Metal-containing carboranes with antitumor activity

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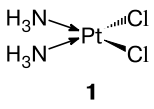
The review summarizes our results and data published in the literature on the synthesis and antitumor activity of metal-containing carboranes. Carboranyl derivatives of platinum and tin and some metallacarboranes exhibit activity against malignant tumors.

Key words: carboranes, metallacarboranes, antitumor activity.

Nowadays, a number of drugs, which are used for the treatment of malignant tumors or investigated for this purpose, involve metal-containing compounds. For instance, as early as in 1969, antitumor activity was found in some platinum compounds.[1] *cis*-Diaminodichloroplatinum(II) (cisplatin) **1** is one of the first representatives, whose activity appeared to be comparable to that of drugs based on organic compounds, such as adriamycin and fluorouracil.[2] Since that time, cisplatin and other platinum complexes, *viz.*, as carboplatin **2**, iproplatin **3**, *etc.*, have been widely used in clinical practice for the treatment of many malignant tumors.



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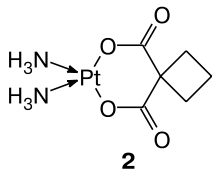

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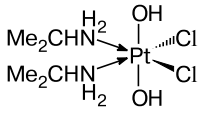

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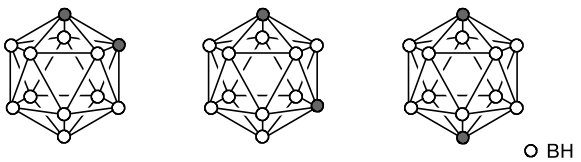
This discovery opened up a new field of application of metal compounds in medicine. The number of publications was so large that the monograph on this topic was published already in 1989.[3] Since 1994, the journal "Metal-Based Drugs" (Freund Publishing House Ltd, London, Ed. M. Gielen) was issued. High antitumor activity of numerous other platinum derivatives and compounds of such metals as aluminum, gallium, indium, thallium, germanium, tin, lead, antimony, bismuth, copper, gold, zinc, and palladium, as well as a series of cyclopentadienyl derivatives of iron, titanium, *etc.*, was documented.

In recent years, researchers have begun to examine prospects of the use of polyhedral boron compounds in medicine.[4—10] Boron neutron capture therapy (BNCT) of cancer has been most extensively studied. This area of investigation has been considered in hundreds of publications and covered in numerous reviews.[6—10] Radionuclide diagnosis and cancer therapy are other possible applications of polyhedral boron compounds, where these compounds can be used for the attachment of radionuclide labels to various biomolecules providing their delivery to tumors. In addition, polyhedral boron compounds can be used for boron neutron capture synovectomy.[11] The application of carboranes as pharmacophores was documented.[8]

The antitumor activity of metal derivatives of carboranes has received less attention. The present review concerns the synthesis and antitumor properties of these compounds.

Antitumor activity of carboranyl derivatives of platinum

Since platinum compounds exhibit high cytotoxicity, carborane-containing platinum derivatives were synthesized and tested for antitumor activity. The following derivatives of icosahedral carboranes were studied:[4,5] 1,2-dicarba-*closo*-dodecaborane 1,2-$C_2B_{10}H_{12}$ (**4**) (hereinafter, *o*-carborane), 1,7-dicarba-*closo*-dodecaborane 1,7-$C_2B_{10}H_{12}$ (**5**) (*m*-carborane), and 1,12-dicarba-*closo*-dodecaborane 1,12-$C_2B_{10}H_{12}$ (**6**) (*p*-carborane).



4 **5** **6**

Scheme 1 shows the synthesis of the 1,7-aminopropyl derivative of *m*-carborane used as the ligand for the synthesis of platinum derivatives.[12,13] The reaction of

