Preparation of [60]fullerene tris-malonate adducts by addend removal from higher adducts *via* the electrochemical retro-Bingel reaction

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Systematic application of the electrochemical retro-Bingel reaction to tetrakis-, pentakis- and hexakis-malonate adducts of C_{60}, produced tris-adducts in *ca*. 30% yield. Of the tris-adducts obtained, the (*trans*-4, *trans*-2, *e*) and the (*trans*-3, *trans*-4, *e*) isomers were the major products, while unexpectedly, the (*e*, *e*, *e*) and (*trans*-3, *trans*-3, *trans*-3) isomers were formed in relatively small amounts. New tetrakis-adducts were also formed *via* the isomerization reaction as indicated by HPLC studies.

Introduction

Ever since its discovery,[1] Buckminsterfullerene, C_{60}, has generated interest as a potentially useful molecule because of its highly symmetrical shape and unique properties. Today, through functionalization of the spherical molecule, novel materials with potential application as sensors,[2] superconductors[3] and non-linear optical materials,[4] have been synthesized. Biological applications of C_{60}-based water-soluble compounds have also been sought and many fullerene derivatives have been tested for biological activity.[5] Promising results have been obtained from C_{60} derivatives as anti-bacterial[6] and anti-viral (specifically, anti-HIV)[7] agents as well as effectors in photodynamic therapy[8] and DNA cleavage.[9]

The C_{60} molecule is known to react efficiently with free radicals, accommodating up to 34 methyl radicals on its surface.[10] This property makes it an ideal antioxidant. This also has implications for neurodegenerative disease treatment, since such diseases are usually caused by an excess of superoxide and nitric oxide free radicals. Recently, *in vitro* and *in vivo* neuroprotective activity of tris-malonic acid adducts of C_{60} was reported.[11] In the presence of the highly symmetrical (*trans*-3, *trans*-3, *trans*-3) (D_3 symmetric) and (*e*, *e*, *e*) (C_3 symmetric) tris-adducts, neuronal death in cortical cells overexcited by exposure to glutamic acid receptor antagonists, *N*-methyl-D-aspartate (NMDA) or 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)propionic acid (AMPA), was dramatically reduced.

With such favorable results, preparation of large quantities of tris-malonic acid adducts is desirable. Mono- and bis-malonate adducts of C_{60} can be simply prepared by the Bingel reaction.[12] However, to obtain tris-adducts regioselectively by this method, a stepwise procedure involving tedious separation and purification is required.[13] Alternatively, a one-pot reaction is not very well controlled and unwanted higher adducts are usually produced even when stoichiometric quantities of reactants are used. Recently, the use of cyclotriveratrylene† (CTV) as a directing group regioselectively produced the CTV tris-adducts with exclusive attachments in the (*trans*-3, *trans*-3, *trans*-3) and (*e*, *e*, *e*) positions (Scheme 1).[14] Although not reported, transesterification of these isomers should yield the pure (*trans*-3, *trans*-3, *trans*-3) and (*e*, *e*, *e*) tris-malonate derivatives in reasonable yields.

Conversely, removal of malonate addends from the fullerene is achievable *via* the electrochemical retro-Bingel reaction introduced by Echegoyen and Diederich and co-workers (Scheme 2),[15a] which involves reduction of the adduct at constant potential, followed by re-oxidation at 0 V.

The retro-Bingel reaction has been applied to mono-, bis-, tris- and tetrakis-adducts of C_{60} and C_{70}, producing the native fullerenes.[15] It has also provided a route for the separation of isomers of the higher fullerenes, including the enantiomers of D_2 C_{76} and D_2 C_{84}.[15,16] Additionally, this protocol has made possible the isolation of new isomers of C_{84} and of a C_{78} bis-adduct[15,16] and may be used as part of a protection–deprotection protocol in the synthesis of non-Bingel adducts with unusual addition patterns.[17]

In this paper, we report the application of the retro-Bingel reaction to tetrakis-, pentakis- and hexakis-malonate adducts of C_{60} in an attempt to maximize the production of tris-adducts (Scheme 3) and analyze the regioisomeric distributions that result. We also determined the relative electrochemical stabilities of the different tris-adducts generated *via* the retro-Bingel reaction of the higher adducts.

