Syntheses, Structures, and Properties of Methanofullerenes

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1 Historical Background

The recent surge of interest[1] in the chemistry and properties of carbon-rich molecules has been driven largely by the discovery[2] and the isolation of macroscropic quantities[3] of the fullerenes – all-carbon molecules which have the form of hollow, closed nets composed of 12 pentagons and n hexagons and the composition C_{20+2n}. The most readily available member of the fullerene family, C_{60} ($n = 20$), possesses icosahedral symmetry, and, as a consequence, all sixty carbon atoms in the sphere are equivalent. However as a result of the presence of both five- and six-membered rings within the structure of C_{60}, there are *two* types of bonds – namely bonds at the junction between two six-membered rings ([6,6]-bonds, Figure 1a), and bonds at the junction between a five- and a six-membered ring ([6,5]-bonds, Figure 1b). The electronic structure[4] of the fullerenes is such that bonds at [6,6]-ring junctions (Figure 1a) have much double-bond character, while bonds at [6,5]-ring junctions (Figure 1b) are essentially single bonds. This arrangement results in C_{60} having a strongly bond-alternated structure which can best be described as a spherical tessellation of [5]radialene and 1,3,5-cyclohexatriene sub-units (Figure 1c). The bond alternation observed in C_{60} governs its reactivity. Far from being 'super-aromatic', C_{60} behaves as an electron-deficient alkene in its solution-phase reactivity. This fact was exploited by several groups to prepare[5] well-characterized organometallic derivatives of C_{60}. The *X*-ray crystal structures of $[\eta^2\text{-}C_{60}Pt(PPh_3)_2]^{5b}$ and $[\eta^2\text{-}C_{60}Ir(CO)(Cl)(PPh_3)_2]^{5c}$ (Figure 2) which incorporate metallacyclopropane sub-units were particularly intriguing to organic chemists. Formally, replacement of the metal atom in the metallacyclopropane by a carbon atom would give an organic derivative of C_{60}, a *methanofullerene*, whose synthesis could be envisaged as the addition of carbenes or their equivalents to the C_{60} sphere. This proposal was further strengthened by the observation made by Diederich *et al.* in early 1991 that fullerene C_{70} reacts during the Krätschmer–Huffman production process with traces of oxygen to form an O-bridged fullerene oxide $C_{70}O$,[6] a finding which was soon after followed by the preparation of $C_{60}O$ by different methods.[7] The presence of two different kinds of bonds in C_{60} suggests that, in principle, two isomers of the methanofullerenes may be formed by such addition reactions – namely the [6,5]-bridged and [6,6]-bridged isomers (Figure 3). Further, by analogy with the methanoannulenes,[8] the possibility of valence isomerism leads to a total of four possible isomers (Figure 3) depending on whether the transannular bond of the methanoannulene sub-unit in the fullerence sphere is 'open' or 'closed'.

Since the first reported synthesis[9] of a methanofullerene by Wudl and co-workers in late 1991, research in this field has expanded rapidly in many different directions. In this Review we will attempt not only to describe the syntheses and electronic structures of the methanofullerenes but also to highlight their potential applications in materials science and as potential therapeutic agents.

2 The Synthesis of Methanofullerenes

The synthetic methods currently utilized to produce methanofullerenes may be conveniently divided into three categories. The most popular route for methanofullerene synthesis is the thermal addition of diazo compounds to C_{60}. The addition of free carbenes to C_{60} has also been demonstrated to give rise to methanofullerenes, as well as reactions which proceed by an addition/elimination mechanism. These methods will be discussed in the following sections.

François Diederich was born in Ettelbrück (Luxemburg) in 1952. After diploma and doctoral studies in chemistry with Heinz A. Staab at the University of Heidelberg, he moved in 1979 to the University of California at Los Angeles (UCLA) for postdoctoral work with Orville L. Chapman. He returned to Heidelberg in 1981, where he pursued research in host–guest chemistry at the Max-Planck-Institute for medical research and received his Habilitation in 1985. He then moved back to UCLA as an acting associate professor and was promoted to full professor in 1989. In 1992 he came back to Europe to accept a chair in the Laboratory for Organic Chemistry at the Eidgenössische Technische Hochschule (ETH) in Zürich.

Lyle Isaacs was born in New York City in 1969. After receiving a B.S. degree from the University of Chicago in 1991, he joined the group of François Diederich at the University of California at Los Angeles on a Department of Defense Graduate Fellowship. He received an M.S. degree in 1992 from UCLA before moving to Zürich to complete his doctoral studies with François Diederich at the ETH.

François Diederich

Lyle Isaacs

Douglas Philp

Douglas Philp was born in Glasgow, Scotland in 1967. He received his B.Sc. degree from the University of Aberdeen in 1989 and his Ph.D. degree from the University of Birmingham in 1993. He spent one year at the ETH, Zürich as a Royal Society European Science Exchange Programme Postdoctoral Fellow before taking up his current post as Lecturer in Organic Chemistry at the University of Birmingham in April 1994.

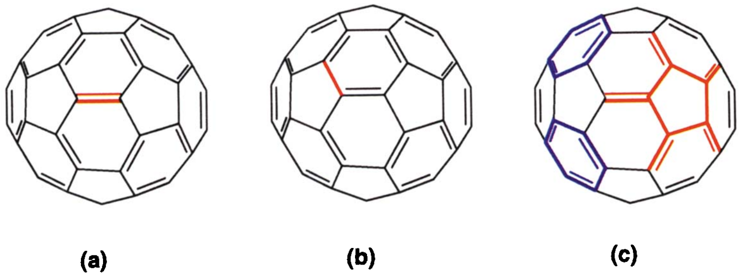


Figure 1 Illustration of (a) a [6,6]-bond; (b) a [6,5]-bond; and (c) the [5]radialene and 1,3,5-cyclohexatriene substructures of C_{60}.

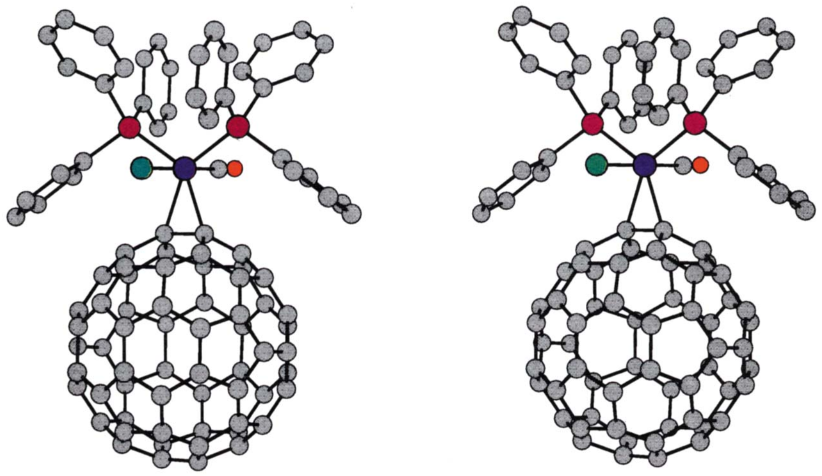


Figure 2 Stereoview of the X-ray crystal structure of η^2-$C_{60}Ir(CO)(Cl)(PPh_3)_2$ [5c]

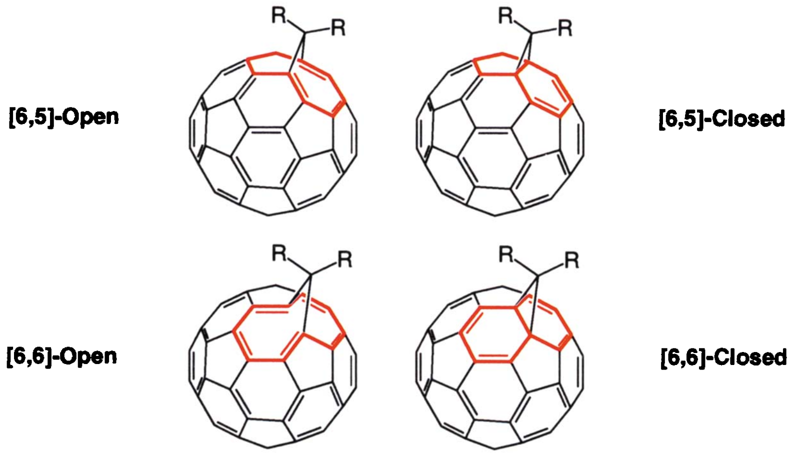


Figure 3 The four possible isomeric methanofullerenes. The methanoannulene-type subunits are highlighted in red.