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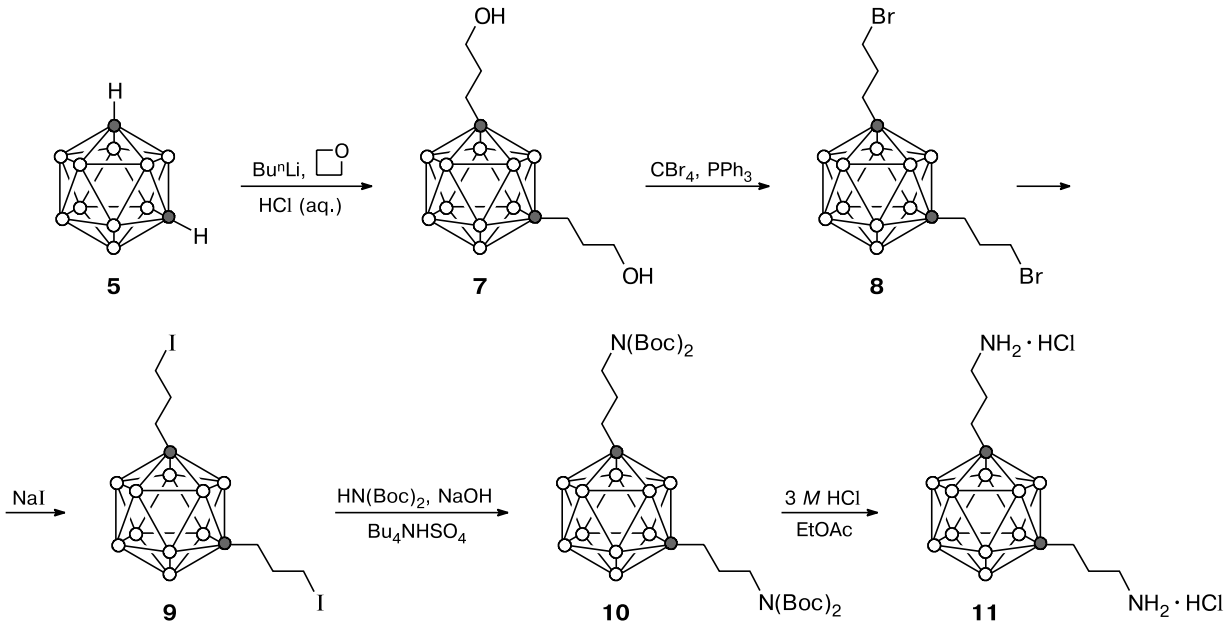
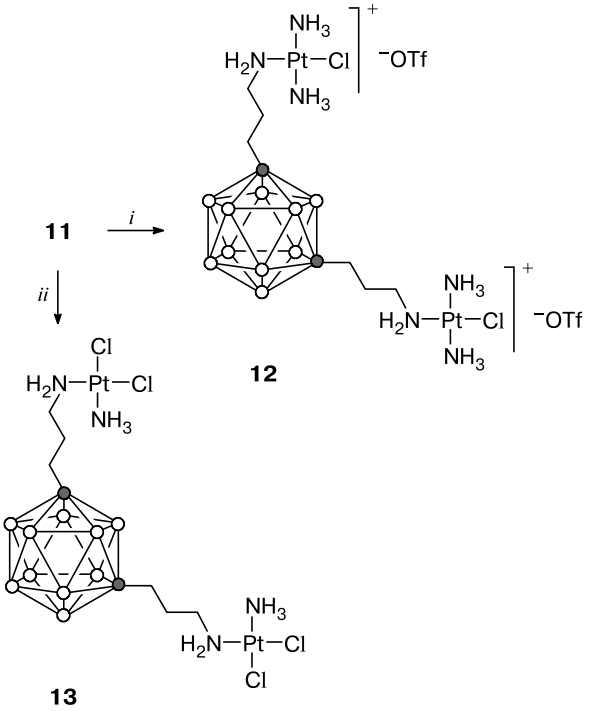
Scheme 1



m-carborane with Bu^{n}Li in THF at −78 °C followed by the addition of oxetane and hydrolysis with $HCl_{(aq)}$ affords dipropanol **7**. The replacement of the hydroxy groups by bromine in the reaction with CBr_4 and PPh_3 in a solution in CH_2Cl_2 at 0 °C gives rise to dibromide **8**, which is transformed into diiodide **9** under the action of NaI in acetone. Alkylation of **9** with bis(*tert*-butoxycarbonyl)amine $HN(Boc)_2$ using phase transfer catalysis affords Boc-protected amine **10**. The reaction of the latter with a 3 *M* HCl solution in ethyl acetate yields amine hydrochloride **11**. Rather unstable free amine can be isolated by the reaction of **11** with a K_2CO_3 solution. However, it is more convenient to use hydrochloride in further synthesis (see Schemes 1 and 2).

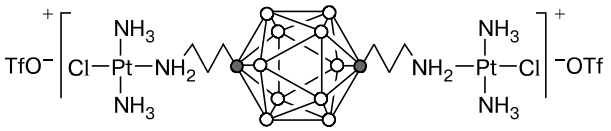
Scheme 2



Reagents: *i*. K_2CO_3 (aq.), *trans*-[PtCl(DMF)$(NH_3)_2$]OTf; *ii*. K_2CO_3 (aq.), *cis*-$[PtCl_2I(NH_3)]K$, $AgNO_3$, HCl (aq.).

The reaction of **11** with the platinum complex *trans*-[PtCl(DMF)$(NH_3)_2$]OTf produces doubly charged compound **12** containing the *m*-carborane fragment and two platinum atoms. The reaction of compound **11** with *cis*-$[PtCl_2I(NH_3)]^-$, which was prepared *in situ* from $[PtCl_3(NH_3)]^-$ and KI in water, followed by treatment with $HCl_{(aq)}$ and $AgNO_3$ in DMF gives complex **13** (see Scheme 2).

Analogously, complexes **14** and **15** were prepared from *p*-carborane.[12,14]



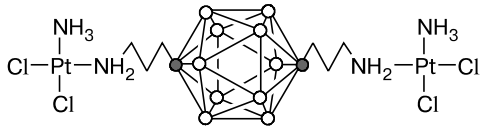


Table 1. *In vitro* antitumor activity IC_{50}* (μmol L^{-1}) of complexes **12** and **13**

Cell line	**12**	**13**	Cisplatin
L1210	1.1	2.0	0.5
L1210/DDP	1.4	2.5	6.9
2008	5.4	13	0.6
C13*5	5.6	13	10

* IC_{50} is the concentration of a compound required to inhibit 50% cell growth.