Results and discussion

The electrochemistry of the C_{60} malonate poly-adducts (**1**–**3**) has been previously reported.[18] Reductive controlled potential electrolysis (CPE) was carried out under high vacuum conditions in dichloromethane at potentials ~100 mV more negative than the second reduction potential of the respective adducts (see the Experimental section for details). These potentials were determined by Osteryoung square wave voltammetry (OSWV) prior to electrolysis.

Under HPLC conditions as described in the Experimental section, the pentakis-adduct mixture **1** was observed to consist of three isomers. The major one, which accounts for ~75% of the mixture, is believed to be the C_{2v} isomer, which has all addends at equatorial sites.

The C_{2v} isomer is expected to predominate, since additions to the C_{60} sphere occur preferentially at equatorial sites due to

† The IUPAC name for cyclotriveratrylene is 10,15-dihydro-2,3,7,8,12,13-hexamethoxy-5*H*-tribenzo[*a*,*d*,*g*]cyclononene.

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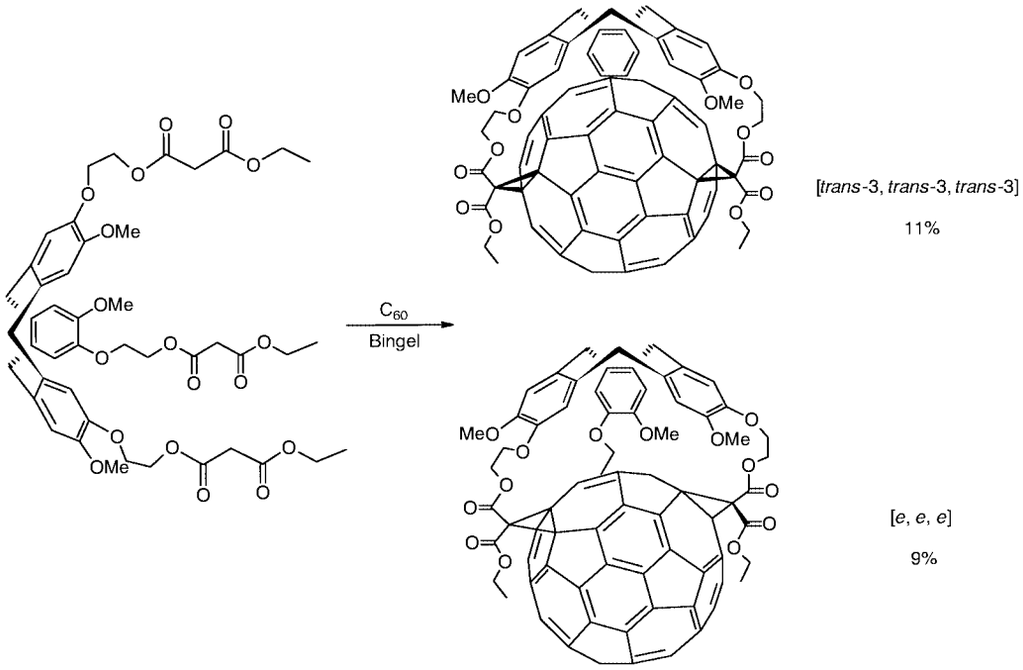
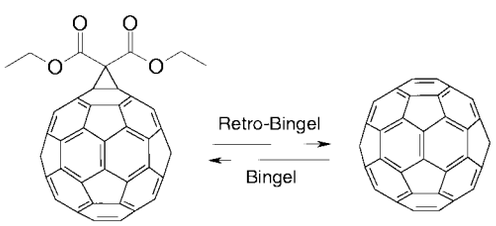
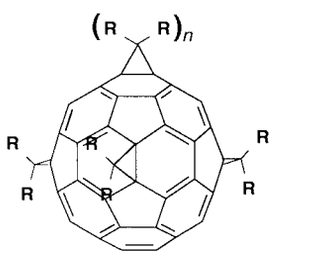