2.1 The Addition of Diazo Compounds to C_{60}

In late 1991, Wudl and co-workers reported[9] that C_{60} reacts with diphenyldiazomethane in toluene solution at room temperature to give a [6,6]-ring bridged adduct. Subsequently, in an *Accounts of Chemical Research* article, it was shown[10] that this reaction tolerates the presence of substituents on the phenyl rings, implying its general applicability to the production of functionalised fullerene derivatives. This account ignited an interesting debate on the structure of methanofullerenes, and the nature and resolution of the fundamental questions raised will be a recurring theme throughout this review.

2.1.1 Scope of the Thermal Addition of Diazo Compounds to C_{60}

The scope of the thermal addition reaction of diazo compounds to C_{60} is quite broad. A complete compilation of the reactions of C_{60} with diazo compounds is presented in Table 1. Mono- and diphenyldiazomethanes bearing a variety of substituents on the phenyl rings have been successfully employed.[9—18] It has also proven possible to add diazomethane itself.[19,20] In three reports, our group has demonstrated the addition of electron-deficient diazoacetates and diazomalonates to C_{60}.[21—23] The addition of the diazoacetates is sluggish and requires refluxing in

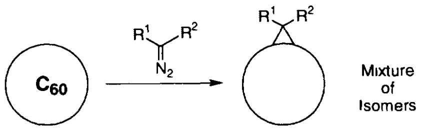
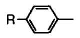
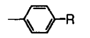
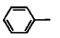
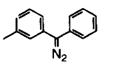
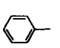
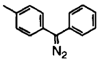
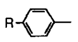
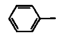
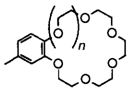
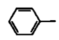
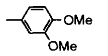
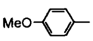
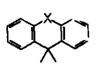
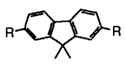
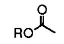
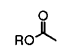
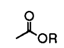
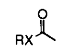


Table 1 Compilation of the reactions of C_{60} with diazo compounds

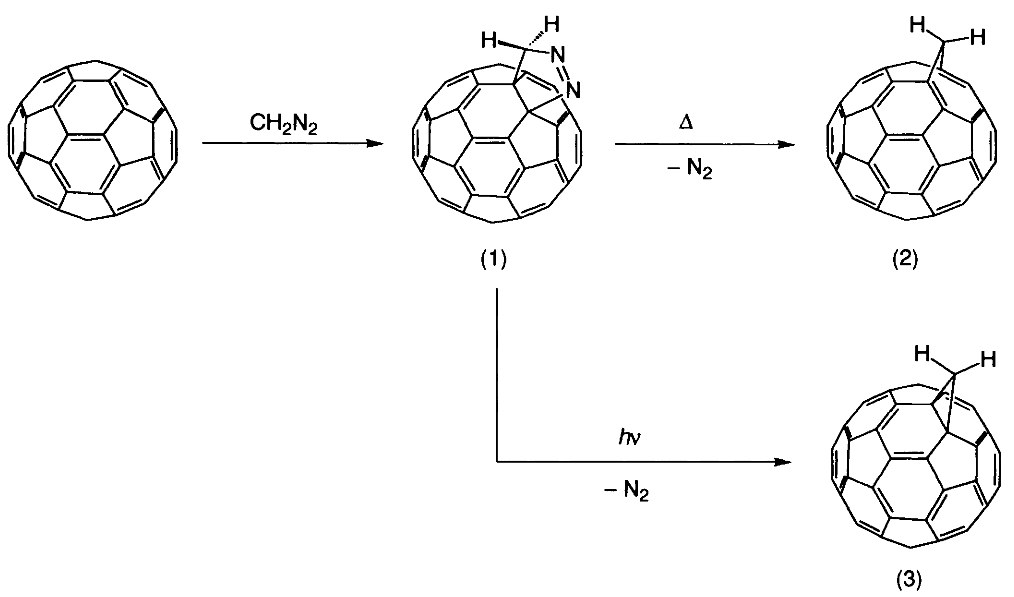
R^1	R^2		Yield (%)	Ref.
		R = H	nr[a]	9
		R = Me	nr	10
		R = Br	nr	10
		R = NMe_2	nr	10
		R = PhO_2C	nr	10
		R = OMe	73	11
		R = OPr^i	nr	15
		R = $(CH_2)_2NHCOCH_3$	38	13
			51[b]	14
			39[b]	14
	H	R = H	nr	10
		R = CO_2Bu^t	nr	12
		$n = 0$	43	16
		$n = 1$	42	17
			30	16
	H		nr	15
	CH_3		nr	15
		X = (CO)	nr	10
		X = $(CH_2)_2$	nr	18
		X = $(CH)_2$	nr	18
		X = 	nr	18
		R = H	nr	10
		R = NO_2	nr	10
H	H		44	19
	H	R = Et	30	21
		R = Bu^t	25	21
		R = CH_2CO_2Et	32	22
		R = Et	10	23
		R = Bu^t	7	23
	H	RX = $N((CH_2)_2)_2O$	20–30	24
		RX = NHBn		24
		RX = $NHCH(Bn)CO_2Bn$		24
		RX = $NH(CH_2)_4CH(NH_2)CO_2Et$		24

[a] Not reported [b] Addition to two C_{60} molecules occurs under formation of dumbbell-type compounds.

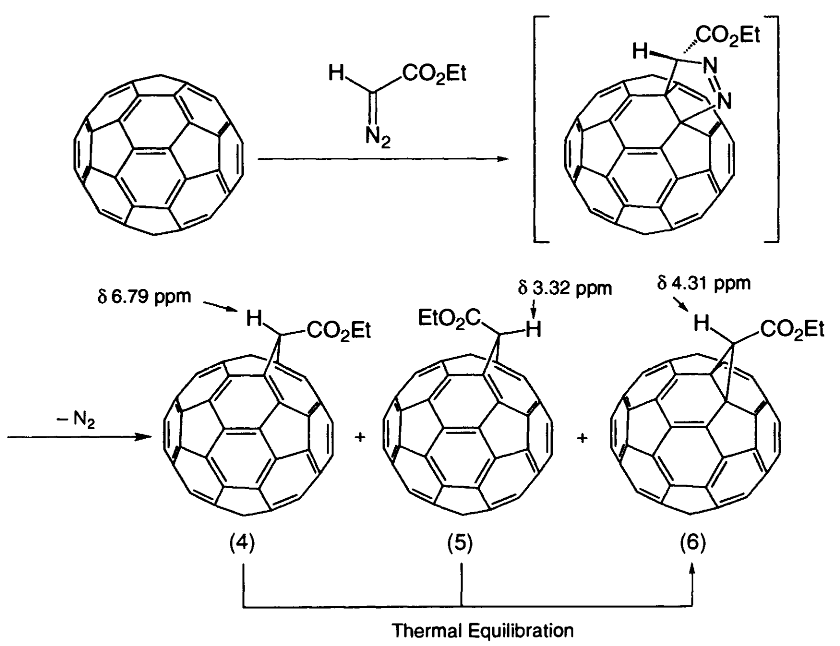
toluene for 7 hours – by comparison, the diphenyl diazomethanes add rapidly at room temperature. The addition of diazomalonates can only be accomplished by the use of high temperatures and long reaction times. More recently, Skiebe and Hirsch described the reaction of C_{60} with diazo amides.[24] In this case, refluxing toluene and a reaction time of 48 hours was required to produce the desired methanofullerenes.