Because of low solubility of *p*-carborane derivatives **14** and **15**, these compounds were not studied in detail. The cytotoxicity only of compounds **12** and **13** was investigated. Cell cultures of mouse leukemia L1210, the cisplatin-resistant cell culture L1210/DDP, and cisplatin-sensitive and -resistant human ovarian carcinoma cells (2008 and C13*5, respectively) were used. The IC_{50} values are given in Table 1.

The results of preliminary tests for compounds **12** and **13** hold promise. The IC_{50} values for **12** and **13** are of the same order of magnitude as IC_{50} for cisplatin, which indicates that these compounds easily penetrate into cells. Drugs based on these compound can serve as antitumor agents and are simultaneously used for BNCT, which can lead to the additive or synergy effects and cancer cell death already at low concentrations of Pt^{II}.

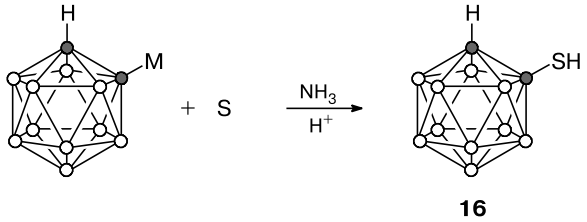
The mechanism of cell growth retardation remains unknown. However, it is reasonable to assume that this is a result of strong DNA binding because the complexes can be bound to plasmid DNA.[15] Complex **12** is more active than **13** on all the cell cultures under study. This fact can be associated with the ionic nature of **12**, which not only increases their solubility in aqueous media but also, presumably, increases the DNA-binding ability through electrostatic interactions. For both the cisplatin-sensitive cell lines L1210 and 2008, complexes **12** and **13** are less efficient in cell growth retardation than cisplatin.

In recent years, considerable attention has been given to metallointercalators for DNA.[15] Such complexes as the platinum(II) complex with 2,2′:6′,2″-terpyridine (trpy), have interesting biological properties, including as potential anticancer agents.[16,17] The $[PtL(trpy)]^{n+}$ complexes (for example, L = Cl, het (het is 2-hydroxyethanethiolate), Me ($n = 1$); L is 4-picoline ($n = 2$)) can form strong bonds with DNA through insertion, thus hindering binding of other intercalators. In this connection, a series of mononuclear platinum(II) complexes with 2,2′:6′,2″-terpyridine were synthesized for thio derivatives of *o*-, *m*-, and *p*-carboranes.

The starting thio derivatives can be prepared by different methods.

The reaction of sulfur with lithium, sodium, or potassium derivatives of *o*-carborane in liquid ammonia produced the previously unknown (1-thiomethyl)-*o*-carborane 1-SH-$C_2B_{10}H_{11}$ (**16**)[18] (Scheme 3).

Scheme 3



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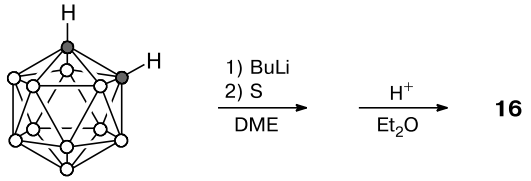
M = Li, Na, K

A more convenient procedure for the synthesis of compound **16** is based on the reaction of sulfur with a monolithium derivative of *o*-carborane, which is produced by the reaction of BuLi with carborane in dimethoxyethane (DME)[19] (Scheme 4).

Scheme 4



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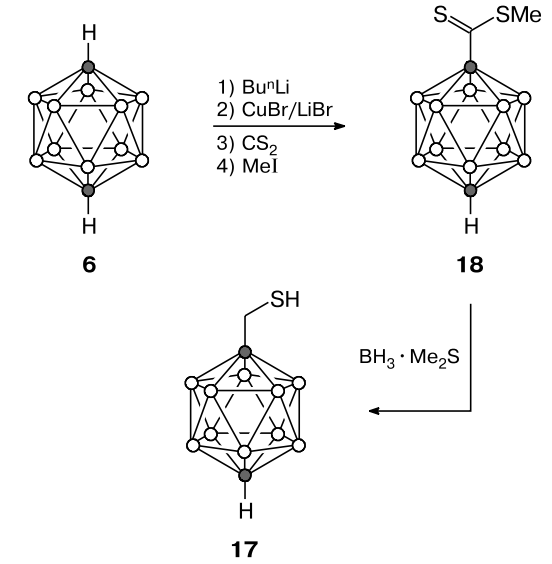
Compound **16** can also be prepared from *o*-$C_2B_{10}H_{12}$ with the use of NaH in DME, but in lower yield.[20]

1-(Thiomethyl)-*p*-carborane (**17**) was synthesized[21] according to Scheme 5. A CuBr/LiBr mixture and an excess of CS_2 were successively added to the monolithium derivative of *p*-carborane to prepare the corresponding lithium carbodithioate. The addition of iodomethane to the latter affords dithioether **18**. Refluxing of **18** with $BH_3 \cdot Me_2S$ in toluene gives 1-(thiomethyl)-*p*-carborane (**17**).