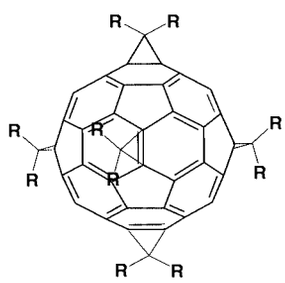
Scheme 1



Scheme 2



Scheme 3



1

frontier orbital coefficient enhancement.[19] In order to determine the ideal conditions for tris-adduct preparation from **1**, CPE experiments were carried out at room temperature (295 K) and at low temperature (277 K), transferring charge corresponding to different numbers of electrons per molecule.

Compound **1** was initially subjected to CPE at the second reduction potential at room temperature, because the first reduction wave was ill-defined. The reaction was stopped after coulometrically determining that 1 electron per molecule had been transferred. This was followed by exhaustive re-oxidation at 0 V (30% charge recovered). There was little change observed between the cyclic voltammograms before and after electrolysis [Fig. 1(a and b)]; much of the irreversible behaviour remained. The product was extracted by evaporation of the CH_2Cl_2 solvent and subsequent removal of the supporting electrolyte by dissolution of the residue in toluene and passage through a short SiO_2 column, eluting first with toluene and then with toluene–ethyl acetate (75 : 25).

The product was analyzed by high performance liquid chromatography (HPLC). The retro-Bingel reaction was observed to have occurred partially, even after only 1 electron per molecule had been discharged, producing predominantly tetrakis-adducts, which appeared as three peaks. Two of these peaks are due to the C_1 and C_s symmetric adducts (*vide infra*), the third possibly due to the D_{4h} isomer. However, over one-half of the starting material remained unreacted. Compound **1** was subsequently subjected to the same electrochemical protocol transferring 4, 6 and 11.5 e at room temperature. The cyclic voltammogram of **1** after 4 e CPE [Fig. 1(c)] showed a loss of complexity compared to the initial voltammogram. There was a positive shift of the first reduction wave and at least two quasi-reversible waves were observed. After 6 e CPE the cyclic voltammogram [Fig. 1(d)] resembled the one after 4 e CPE, except that the waves were more distinct and appeared to be more reversible. The cyclic voltammogram of **1** after 11.5 e CPE

Table 1 Distribution[a] of products after CPE determined by HPLC analyses

Starting material + conditions	C_{60}	Mono	Bis	Tris	Tetrakis	Pentakis	Hexakis	Other products
2 + 4 e	0	0	5	41	39	—	—	15
2 + 5 e	0	1	15	48	29	—	—	7
1 + 1 e	0	0	0	1	35	51	—	13
1 + 4 e	0	0	4	25	49	21	—	1
1 + 6 e	1	7	12	30	35	6	—	9
1 + 6 e 4 °C	0	0	7	31	27	19	—	16
1 + 11.5 e	48	5	8	11	7	6	—	15
3 + 8 e	0	0	6	24	15	5	7	43
3 + 11 e	0	4	10	29	21	1	0	35

[a] Determined from ratios of integrated HPLC peak areas to total area.

Table 2 Distribution[a] of products after CPE at room temperature (in mol%)

Starting material + conditions	C_{60}	Mono	Bis	Tris	Tetrakis	Pentakis	Hexakis	Overall recovery
1 + 6 e	2	11	15	34	28	5	—	95
2 + 4 e	0	0	4	29	25	—	—	58
3 + 8 e	0	0	9	29	16	4	6	64

[a] Determined from integrated HPLC areas and the isolated mass of products.