2.1.2 *The Initial [1,3]-Dipolar Cycloaddition of Diazo Compounds to C_{60}*

Wudl and co-workers proposed[9] that diphenyldiazomethane adds initially as a [1,3]-dipole to C_{60}, and that the pyrazoline intermediate, which was not isolated, subsequently extrudes nitrogen. When the addition of diazomethane to C_{60} was conducted in benzene at room temperature,[19] a brown, thermally unstable, compound was isolated (Scheme 1). This compound was assigned the pyrazoline structure (1) on the basis of (i) a singlet in the ^1H NMR spectrum at 6.51 ppm, (ii) the presence of 30 carbon resonances in the fullerene region of the ^{13}C NMR spectrum (consistent with the assigned C_s symmetry), and (iii) a N=N stretching vibration at 1560 cm^{-1} in the infrared spectrum. Thermolysis of (1) in refluxing toluene afforded (2) in quantitative yield. The ^1H NMR spectrum of (2) showed two doublets centred at 2.87 and 6.35 ppm, and the ^{13}C NMR spectrum displayed 32 resonances between 135 and 150 ppm, in addition to a signal at 38.85 ppm, in agreement with the assigned [6,5]-open structure (2). Taken together, these experiments suggest that the initial step in the addition of diazo compounds to C_{60} is indeed a [1,3]-dipolar cycloaddition followed by thermal loss of nitrogen. However, all of the phenyl- and diphenyl-substituted methanofullerenes isolated previously[10] were bridged at the [6,6]-ring junction, and not at the [6,5]-ring junction. Thus, it was unclear whether the results obtained in the diazomethane addition, which yielded only a very small amount of the [6,6]-closed isomer,[19] applied to the reactions of C_{60} with



Scheme 1



Scheme 2

diazo compounds in general. In all of the previous cases, the initial product of the reaction was a mixture of at least two isomers. Furthermore, it was possible to convert this isomeric mixture thermally into a single [6,6]-ring bridged compound which had high symmetry (C_{2v}) – readily identified by the simplicity of its ^1H and ^{13}C NMR spectra. These two generalizations apparently did not apply to the diazomethane adduct (2). A connection between these seemingly unrelated facts was needed.

2.1.3 Kinetic versus Thermodynamic Products

In the middle of 1992, our group observed[21] that the addition of alkyl diazoacetates to C_{60} in refluxing toluene for 7 h (Scheme 2) gave rise to three isomeric products (as determined by ^1H NMR spectroscopic analysis) under kinetic control. Interestingly, one of the isomers predominated by a factor of three over the other two. When this isomeric mixture, which like C_{60} solutions was purple, was heated in refluxing toluene for 24 hours, a wine-red solution was produced whose ^1H NMR spectrum showed only a single set of resonances. This pure compound corresponded to one of the two minor components in the isomeric mixture and was obviously thermodynamically more stable than the other two isomers. This compound was assigned the [6,6]-closed structure (6) based on its ^{13}C NMR spectrum and the $^1J_{CH}$ value for the methine carbon which clearly supported the presence of a cyclopropane ring (see Section 3 below). However, the ^{13}C spectrum and $^1J_{CH}$ values of the isomeric mixture established that the two other isomers, which were produced under kinetic control, had the [6,5]-open structures (4) and (5). The mechanism of diazo additions to C_{60} (Scheme 2) was now reasonably secure. The initial reaction affords, as was shown by Wudl, a pyrazoline which is thermally unstable under the experimental conditions and loses nitrogen rapidly to give [6,5]-open methanofullerenes, together with some [6,6]-closed isomer. Thermal equilibration of the isomeric mixture leads to the thermodynamically most stable [6,6]-closed methanofullerene.

Nearly identical results were subsequently reported[15] by Wudl and co-workers for the addition of bis(4-*iso*-propyloxyphenyl)-diazomethane, (*p*-methoxyphenyl)diazomethane, and (*p*-methoxyphenyl)diazoethane to C_{60}. Similar to the results in the addition of alkyl diazoacetates, they found that the [6,5]-open diastereoisomer with the bulkier substituent located above the five-membered ring predominated in the product mixture formed under kinetic control. Related studies by Vögtle and co-workers,[16] and those of Skiebe and Hirsch[24] demonstrated the same phenomenon, suggesting that this diastereoselectivity in the formation of the kinetic [6,5]-open isomers may be a general phenomenon. Structures of the two [6,5]-open diastereoisomers, in all cases, were assigned based on the ^1H NMR spectra which showed a strong downfield shift of the resonance for the methano bridge proton located above a pentagon as compared to the resonance of the proton above a hexagon (Scheme 2).

In the case of the parent methanofullerene $C_{61}H_2$, it has not proved possible thermally to rearrange the [6,5]-open isomer (2) to the [6,6]-closed compounds (3). The latter could, however, be synthesized by Smith *et al.* by photolysis of pyrazoline (1).[20] This reaction afforded both (2) and (3) in a 4:3 ratio, and separation of the mixture by HPLC on a C_{18} reverse-phase column gave (3), whose structure was convincingly elucidated by ^1H and ^{13}C NMR spectroscopy. The fact that (3) cannot be isomerized to (2) under either thermal or photolytic conditions implies that there is no easily accessible, low-energy pathway for their interconversion.

Thermal isomerization of the diazoamide adducts of C_{60}, reported by Skiebe and Hirsch,[24] is also impossible, leading to decomposition of the [6,5]-open isomers, rather than equilibration to the corresponding [6,6]-closed isomers.

2.2 The Addition of Carbenes to C_{60}

The reaction of C_{60} with carbenes is less complicated than the addition of diazo compounds, since singlet carbenes seem to add exclusively to the [6,6]-ring junction of C_{60} in one step, as would be expected if C_{60} behaves as an electron-deficient alkene. It appears that any method which generates carbenes is suitable for application in the synthesis of methanofullerenes.

2.2.1 *Diazirines*

The two reported examples of the addition of diazirines to C_{60} both come from the work of Vasella *et al.*[25] who, as a result of their interest in the potential biological activity of amphiphilic water-soluble fullerene derivatives, prepared fullerene–sugar conjugates. Thus, the reaction of the protected sugar derivatives (7) and (8) with C_{60} in toluene (Table 2) afforded the enantiomerically pure methanofullerenes (9) and (10) in 55 and 54% yield, respectively. The isolated compounds consisted of single structural isomers each showing two fullerene resonances between 77 to 80 ppm in the sp^3-C-atom region of their respective ^{13}C NMR spectra. These compounds were therefore assigned a [6,6]-closed structure. This finding is consistent with the intermediacy of the nucleophilic glycosylidene carbene, since a mechanism involving the isomeric diazo compound would presumably give rise to both [6,5]-open and [6,6]-closed methanofullerenes.

2.2.2 *Pyrolysis of α-Halo Carboxylates*

The addition of dichlorocarbene to C_{60} has been described by Nogami and co-workers.[26] The pyrolysis (Table 2) of sodium trichloroacetate (11) in a mixture of benzene and diglyme generates dichlorocarbene which then adds, as expected on mechanistic grounds, directly to the [6,6]-ring junction giving the [6,6]-closed methanofullerene (12). The structure of the product was confirmed by the observation of a molecular ion at *m*/*z* 803 amu in the negative ion fast atom bombardment (FAB) mass spectrum, and the presence of the 18 resonances in the ^{13}C NMR spectrum expected for a C_{2v}-symmetrical product. Sixteen of these resonances were observed between 138 and 146 ppm. A further two resonances are located at 64.1 and 80.1 ppm and are ascribed to the methano and bridgehead C-atoms, respectively.

2.2.3 *Thermolysis of Oxadiazoles*

The reaction of C_{60} with oxadiazole (13) in refluxing toluene, reported[22] by Isaacs and Diederich, afforded [6,6]-closed (14) as the only one detectable monoaddition product, arising from the

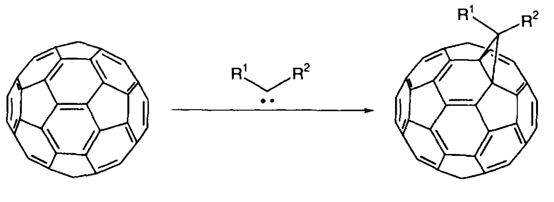
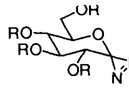
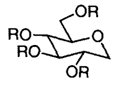
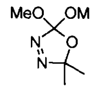
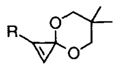
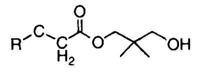
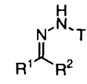


Table 2 Synthesis of methanofullerenes by carbene addition

Precursor		R¹	R²		Yield (%)	Ref.
	(7) R = Bn[a] (8) R = Piv[a]			(9) R = Bn (10) R = Piv	55 54	25 25
$Cl_3CCOONa$	(11)	Cl	Cl	(12)	25	26
	(13)	OMe	OMe	(14)	32	22
	(15) R = H (16) R = Ph			(17) R = H (18) R = Ph	44 10	29 29
	(19) (20) (21)	C≡CTIPS C≡CTMS C≡CTIPS	C≡CTIPS C≡CTMS C≡CTMS	(22) (23) (24)	32 24 28	30 30 31

[a] Bn = $PhCH_2$, Piv = $(CH_3)_3CCO$.

addition of dimethoxycarbene to a [6,6]-ring junction. This compound was synthesized in order to assess the effect of methano bridge substituents on the position of the theoretically possible [6,6]-closed $\rightleftharpoons$ [6,6]-open valence isomeric equilibrium. Such effects are well established in 1,6-methano[10]annulenes, where an electron-withdrawing substituent like the cyano group at the bridging C-atom favours a closed transannular bond whereas electron-donating substituents like the methyl group favour an open transannular bond or an electronic structure somewhere between the two extreme valence isomers.[27,28] The ^{13}C NMR spectrum of (14) showed no unusual chemical shifts, thereby strongly supporting exclusive formation of a [6,6]-closed structure. This finding indicates that the fullerene itself and not the methano bridge substituents determine the preferred valence isomer. A simple rationale for this observation will be presented in Section 3.