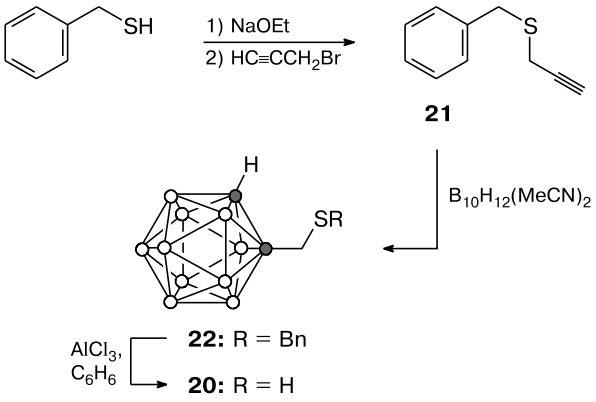
1-(Thiomethyl)-*m*-carborane 1-SH-1,7-$C_2B_{10}H_{11}$ (**19**) and 1-(thiomethyl)-*o*-carborane 1-SH-1,2-$C_2B_{10}H_{11}$ (**20**) were synthesized analogously; however, compound **20** was obtained in low yield.[22] An alternative procedure is based on condensation of terminal alkynes with decaborane $B_{10}H_{14}$ in the presence of MeCN (Scheme 6). Alkyne **21** is refluxed with the adduct of MeCN and decaborane to prepare the carborane derivative 1-BnS-1,2-$C_2B_{10}H_{11}$ (**22**). The reaction of the latter with sublimed $AlCl_3$ in benzene produces thiol **20**.

This method is also used for the synthesis of the carborane derivatives 1-HS$(CH_2)_2$-1,2-$C_2B_{10}H_{11}$ (**23**) and 1-HS$(CH_2)_3$-1,2-$C_2B_{10}H_{11}$ (**24**) in low yields by the re-

Scheme 5

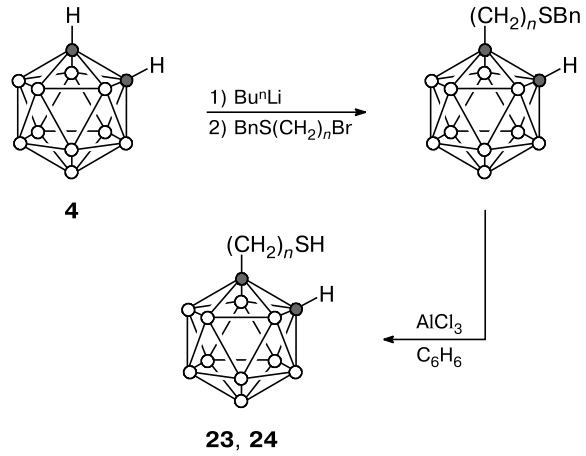


Scheme 6



actions of $B_{10}H_{12}(MeCN)_2$ with 1-(benzylthio)-3-butyne and 1-(benzylthio)-4-pentyne, respectively. An alternative approach was applied to the synthesis of **23** and **24**. In this approach, the protected thiol group is introduced into the starting *o*-carborane through its monolithiated intermediate (Scheme 7).

Scheme 7

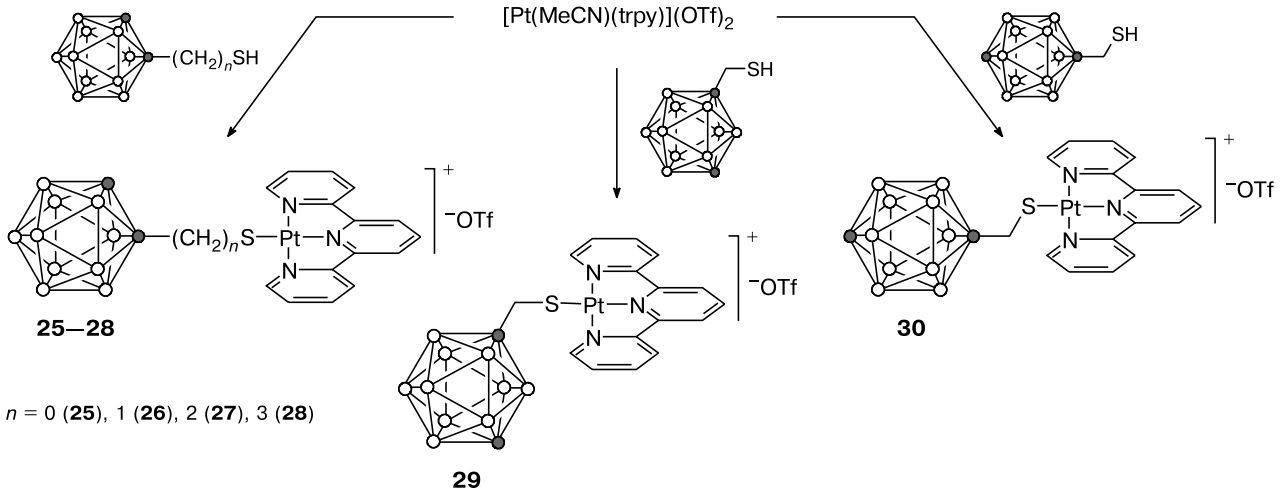


n = 2 (**23**), 3 (**24**)

Final platinum complexes **25—30** can be synthesized with the use of the [Pt(trpy)(DMF)](OTf) complex derived from $[PtCl(trpy)]Cl \cdot 2H_2O$ and AgOTf in DMF.[23] However, it is more convenient to use $[Pt(MeCN)(trpy)](OTf)_2$ (see Ref. 24) (Scheme 8).