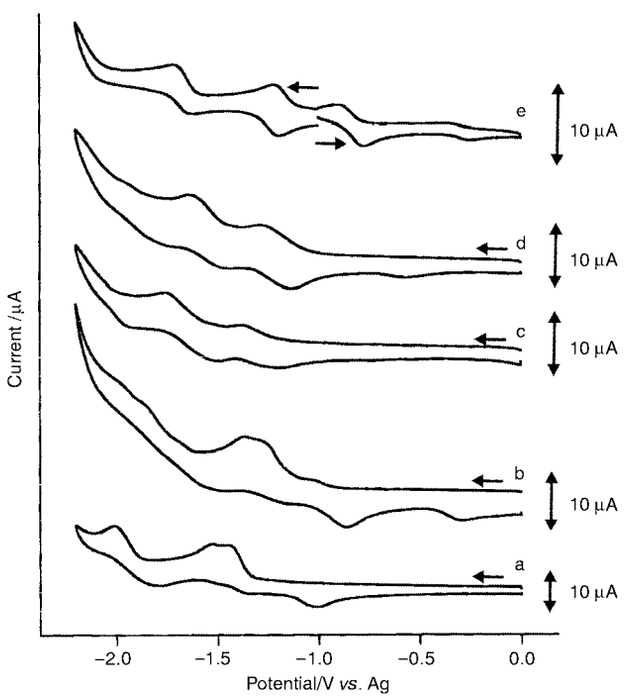
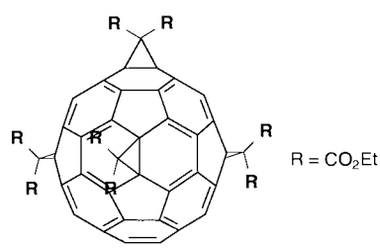


Fig. 1 Cyclic voltammograms in CH_2Cl_2 (+0.1 M Bu_4NPF_6) under vacuum at room temperature, scan rate 0.1 V s^{-1}: (a) pentakis-adduct **1** (b) **1** after 1 e CPE (c) after 4 e CPE (d) after 6 e CPE (e) after 11.5 e CPE.

[Fig. 1(e)] clearly showed three reversible waves corresponding to native C_{60}, as corroborated by comparison to an authentic sample. The relative product distributions determined by HPLC that result from the electrolyses are outlined in Table 1. It is shown that increasing the number of electron equivalents transferred to 4 (15% charge recovered) enhanced addend removal from **1**, producing an increased amount of tetrakis-, tris- and bis-adducts. Transfer of 6 e (30% charge recovered) at room temperature produced a relatively high yield of tris-adducts with minimal amounts of unreacted starting material and reduced production of tetrakis-adduct compared to 4 e CPE. Thus, the tetrakis-adducts formed by the retro-Bingel reaction of **1**, undergo further addend removal when sufficient charge is provided. When 6 e CPE (15% charge recovered) was performed at low temperature, the retro-Bingel reaction was inhibited, decreasing the formation of tetrakis-, tris- and bis-adducts. The transfer of 11.5 electron equivalents (11% charge recovered) results primarily in C_{60} formation with the mono- to tris-adducts appearing in increasing amounts. The most favourable conditions for tris-adduct formation from the pentakis-adduct **1** were therefore found to be 6 e CPE at room temperature, in accord with the previously reported number of electrons needed for the removal of 2 addends (*i.e.* two electrons per addend plus two to form the stable dianion, C_{60}^{2-}).[15a] Table 2 gives the actual product distribution under the most favourable retro-Bingel conditions.

Compound **2** was determined by HPLC to be a mixture of



C_s symmetric tetrakis-adduct

2

two tetrakis-adducts in the ratio 1:2. This is similar to the observation of Hirsch *et al.* in the synthesis of tetrakis-adducts from the (*e*, *e*, *e*) tris-adduct which yielded only an as yet undetermined C_1 isomer and a C_s isomer in an identical ratio.[20]

The mixture was subjected to 4 e CPE (25% charge recovered) in order to remove one Bingel addend to form the tris-adduct. The relative and actual distributions of products obtained are listed in Tables 1 and 2, respectively. HPLC analysis shows that only approximately 60% of the tetrakis-adduct mixture underwent the retro-Bingel reaction, producing primarily tris-adducts. However, the chromatogram shows peaks due to compounds of intermediate polarity between the (*e*, *e*, *e*) tris-adduct and the C_1 symmetric tetrakis-adduct. These peaks, which are also observed in the chromatograms of the products