2.2.4 *Thermolysis of Cyclopropenone Acetals*

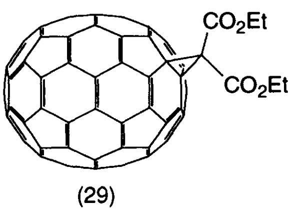
Nakamura and co-workers have described[29] the reaction of C_{60} with the cyclopropenone acetals (15) and (16). In this case, the production of the carbene intermediate occurs by isomerization, generating vinyl carbenes which then undergo addition to C_{60}. Hydrolysis of the intermediate ketene acetals gives the observed products (17) and (18) in 44 and 10% yield, respectively. Interestingly, when R = Et, a [3 + 2]-cycloaddition product is formed, indicating that this method of generating carbenes may not be the one of choice if methanofullerenes are the desired products.

2.2.5 *Thermolysis of Tosylhydrazone Lithium Salts*

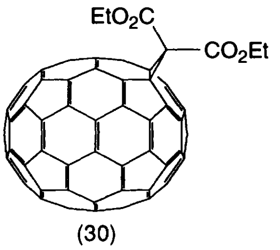
Two reports by Rubin and co-workers[30] and Diederich and co-workers[31] demonstrated the use of diethynyl carbenes in the production of diethynylmethanofullerenes. Thermolysis of the lithium salts of tosylhydrazones (19), (20), and (21), derived from the corresponding 1,4-pentadiyne-3-ones (Table 2), produces diethynylmethylene carbenes which add readily to C_{60} to give the symmetrically and unsymmetrically silyl-protected (TMS = trimethylsilyl, TIPS = triisopropylsilyl) [6,6]-closed diethynyl derivatives (22)—(24).

2.3 Reactions Occurring by Addition/Elimination Mechanisms

C_{60} is capable of reacting with nucleophiles of all types, and the intermediate anions can be trapped with suitable electrophiles.[1b,c,10] Bingel demonstrated[32] that C_{60} reacts with several stabilized α-halocarbanions (Table 3) to give the methanofullerenes (25)—(28). This reaction is formulated as an addition of the stabilized α-halocarbanion to C_{60}, followed by intramolecular displacement of halide by the anionic centre generated on the fullerene sphere. The reaction is fast, clean, and proceeds in fair to good yield. Furthermore, it gives only [6,6]-closed methanofullerenes, which obviates the need for tedious and time consuming thermal equilibration. By this method, Bingel prepared the first well-characterized C_{70}-derived methanofullerene. Addition was expected to occur to one of the two [6,6]-bonds in the regions of highest curvature and therefore highest reactivity on the C_{70} sphere – not unexpectedly only the one closest to the polar cap reacted. Conversion of C_{70} with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) and bromodiethylmalonate in toluene at room temperature afforded (29) in 60% yield, whereas (30) was not detected in the reaction mixture.



(29)



(30)

This methodology was extended (Scheme 3) by Hirsch *et al.* to produce well-characterized bis- and tris-adducts of C_{60}.[33] They found that, upon addition of bromodiethylmalonate to (25) in the presence of NaH as a base, a mixture of bisadducts with [6,6]-closed structures was produced. Of the eight theoretically possible regioisomers, seven were isolated by HPLC from the reaction mixture – the formation of the remaining isomer, the so-called '*cis*-1' isomer, is impossible on steric grounds. Furthermore, repeating the same reaction (Scheme 3) on purified (31) and (32) gave the tris-adducts (33) and (34) in close to 40% yield. These compounds were isolated by HPLC, and their structures were assigned on the basis of their ^{13}C NMR spectra.

Lastly, in a recent report[31] from this laboratory, it was shown that TMS-protected 3-bromopenta-1,4-diyne reacts (Table 3)

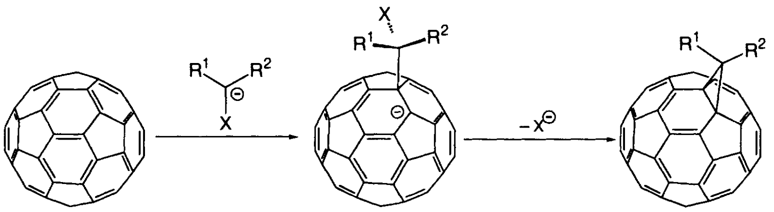
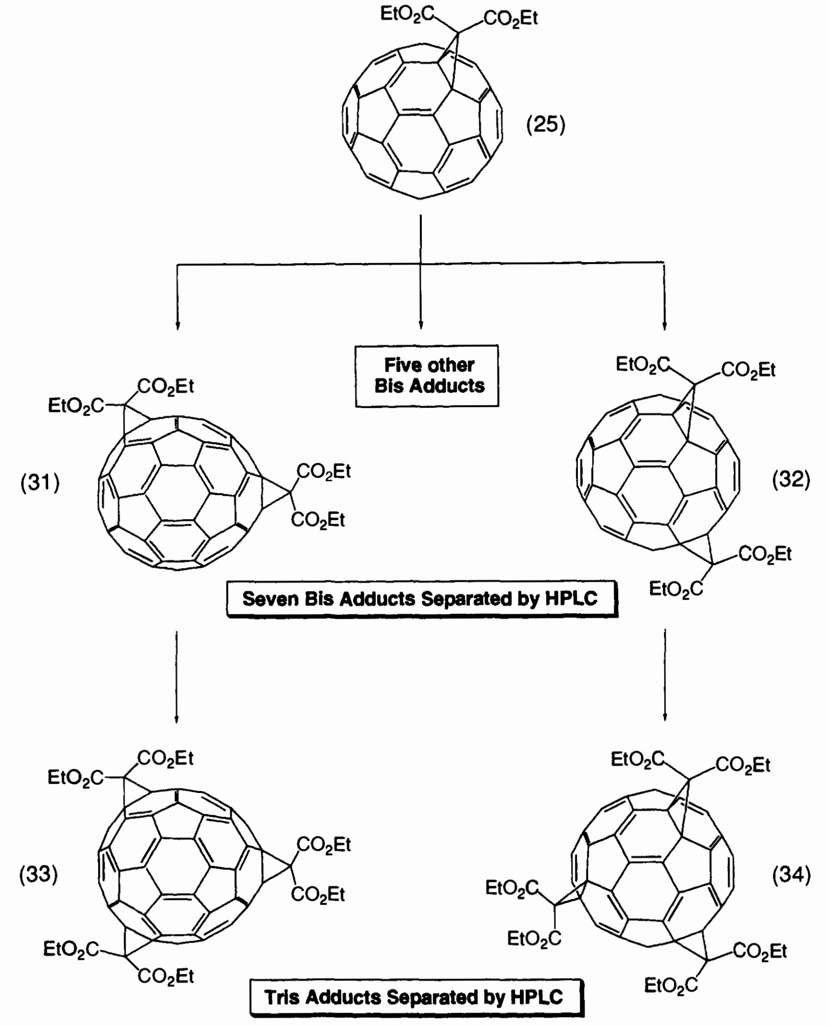


Table 3 Methanofullerenes by addition/elimination mechanisms

R^1	R^2	X		Yield (%)	Ref.
CO_2Et	CO_2Et	Br	(25)	45	32
$COCH_3$	CO_2Me	Cl	(26)	27	32
COPh	H	Br	(27)	21	32
COPh	Ph	Cl	(28)	25	32
C≡CTMS	C≡CTMS	Br	(22)	55	31



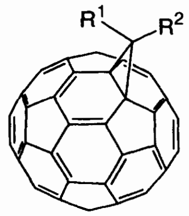
Scheme 3

with C_{60} in the presence of DBU to give diethynyl methanofullerene (22). The addition could proceed either *via* direct deprotonation of the TMS-protected 3-bromopenta-1,4-diyne by DBU or, alternatively, by nucleophilic displacement of the bromide with DBU to give a more acidic salt, which could be deprotonated to form an ylid, which could attack C_{60}.