The *in vitro* activity of complexes **26** and **28—30** against the human ovarian cancer cell line 2008 and against cisplatin-protected cells 2008/C13[22] was studied. The concentrations required to inhibit 50% cell growth (IC_{50}) for

Scheme 8



n = 0 (**25**), 1 (**26**), 2 (**27**), 3 (**28**)

Table 2. *In vitro* antitumor activity IC_{50} (μmol L^{-1}) of complexes **26** and **28—30**

Complex	2008	C13
26	1.7	2.1
28	5.3	4.1
29	4.6	5.1
30	26	21
Cisplatin	0.6	10

both types of cells are given in Table 2 (cisplatin was used as a reference compound).

As can be seen from Table 2, complexes **26**, **28**, and **29** exhibit substantially higher activity against cells 2008 than **30**. Evidently, this is attributed to substantially lower solubility of **30** in polar media, because precipitation of compound **30** during the incubation period considerably decreases the cytotoxic effect. A comparison of the cytotoxicity of complexes **26**, **29**, and **30**, which differ only in the structure of the carborane cage, shows that compound **26** is most active against these types of cells, and the nature of the carborane fragment has a strong effect on biological activity of the complexes. This is apparently associated with a decrease in solubility of the complexes in water in the series of *o*-, *m*-, and *p*-carboranes (**26**, **29**, and **30**, respectively). The biological activity of complex **28** is lower than that of **26**, which can be attributed to a decrease in solubility of compound **28** in polar solvents as the length of the alkyl chain increases. The IC_{50} values determined for all complexes, both for cisplatin-sensitive and -resistant cell lines, indicate that the mechanism of cytotoxicity of these complexes differs from that of cisplatin but provide no evidence for the nature of the mechanism.

Dinuclear Pt^{II} complexes with 2′:6′,2″-terpyridine show bifunctional DNA intercalation with a higher affinity for DNA compared to their mononuclear analogs.[16,17]

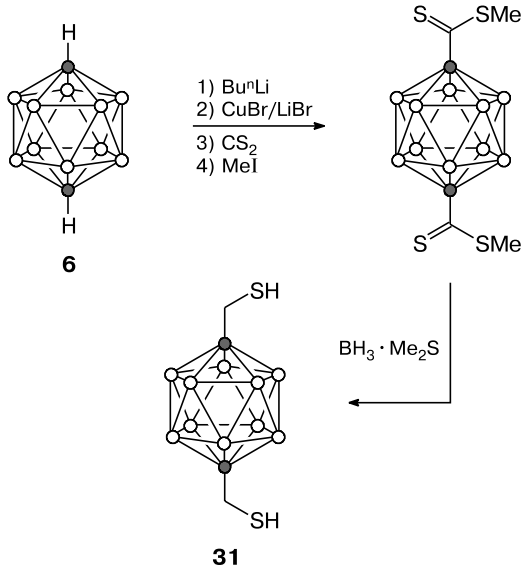
To prepare dinuclear Pt^{II} carborane complexes with 2,2′:6′,2″-terpyridine, bis(thioalkyl)carboranes were presynthesized. For example, bis(thiomethyl)-*p*-carborane 1,12-$(HSCH_2)_2$-1,12-$C_2B_{10}H_{10}$ (**31**) was synthesized from *p*-carborane analogously to Scheme 5 (Scheme 9).[25]

The dithio derivative 1,12-$[HS(CH_2)_3]_2$-1,12-$C_2B_{10}H_{10}$ (**33**) was synthesized analogously to **8** from the dibromo derivative of *p*-carborane **32** derived from *p*-carborane (Scheme 10).

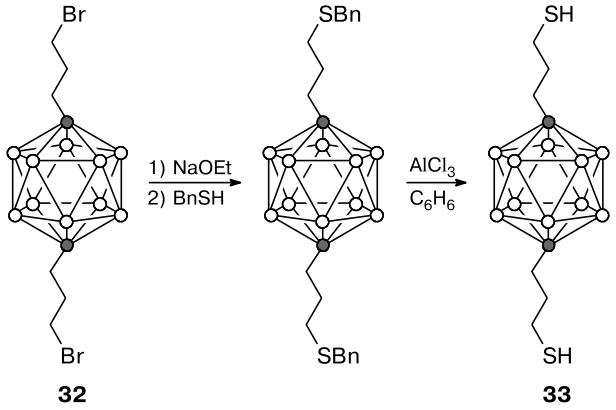
The same method was used for the synthesis of the dithio derivatives of *m*-carborane 1,7-$[HS(CH_2)_3]_2$-1,7-$C_2B_{10}H_{10}$ and *o*-carborane 1,2-$[HS(CH_2)_3]_2$-1,2-$C_2B_{10}H_{10}$.

