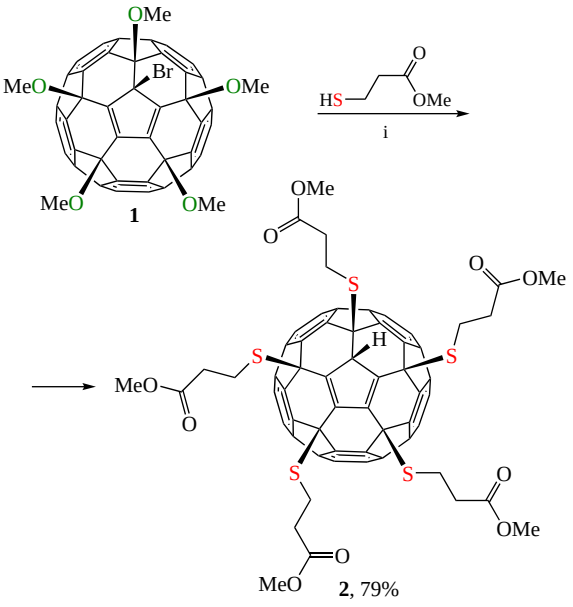
where HSR is 3-mercaptopropanoate.

Conversion of $C_{60}(SR)_5Br$ to $C_{60}(SR)_5H$, most probably, occurs *via* the following pathway:

$$C_{60}(SR)_5Br + 2\,HSR \rightarrow C_{60}(SR)_5H + HBr + RS{-}SR,$$

$$\Delta H_{298} = -24.7 \text{ kcal mol}^{-1}.$$

This reaction is also exothermic, and the total thermal effect of the two stages is 40.6 kcal mol^{-1}. The optimized molecular structure of $C_{60}(SR)_5H$ is shown in Figure 2(*a*). The generated HBr reacts with Pr^i_2NEt forming the salt $[HNPr^i_2Et]^+Br^-$ in a low-polar medium [Figure 2(*b*)]:



Scheme 1 *Reagents and conditions*: i, Pr^i_2NEt, PhMe, Ar, room temperature, 10 min.

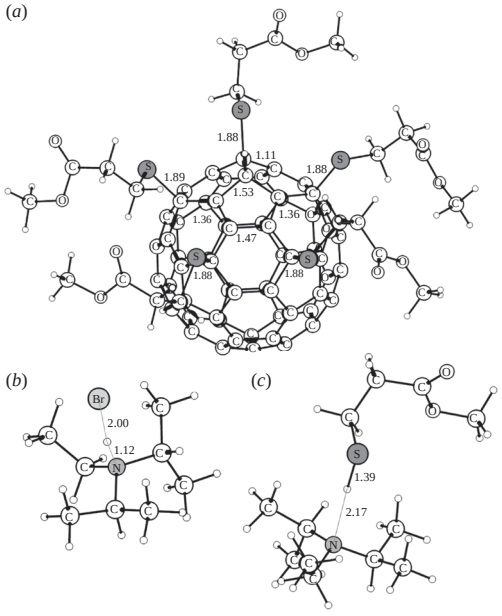


Figure 2 Calculated structures of (*a*) $C_{60}(SR)_5H$, (*b*) $[HNPr^i_2Et]^+Br^-$ and (*c*) RSH···NPr^i_2Et. Bond lengths are indicated in Å.

$HBr + Pr^i_2NEt \rightarrow [HNPr^i_2Et]^+Br^-$, $\Delta H_{298} = -15.3$ kcal mol^{-1}.

In the absence of amine, the reaction does not proceed. Apparently, the role of the base is not to only scavenge HBr, but also to activate thiol molecules. The formation of a weakly bound (3 kcal mol^{-1}) complex RSH···NPr^i_2Et [see Figure 2(*c*)] is accompanied by a charge transfer of –0.056 to the thiol molecule, mainly to the SH group.

Examples of replacement of alkoxy groups by alkylthio ones have been reported previously for aromatic systems.[29] It should be noted that classical ethers do not undergo this kind of transformation, especially under mild conditions. This example once again emphasizes the unusual reactivity of functional groups attached to the fullerene cage. In summary, we have demonstrated the possibility of complete replacement of alkoxy groups by thiol residues in the fullerene derivatives with cyclopentadienyl-type addition pattern.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.04.032.

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