3 The Electronic Structure of the Methanofullerenes

The electronic structure of C_{60} is best described[4] as a fusion of [5]radialene and 1,3,5-cyclohexatriene substructures (Figure 1), and this strong, yet poorly understood propensity of C_{60} to avoid placing double bonds in five-membered rings results in poor electronic delocalization and gives C_{60} its alkene-like properties. Bridging can occur at both the [6,5]- or the [6,6]-ring junctions, and the possibility of valence isomerization potentially gives rise to four isomeric methanofullerenes (Figure 3). The chemistry of methanoannulenes[8] has shown that the substituents at the bridging methylene carbon[27,28] play an important role in the determination of the valence isomeric equilibrium between the π-homoaromatic bond-open form and the σ-homoaromatic bond-closed form; thus the electronic structure and valence isomeric preferences of the methanofullerenes were of great interest.

In their initial report[9] on their synthesis of methanofullerenes, Wudl and co-workers assigned a [6,6]-open structure to (35) on the basis of its ^{1}H NMR spectrum and the similarity of its UV/VIS spectrum and cyclic voltammogram to the corresponding data of C_{60} itself; however, the compound was too insoluble to record a ^{13}C NMR spectrum. Subsequently, a crystal structure of (36) was reported[10] in which the transannular bond length at the [6,6]-bridge was found to be 1.84 Å, which, although shorter than an open transannular bond in methanoannulenes[8], is clearly much longer than the normal sp^3–sp^3 bond length of 1.54 Å. This result must however, be treated with caution since the crystals were of poor quality and probably contained more than one isomer. In addition, Wudl also determined the $^{1}J_{CH}$ coupling constant at the bridging carbon for (37).[10] The measured value of 140 Hz is almost exactly that found in 11-phenyl-1,6-methano[10]annulene with an open transannular bond, and thus was considered clear evidence for a [6,6]-open structure. Caution should be exercised, however, since, without ^{1}H and ^{13}C NMR spectra of all three isomers, it is impossible to distinguish whether bridging had occurred at the [6,5]- or the [6,6]-ring junctions of the fullerene sphere. Despite these reservations the matter seemed settled in favour of the [6,6]-open structure, at this point. However, the synthesis[25] of fullerene sugars by



(35) $R^1 = R^2 = Ph$
(36) $R^1 = R^2 = p\text{-}BrC_6H_4$
(37) $R^1 = H, R^2 = Ph$
(38) $R^1 = R^2 = CO_2{}^t\!Bu$

Vasella *et al.* raised new questions. Compounds (9) and (10) (R = Bn or Piv) were soluble enough to permit the recording of high quality ^{13}C NMR spectra, which clearly showed peaks corresponding to fullerene resonances in the 70 to 80 ppm region providing evidence for a [6,6]-closed structure. The synthesis of (6), (14), and (38) by Diederich and co-workers[21—23] helped to clarify the situation further. Despite the widely different properties of the substituents at the bridging carbon atom in these three compounds, ^{13}C NMR data for the bridgehead fullerene resonances and the $^{1}J_{CH}$ coupling constant at the bridging C-atom clearly demonstrated that all three compounds had [6,6]-closed structures. All three compounds displayed fullerene resonances in the 70 to 85 ppm region, corresponding to the sp^3-hybridized fullerene C-atoms in cyclopropane rings, and, in addition, the $^{1}J_{CH}$ coupling constant at the bridging C-atom in (6) was found to be around 165 Hz, typical of a cyclopropane ring. Close examination of the isomeric mixture of (4), (5), and (6) produced under kinetic control during the synthesis of (6) revealed that in both cases, the [6,5]-bridged isomers had an open transannular bond – the $^{1}J_{CH}$ coupling constants at the bridging C-atom in (4) and (5) were found to be around 140—145 Hz, characteristic of a 1,6-methano[10]annulene-type structure, and all 32 resonances (C_s-symmetry) of the carbon sphere appeared in the fullerene region above 130 ppm. Further support for the assignment of the closed structure to the [6,6]-isomer of methanofullerenes came from the photochemical preparation of the [6,6]-bridged isomer of the parent methanofullerene $C_{61}H_2$ (3) by Smith *et al.*[20] The ^{13}C NMR spectrum of (3) contained 18 signals, 16 between 136 and 150 ppm, and more importantly, one at 30 ppm and one at 71 ppm which was assigned to the cyclopropane C-atoms in the fullerene sphere. Further evidence for the [6,6]-closed structure was obtained from the $^{1}J_{CH}$ coupling constant at the bridging C-atom, which, at 167 Hz, is clearly characteristic of a cyclopropane ring. In contrast, Wudl and co-workers did not observe any resonances in the 70—80 ppm region in the ^{13}C NMR spectrum of the [6,5]-bridged isomer of $C_{61}H_2$ (2).[19] They measured a $^{1}J_{CH}$ coupling constant at the bridging C-atom of around 146 Hz which, together with the ^{13}C NMR data, provided clear evidence that the [6,5]-bridged isomer of $C_{61}H_2$ had an open transannular bond. All these results called into question the original assignment of a [6,6]-open structure to (35) and indeed, at this point, (35) and its derivatives were reformulated[15] as the corresponding [6,6]-closed structures. Thus, all the then-known [6,6]-bridged methanofullerenes had a closed transannular bond. Subsequent work has shown that this statement is almost certainly true for *all* [6,6]-bridged methanofullerenes, and that the substituent effects at the bridging C-atom which are observed in methanoannulenes are overwhelmed in the methanofullerenes by electronic and structural preferences of the fullerene sphere. In retrospect, it was not until [6,5]- and [6,6]-bridged compounds bearing the same substituents at the bridging C-atom became available, and were fully characterized, that all of the pieces of the puzzle could be fitted together. Today, it is clear that all [6,5]-bridged compounds possess an open transannular bond, and all [6,6]-bridged compounds have a closed transannular bond.

Once the valence isomeric preferences of the [6,5]- and [6,6]-isomers of the methanofullerenes had been established experimentally, the attention turned to the interrelationship between the two isomers. Several groups had reported[15,16,19,21,24] that the [6,5]-open isomer was the kinetic product of the addition of diazo compounds to C_{60} and that, in some cases, it could be isomerized thermally to the [6,6]-closed isomer. Clearly a simple rationale was desirable to explain the relative stabilities of the two experimentally isolated isomers and to link them *via* a feasible interconversion pathway. Progress in this area has come primarily from computational studies.

Raghavachari and Sosa studied[34] the parent methanofullerene $C_{61}H_2$ using high-level *ab initio* methods. These calculations showed that the [6,6]-bridged isomer had a closed transannular bond (the [6,6]-open structure did not exist as a local minimum on the potential energy surface) and was between 3 and 9 kcal mol^{-1} more stable than the corresponding [6,5]-bridged isomer, which was found to have an open transannular bond.

We carried out a comprehensive computational study[23] of five experimentally-known methanoannulenes (14), (25), (35), (38), and the parent $C_{61}H_2$ using the semi-empirical PM3 SCF-MO method. In all five cases studied, the [6,6]-bridged isomer was found to have a closed transannular bond, while the [6,6]-open isomer could not be located as a local minimum on the potential energy surface. In constrast, the [6,5]-bridged isomer was found strongly to prefer an open transannular bond. In four of the five cases studied, namely (14), (25), (35), and (38) the [6,6]-closed isomer was found to be significantly more stable thermodynamically than the corresponding [6,5]-open structure, the exception being the parent compound $C_{61}H_2$. These calculations also indicated the absence of classical substituent effects – the calculated geometries varied very little between compounds – suggesting that it is the electronic structure of the fullerene sphere which is dictating the valence isomeric preference of the [6,5]- and [6,6]-bridged isomers. Interestingly, we were able to locate shallow local minima corresponding to a [6,5]-closed isomer in all cases except that of $C_{61}H_2$. These structures were around 16 kcal mol^{-1} less stable than the corresponding [6,5]-open isomers. Examination of the calculated geometries and bond orders within the three isomers revealed the electronic basis for the observed trend in the relative stabilities. The [6,5]-closed isomer is forced (Figure 4a) to locate two double bonds within five-membered rings of the fullerene sphere, thus disrupting the strongly preferred [5]radialene type bonding seen in C_{60}. The [6,5]-open isomer (Figure 4b) can avoid this fate, but only at the expense of placing double bonds at the bridgehead atoms, in violation of Bredt's Rule. Evidence for the strain induced in the structure by this compromise is found in the geometry of the formally sp^2-hybridized bridgehead C-atoms – these are pushed out of the plane of the three adjacent C-atoms by almost 0.25 Å. The [6,6]-closed isomer (Figure 4c) can both avoid placing double bonds in five-membered rings and violating Bredt's rule by having sp^3-hybridized bridgehead atoms, which, although located in a cyclopropane ring, cannot be viewed as particularly unfavourable. This analysis also explains why the [6,6]-open isomer cannot be detected. Not only is it forced to locate three double bonds in five-membered rings (Figure 4d), but also two of these double bonds occur at the bridgeheads, making this isomer the least stable of the four.