The corresponding complexes **34—37** were synthesized from these bis(thioalkyl)carboranes by the reaction with $[Pt(trpy)(MeCN)](OTf)_2$ (analogously to Scheme 8).[25]

Scheme 9



Scheme 10



The activity of dinuclear complexes **34—37** against mouse leukemia L1210 was tested. For comparison, cisplatin and mononuclear platinacarboranes were used. Complex **26** was studied to reveal the difference in cytotoxicity of mono- and dinuclear compounds. The concentrations required to inhibit 50% growth cell (IC_{50}) are given in Table 3.

The cytotoxicities of compounds **26** and **34—37** are similar for both the cisplatin-sensitive cell line L1210 and the cisplatin-resistant cell line L1210/DDP. This is evidence that the mechanism of cytotoxicity of these complexes differs from that of cisplatin. In addition, complexes **34—36** are poorly active due to the presence of the *m*- or *p*-carborane fragments. Although the differences in biological activity can be attributed to fine electronic effects associated with the nature of the carborane cage, it is more reasonable to relate these results to low solubility of

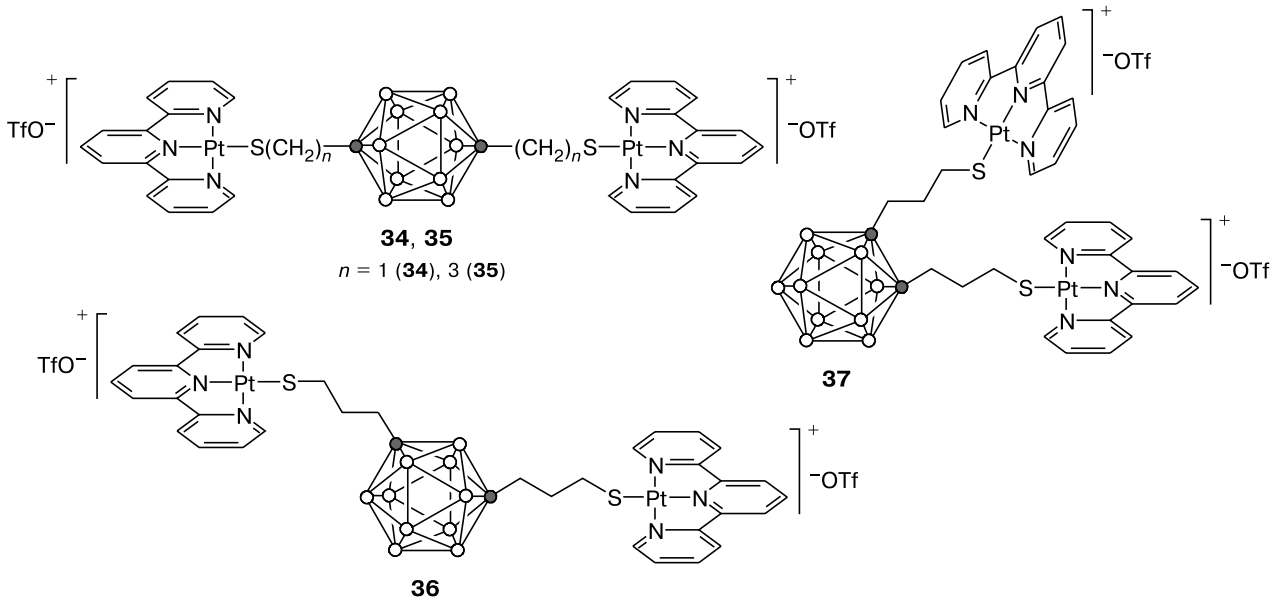


Table 3. *In vitro* antitumor activity IC_{50} (μmol L^{-1}) of complexes **26** and **34—37**

Cell line	Cisplatin	**26**	**34**	**35**	**36**	**37**
L1210	0.5	1.6	24.5	5.3	7.4	0.9
L1210/DDP	6.9	0.9	26.5	7.0	10	0.8

compounds **34—36** in aqueous media. In any case, the observed cytotoxicity cannot be explained without the precise knowledge of the mechanism of action.

Antitumor activity of organotin derivatives of carboranes

Beginning in 1970s, a vast diversity of organic derivatives of tin were tested for *in vitro* and *in vivo* antitumor activity.[26,27] Many of these compounds exhibit rather high activity against cancer cells. In the last 12 years, a series of tin derivatives of carboranes were synthesized and tested for antitumor activity. In some compounds, the tin atom is directly bound to the carborane fragment through the boron or carbon atom. In other compounds, the carborane fragment is bound to the tin atom of the distannoxane fragment through the COO or CH_2COO groups.

Carborane derivatives containing substituents at the boron atom were synthesized by mercuration of *o*- and *m*-carboranes with mercury trifluoroacetate in trifluoroacetic acid.[28] Then symmetrization with cadmium amalgam in acetone or the reaction with lithium naphthalene in THF afforded bis-(*o*-carboranyl)mercury and bis-(*m*-carboranyl)mercury, respectively.[29] The reactions of these compounds with $SnCl_2$ produce the corresponding bis(*o*-carboranyl)tin dichloride (1,2-$C_2B_{10}H_{11}$-9-)$_2SnCl_2$ (**38**) and bis(*m*-carboranyl)tin dichloride (1,7-$C_2B_{10}H_{11}$-9-)$_2SnCl_2$ (**39**).[30] Bis(carboranyl)tin dichlorides react with alkali to form the corresponding oxides (1,2-$C_2B_{10}H_{11}$-9-)$_2SnO$ (**40**) and (1,7-$C_2B_{10}H_{11}$-9-)$_2SnO$ (**41**)[31] (Scheme 11).