Table 3 Distribution of tris-adduct products after CPE determined by HPLC analyses

Starting material + conditions	*t3t3t3*	*t2t3e/t4t4t2*[a]	*t3t3t4*	*t4t2e*	*t3t4e*	*eee*	Other tris isomers
1 + 6 e	5	5	4	36	31	1[b]	18
2 + 4 e	0[b]	5	6	46	15	6	22
3 + 8 e	18[c]	5	1	31	3	16	26

[a] Isomers indistinguishable by co-injection. [b] Low quantity possibly due to initiating collection late or ending collection too early. [c] Possible mixture of 2 isomers.

of 6 e CPE of **1**, are probably due to tetrakis-adducts formed electrochemically by the "walk on the sphere" or "shuffle" reaction, an isomerization similar to that which occurs in the case of the bis-adducts.[21] The ratio of the C_s:C_1 isomers also decreases, suggesting that the dianion of the C_s isomer is less stable under the electrochemical conditions, converting to other more stable isomers. CPE of **2** was repeated, this time with the transfer of 5 electrons (12.5% charge recovered), in order to possibly increase the yield of tris-adducts. HPLC product analysis showed that the retro-Bingel reaction was indeed enhanced by ~25% with the application of an additional electron per molecule. However, the production of tris-adducts was only improved by 7%, while bis-adduct production was increased by 10% (Table 1).

The hexakis-adduct **3** was determined by HPLC to be isomerically pure. It is expected to be the (pseudo-octahedral) T_h symmetric isomer with all addends in equatorial positions. Compound **3** was similarly subjected to 8 e CPE (12.5% charge recovered) at room temperature in order to produce tris-adducts. The relative and actual distributions of products obtained are given in Tables 1 and 2, respectively. Most of the starting material underwent the retro-Bingel reaction, producing tetrakis- and tris-adducts, as well as some unidentified products. In this case, the C_s symmetric tetrakis-adduct isomer is almost completely absent from the HPLC chromatogram, while the previously observed products tentatively assigned as "shuffled" tetrakis-adduct isomers are again present in significant quantities. Together with the known tetrakis-adducts, they account for almost one-half of the products formed. Therefore, CPE transferring 11 electrons per molecule was done in order to enhance tris-adduct formation. The resulting chromatogram shows small increases in the amounts of mono- to tetrakis-adducts at the expense of **1** and **3**.

The tris-adducts produced by the retro-Bingel reaction of the higher adducts were isolated by HPLC and analyzed. At least 8 peaks were observed of the 46 theoretically obtainable tris-adducts. Five of these were unequivocally identified, based on their retention times, by co-elution with the 7 tris-adducts known so far.[22] Surprisingly, the major isomers were the unsymmetrical (*trans*-4, *trans*-2, *e*), and (*trans*-3, *trans*-4, *e*) isomers (Fig. 2). Production of the former is not favored synthetically, starting from any of the three possible precursor bis-adducts, while the latter is the main product only of addition to the *trans*-4 precursor.[20] Table 3 shows the relative distribution of tris-adducts from the retro-Bingel reaction of all 3 higher adducts. It was expected that the (*e*, *e*, *e*) isomer would be the main product since it would be easily obtainable after addend removal from the higher adducts with octahedral addition patterns, without subsequent rearrangement. Instead, both the highly symmetrical (*e*, *e*, *e*) and (*trans*-3, *trans*-3, *trans*-3) isomers are produced in relatively small quantities. The (*trans*-3, *trans*-2, *e*) isomer, which appears to be the most stable synthetically, is also produced in very low yields *via* the retro-Bingel reaction.