The location of a [6,5]-closed structure for (14), (25), (35), and (38) but not for $C_{61}H_2$ intrigued us and led us to propose the two-step pathway – valence isomerization followed by 1,5-shift – shown in Figure 5 for the interconversion of the [6,5]-open isomer into the thermodynamically more stable [6,6]-closed isomer. Thermal rearrangement takes place only in the case of substituted derivatives, for which a [6,5]-closed structure is located, whereas the parent methanofullerene $C_{61}H_2$, for which no [6,5]-closed structure was located, does not rearrange. This proposal awaits further experimental investigation.

The experimental and computational results detailed above illustrate that the structural chemistry of the methanofullerenes is determined by the propensity of the fullerene sphere to retain the [5]radialene-type bonding found in C_{60}. The preference for this bonding arrangement overwhelms any substituent effects expected on the basis of the presence of a methanoannulene subunit within the fullerene sphere. The control of the reactivity and the determination of the relative stability of adducts by the electronic characteristics of the carbon sphere may be a general feature of the chemistry of fullerenes,[35] and the studies described above developed some of the rules involved.

4 Potential Applications of Fullerene Derivatives – Further Functionalization of Methanofullerenes

Much speculation has appeared in the literature regarding the possible uses of the fullerenes and their derivatives, and, although no commercial applications of fullerene derivatives

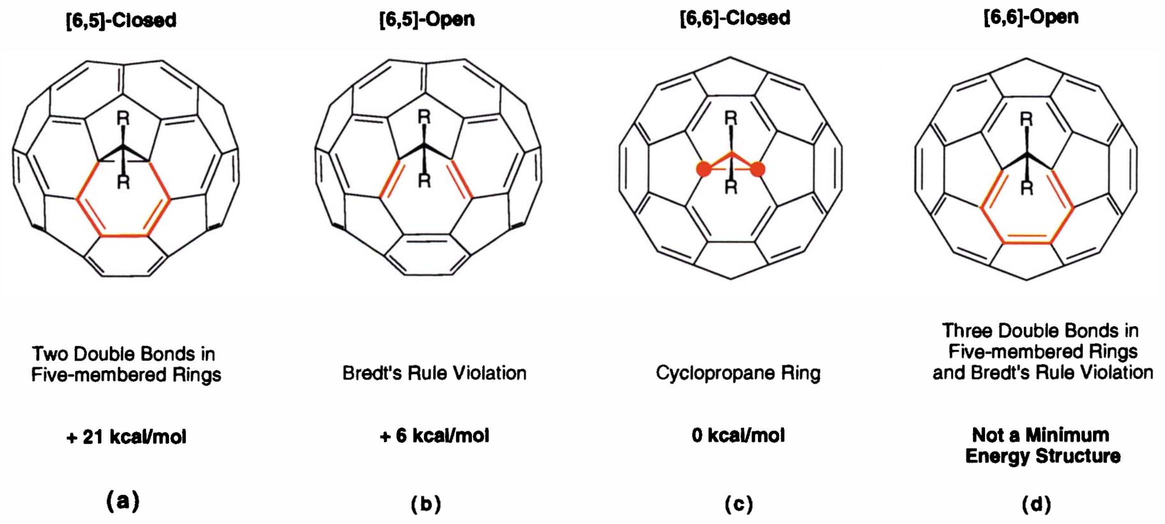


Figure 4 Unfavourable structural elements (highlighted in red) of the four isomeric methanofullerenes and their relative energies from PM3 calculations. The quoted relative energies are the average over compounds (14), (25), (35), and (38).

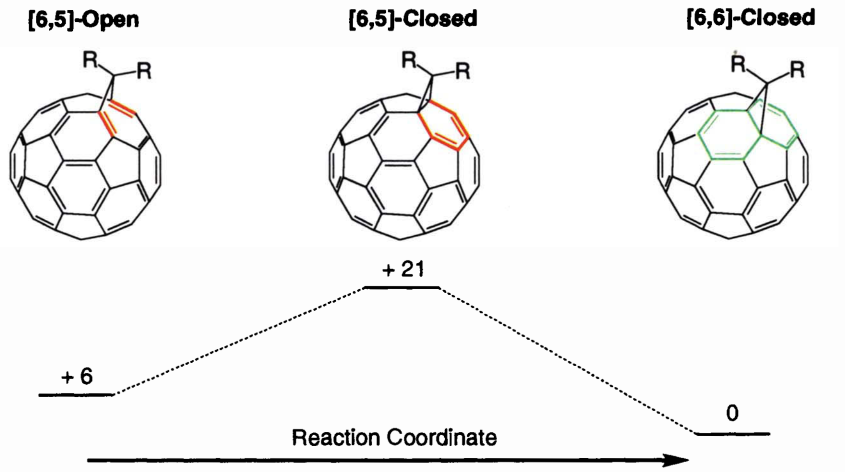


Figure 5 The proposed reaction coordinate for the thermal isomerization of [6,5]-open to [6,6]-closed methanofullerenes proceeding *via* the [6,5]-closed valence isomer. Relative energies are quoted in kcal mol^{-1}.

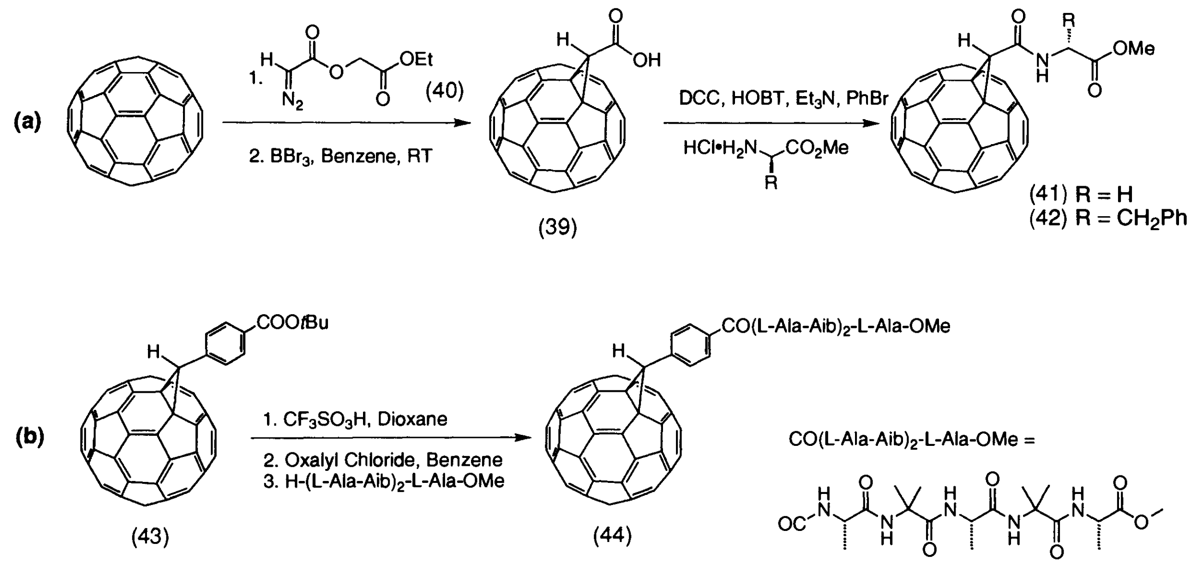
have emerged, the synthetic elaboration of a methanofullerene core has allowed several groups to explore the utility of fullerene derivatives in both biological and materials applications.