The reaction of *o*- and *m*-carboranyltin oxides in a ratio of 1 : 1 with 2,6-pyridinedicarboxylic acid in an ethanol—toluene mixture is accompanied by elimination of water to give complexes **42** and **43**, respectively (Scheme 12).[31]

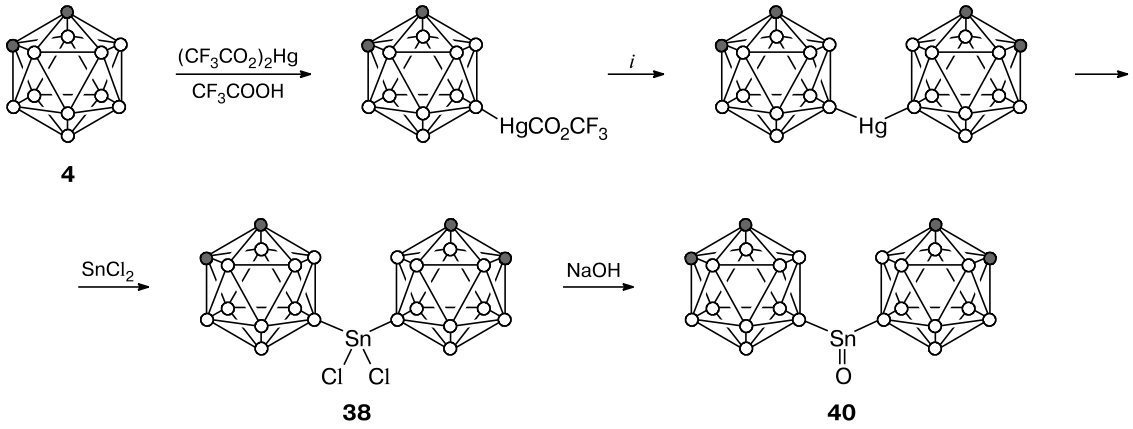
ortho-Carboranyltin oxide **40** reacts analogously with L-pyrrolidone-5-carboxylic acid in a 1 : 2 ethanol—benzene mixture to form compound **44** (Scheme 13).

Table 4 gives data on the *in vitro* cytotoxicity of compounds **42—44** compared to that of some other compounds used in clinical practice against malignant tumors.[31]

It is worthy of note that **42** and **43** have high (comparable with that of doxorubicin) *in vitro* antitumor activity, particularly against MCF-7. Bis(1,7-carboranyl)tin dichloride **39** exhibits even higher activity against MCF-7 and WiDr than doxorubicin. The activity of compound **44** is lower, though it is higher than that of cisplatin.

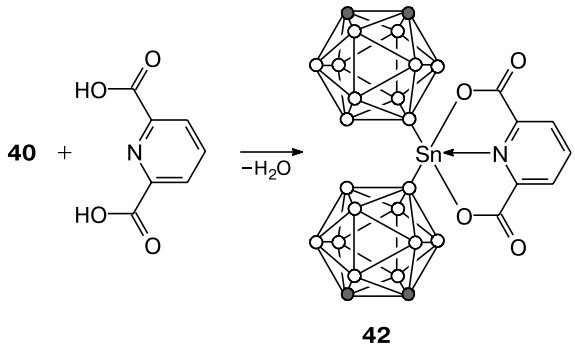
The effect of compound **43** on the *in vivo* tumor formation was studied on DBA/2 mice bearing L1210 leukemia tumor.[31] The prolonged effect was observed at doses of 7 and 10 mg kg^{-1} (the survival time was increased). At a dose of 14 mg kg^{-1}, compound **43** is toxic (Table 5). In addition, one mouse survived at a dose of 7 mg kg^{-1}.

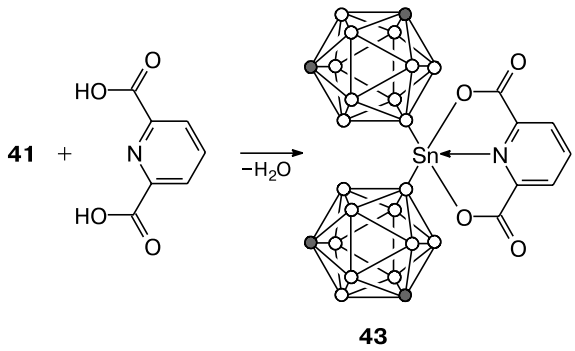
Scheme 11



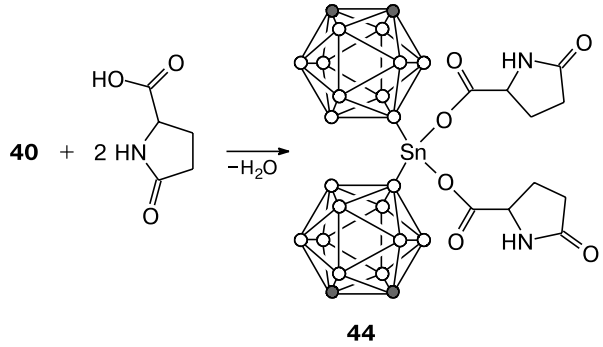
i. $C_{10}H_8^-Li^+$ or Cd/Hg.