Electrochemical "shuffle" reactions done on the tris-malonate adducts in a separate study indicate that the (*trans*-4, *trans*-2, *e*) and (*trans*-3, *trans*-4, *e*) isomers are indeed formed preferentially under electrochemical conditions. This is supported by PM3 and AM1 calculations of the heats of formation of the tris-adduct dianions of C_{60}.[23]

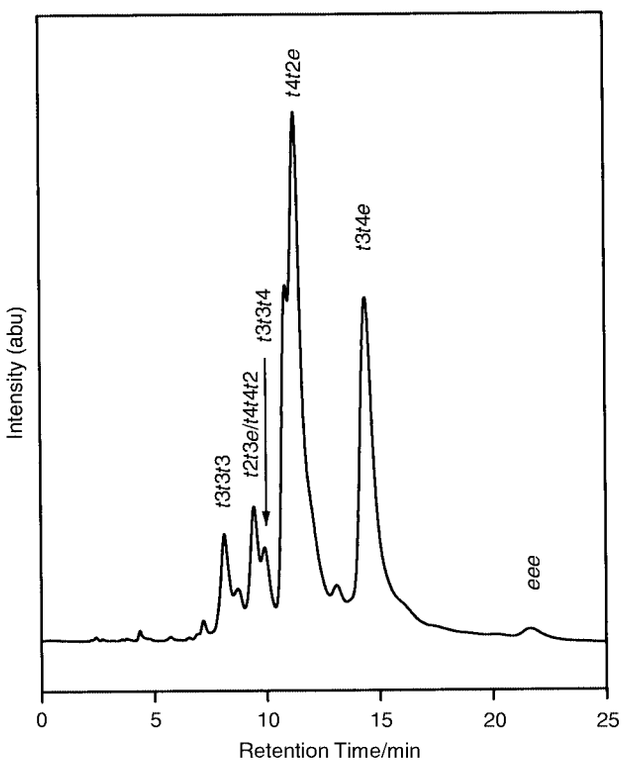


Fig. 2 HPLC chromatogram of tris-adducts obtained from 6 e CPE (retro-Bingel) of **1**.

Conclusion

Removal of one, two, or three malonate addends from tetrakis-, pentakis-, or hexakis-adducts, respectively, *via* the retro-Bingel reaction, produces tris-adducts in reasonably high yields (~30%). The major isomers formed are (*trans*-4, *trans*-2, *e*) and (*trans*-3, *trans*-4, *e*) in agreement with theoretical predictions. Tetrakis-adducts not usually obtained by the Bingel reaction are also produced under electrochemical conditions due to the relative stabilities of the adducts' dianions. The retro-Bingel reaction is therefore again proven to be a useful tool in the preparation of fullerene adduct isomers that are not easily obtained by direct synthesis.

Experimental

Synthesis

The C_{60} malonate poly-adducts (**1**–**3**) were prepared as described in the literature.[24]

Retro-Bingel

In a typical experiment, the adduct (2–3 μmol) was added to one compartment of an H-cell, the two sections of which were

separated by a glass frit #4. The cell containing the supporting electrolyte Bu_4NPF_6 (0.6 g) and the sample was degassed and pumped to 10^{-6} Torr before P_2O_5-dried and degassed CH_2Cl_2 (12 mL), pumped to the same pressure, was vapor-transferred directly into it. Controlled potential electrolysis (CPE) at 277 or 295 K was performed on a Pt mesh (100 mesh, 6.5 cm^2) working electrode. An Ag wire separated from the solution by a Vycor tip, acted as a pseudo-reference electrode, while a Pt mesh electrode fitted to the anodic compartment served as the counter electrode. After reductive electrolysis was completed, the solution was re-oxidized at 0 V *vs*. Ag.

HPLC

Analysis was done on a Lichrosorb Si60 SiO_2 column (250 × 4 mm id; toluene–ethyl acetate (95 : 5 for electrochemical product or 99 : 1 for tris-adducts), flow rate 1 mL min^{-1}), while separation was done using a Supelcosil LC-Si SiO_2 column (250 × 10 mm id; toluene–ethyl acetate (95 : 5), flow rate 1 mL min^{-1}).

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