4.1 Targeted Applications in Biomedical Science

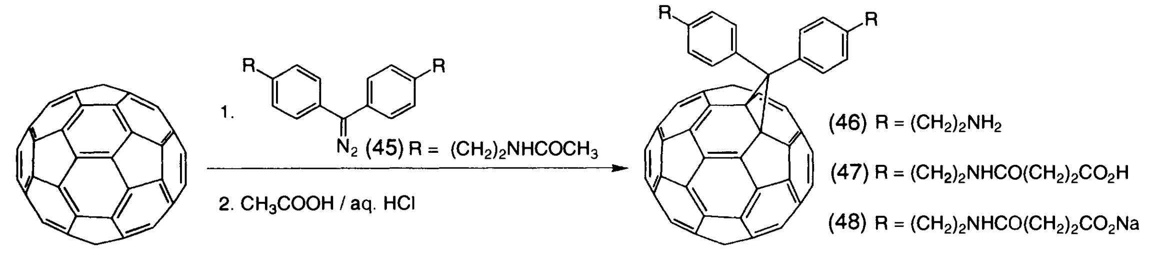
For potential biological applications of fullerene derivatives, it might prove desirable to combine the properties of biomolecules with particular physical properties of the C_{60} sphere such as efficient sensitization of singlet oxygen formation.[36,37] Thus synthetic approaches to methanofullerene-based amino acids and peptides have received significant attention.

Our approach[22] to the synthesis of methanofullerene amino acids focused on the production of the carboxylic acid (39) as a versatile intermediate. The synthesis of (39) (Scheme 4a) was achieved by the addition of (40) to C_{60}, thermal isomerization of the isomeric mixture produced to the single [6,6]-closed isomer, and deprotection using BBr_3 in benzene. Amide bond forming reactions (Scheme 4a) with amino acids esters under peptide coupling conditions [dicyclohexyl carbodiimide (DCC), 1-hydroxybenzotriazole (HOBT)] gave the methanofullerene amino acids (41) and (42) in 71 and 80% yields, respectively. In the case of the phenylalanine derivative (42), the CD spectrum indicated that the coupling reaction had proceeded without racemization, allowing access to optically pure methanofullerene amino acids. Prato *et al.* utilized a similar approach[12] in their preparation of a fullerene pentapeptide (Scheme 4b). Reaction of C_{60} with [4-(t-butoxycarbonyl)phenyl]diazomethane, after isomer equilibration, gave (43), which was converted with excess trifluoromethanesulfonic acid in dioxane into the corresponding acid. After activation with oxalyl chloride in benzene, reaction with an *N*-deprotected pentapeptide gave (44) in 31% yield.

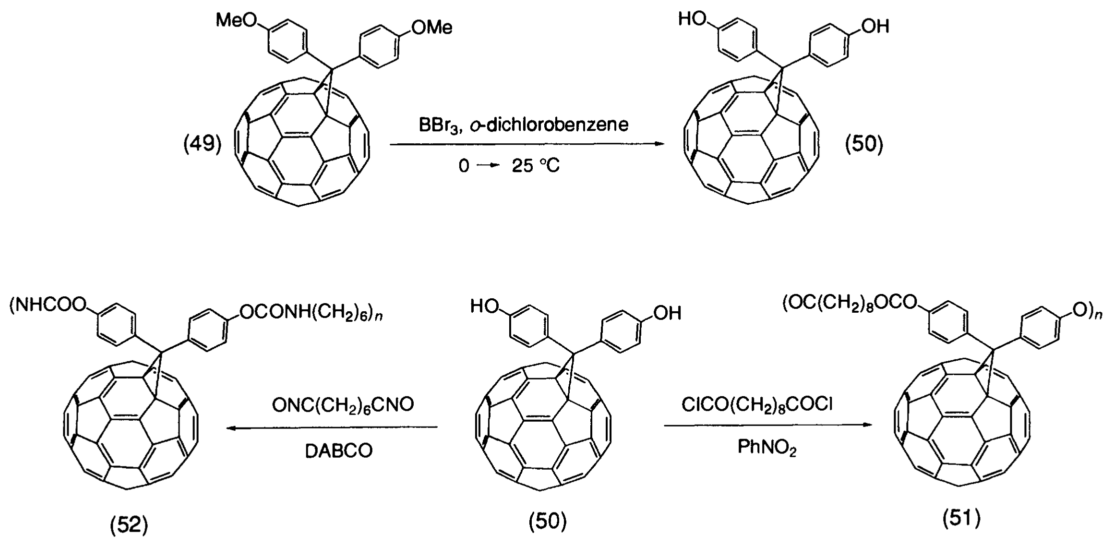
An exciting first step towards fullerene-based agents with possible therapeutic potential was taken by Wudl, Kenyon, and co-workers.[38] One of the major targets in AIDS therapy is the Human Immunodeficiency Virus (HIV) protease, an aspartyl protease. This interdisciplinary group of scientists recognized that the active site of the HIV protease, which may be described as an open-ended cylinder, has an interior diameter approximately the same size as C_{60}. Since both the fullerene surface and the walls of the enzyme active-site are of pronounced hydrophobic character, it was reasoned that the protease could be inhibited by suitably designed water-soluble C_{60} derivatives which would be bound through strong hydrophobic interactions. To test this hypothesis, the water-soluble methanofullerene (48) was prepared (Scheme 5) starting with the addition of (45) to C_{60}.[13] Thermal equilibration to the [6,6]-closed isomer, followed by hydrolysis of the acetamide groups afforded the diamine (46) as its bis(hydrochloride) salt. Homologation of (46)



Scheme 4



Scheme 5



Scheme 6

with succinic anhydride in pyridine afforded diacid (47) whose bis(sodium) salt (48) was water-soluble to an extent of 1 mg ml^{-1}. Biological testing vindicated the prediction of anti-HIV protease activity – it was found that (48) inhibits the enzyme with a K_i of 5.3 μM.

4.2 Targeted Applications in Materials Science

The unusual physical and chemical properties of C_{60} prompted several groups to investigate the possibility of preparing polymers containing C_{60} spheres, either as pendant groups or incorporated within the polymer backbone itself.

Wudl and co-workers reported[11] the formation of polyesters and polyurethanes which incorporate methanofullerenes in the polymer backbone. The reaction of bis(4-methoxyphenyl)diazomethane (Scheme 6) with C_{60}, followed by isomer equilibration, gave the [6,6]-closed isomer (49). After cleavage of the methyl ethers using BBr_3, condensation of the diphenol (50) with sebacoyl chloride or hexamethylene diisocyanate/diazabicyclooctane (DABCO) (Scheme 6) gave the soluble polyester (51) and an insoluble polyurethane (52). The UV/VIS spectrum and cyclic voltammogram of the polymer were almost identical to those of the monomeric methanofullerene, suggesting that the properties of methanofullerene monomers can be transferred unaltered to the polymers.

61,61-Diethynyl-1,2-methano[60]fullerene ($C_{65}H_2$), (53),

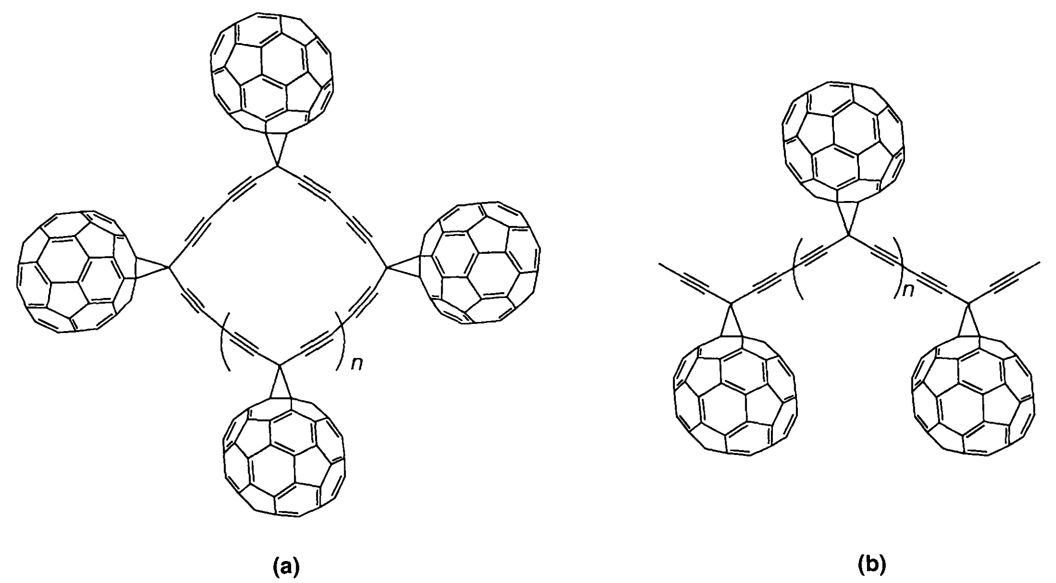
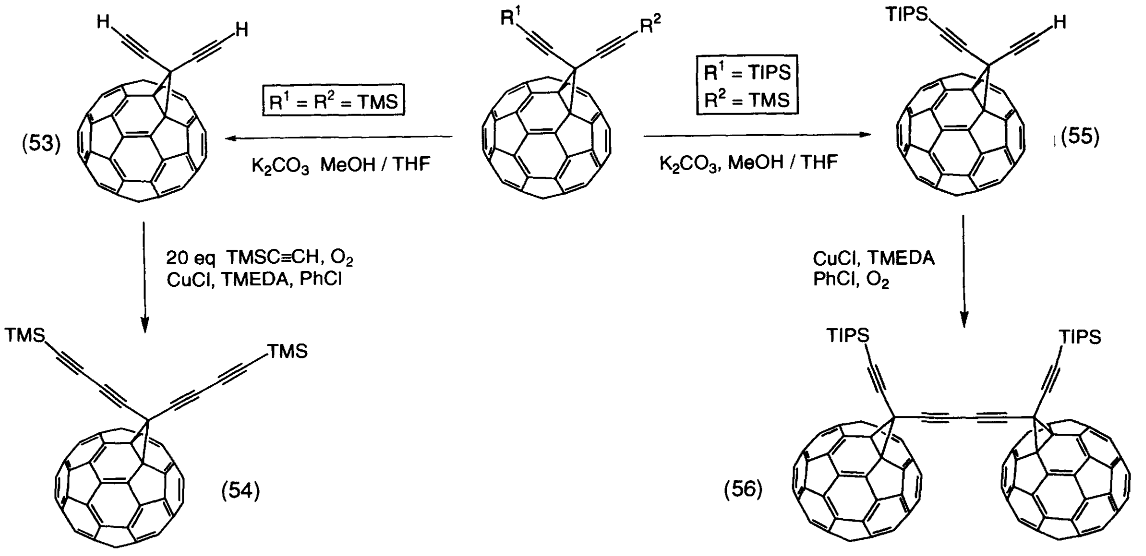


Figure 6 (a) Glaser–Hay coupling of deprotected (56) should allow access to new molecular carbon allotropes consisting of a cyclic acetylenic core peripherally protected by C_{60} spheres (b) The same reaction with the diethynylmethanofullerene (53) could afford all-carbon polymers possessing pendant methanofullerene units



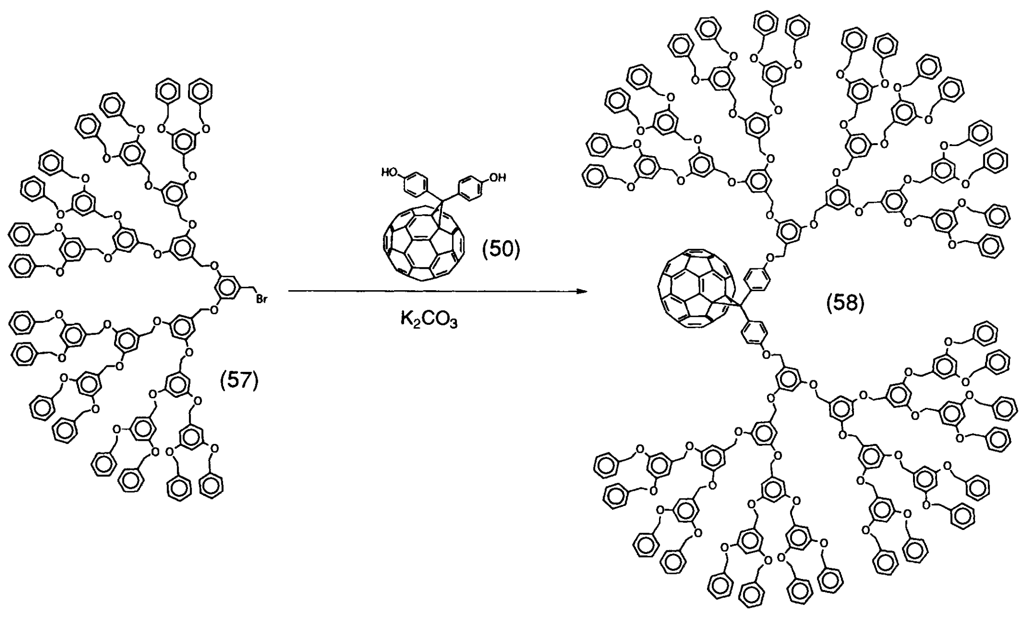
Scheme 7

represents a key component in a variety of novel molecular and polymeric carbon allotropes (Figure 6) The recent synthesis of this compound and its silyl-protected analogues (22), (23), and (24) by Rubin and co-workers[30] and our own group[31] opens the way for a thorough investigation of its potential as a monomeric unit for all-carbon objects This initial work showed that the basic framework of (53) can be extended through oxidative acetylenic coupling, a critical methodology in the construction of all-carbon molecules and networks[1a] Thus, the removal of the TMS protecting groups in (22) could be accomplished (Scheme 7) with potassium carbonate/methanol in THF Glaser–Hay heterocoupling [CuCl·TMEDA (*N*,*N*,*N*′,*N*′-tetramethylenediamine), O_2] of (53) with excess trimethylsilylacetylene afforded the butadiyne derivative (54) Similarly, selective deprotection of (24) permitted the homocoupling of (55) under Glaser–Hay conditions, producing the soluble dumbbell (56) Cyclization of deprotected (56) under similar conditions should give rise to new molecular carbon allotropes (Figure 6a), whereas the oxidative polymerization of (53) could provide a route to synthetic, all-carbon polymers (Figure 6b)

Another area of interest is the encapsulation of a fullerene sphere within a dendritic shell The groups of Fréchet and Wudl[39] synthesized the dendritic methanofullerene (58) using established dendrimer growth procedures (Scheme 8) The reaction of diphenol (50) with a four-fold excess of the fourth generation dendritic branch (57) in the presence of K_2CO_3 afforded (58) as a light brown glass in 79% yield The dendritic arms dramatically increase the solubility of the fullerene and provide a more compact insulating layer than linear polymers Dendritic encapsulation techniques should in the future allow the preparation and study of fullerene molecules which, as a result of their isolation in a designed environment, may have altered physical properties compared to free fullerenes in bulk solid or liquid phase

5 Perspectives

The fullerenes in general and the methanofullerenes in particular have already stimulated a tremendous amount of experimental and theoretical work Experimentally, there is still much chemistry to be explored The facile access to regio- and stereospecific multiple adducts is still an unsolved problem Are there



Scheme 8

hitherto unrecognized solutions to fullerene regiochemistry similar to those developed for benzene derivatization? Well-defined multiple adducts of C_{60} would be desirable for several purposes – as cores for starburst dendrimers or for high-activity HIV protease inhibitors The field of fullerene chemistry in general has much to offer to the domain of synthetic methodology The successful elaboration of methanofullerene side chains is a challenging task, because it is necessary to find the mildest conditions possible in order to avoid competitive reactions with the methanofullerene core This will almost certainly lead to the development of new synthetic methodology in the years to come On the other hand, the potential for methanofullerene-based materials and industrial applications looks very promising Pure C_{60} itself has shown many intriguing properties [40] Among these are the superconductivity of its alkali metal salts M_3C_{60} as well as its non-linear optical properties [41] It has already proven possible to prepare methanofullerene-based polymers which retain the interesting optical and electrochemical properties of the parent methanofullerenes Methanofullerenes may become components in new molecular and polymeric carbon allotropes with fascinating materials properties [1a] Lastly, methano-bridged derivatives of C_{70} and the higher fullerenes,[42] whose chemistry has only begun to be explored, might hold additional surprises in store The absorbance of the higher fullerenes in the near IR, when coupled to the efficient sensitization of singlet oxygen formation, promises potential applications in photodynamic therapy [37] For these reasons it is highly probable that the advances already made only represent the beginning of a long stream of methanofullerene-based developments in the realm of synthetic methodology as well as materials and biomedical applications

Note Added in Proof Two accurate low-temperature *X*-ray crystal structures of (54) as CS_2 and toluene solvates definitely confirm that methanofullerenes bridged at the [6,6]-ring junction have a closed transannular bond [1 574(3) Å], H L Anderson, C Boudon, F Diederich, J-P Gisselbrecht, M Gross, and P Seiler, *Angew Chem , Int Ed Engl*, 1994, **33**, in press

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