Scheme 12





Scheme 13



A series of compounds, in which the fragment containing the tin atom is bound to the carborane cage at the carbon atom, were synthesized. For this purpose, a series of carboranecarboxylic acids were prepared.

The reaction of equimolar amounts of 1-phenyl-*o*-carborane 1-Ph-1,2-$C_2B_{10}H_{11}$ and butyllithium produces 2-phenyl-1-lithium-*o*-carborane, whose carboxylation with CO_2 followed by acid hydrolysis affords 2-phenyl-*o*-carborane-1-carboxylic acid 1-HCOO-2-Ph-1,2-$C_2B_{10}H_{10}$ (**45**).[32]

Dimeric bis[(2-phenyl-1,2-dicarba-*closo*-dodecaborane-1-carboxylato)-di-*n*-butyltin] oxide {[(2-Ph-1,2-$C_2B_{10}H_{10}$-1-COO)$Bu_2Sn]_2O\}_2$ (**46**) was prepared by condensation of dibutyltin(IV) oxide with 2-phenyl-*o*-carborane-1-carboxylic acid **45** in a ratio of 1 : 1 in benzene (Scheme 14).[33]

Condensation of dibutyltin(IV) oxide with (2-methyl-*o*-carboranyl)acetic acid 1-$HOOCCH_2$-2-Me-1,2-$C_2B_{10}H_{10}$ (**47**)[34] afforded the 1-(2-methyl-1,2-carboranyl)acetate derivative {[(2-Me-1,2-$C_2B_{10}H_{10}$-1-CH_2-COO)$Bu_2Sn]_2O\}_2$ (**48**) (Scheme 15).[33]

Condensation of dibutyltin(IV) oxide with *m*-carborane-1-carboxylic acid 1-HOOC-1,7-$C_2B_{10}H_{11}$ in a ratio of 1 : 1 gave bis(di-*n*-butyltin-*m*-carborane-1-carboxylato) oxide {[(1,7-$C_2B_{10}H_{11}$-1-COO)$Bu_2Sn]_2O\}_2$ (**49**).[35]

o-Carborane-9-carboxylic acid 9-HOOC-1,2-$C_2B_{10}H_{11}$ (**50**), in which the carboxy group is bound to the carborane cage at the boron atom, can be synthesized according to Scheme 16. The iodine atom is introduced at

Table 4. *In vitro* antitumor activity IC_{50} (ng mL^{-1}) of compounds **42—44** against the cell lines MCF-7 and EVSA-T (two types of breast cancers), IGROV (ovarian cancer), M19 MEL (skin cancer, melanoma), and A498 (renal cancer) compared to the clinically used drugs, carborane *o*-$C_2B_{10}H_{12}$, and (*m*-$C_2B_{10}H_{11}$-9)$_2SnCl_2$ (**39**)

Compound	MCF-7	WiDr	EVSA-T	IGROV	M19MEL	A498
o-$C_2B_{10}H_{12}$	36817	22456	—	—	—	—
39	5	31	—	—	—	—
42 (DMSO)	10	102	—	—	—	—
(EtOH)	14	197				
43	11	45	—	—	—	—
44	60	410	48	3	30	110
Doxorubicin	8	20	6	28	5	5
Cisplatin	800	1200	650	79	530	1200

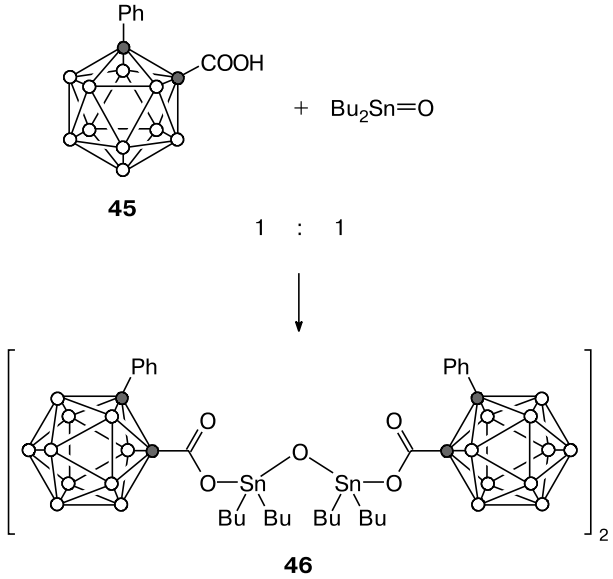
Note. The activity of compound **44** against other cell lines: A204, 49; IgR-37, 12; T24, 32.

Table 5. Results of *in vivo* antitumor tests for compound **43** on DBA/2 mice bearing L1210 leukemia tumor. The substance under study was administered once intraperitoneally

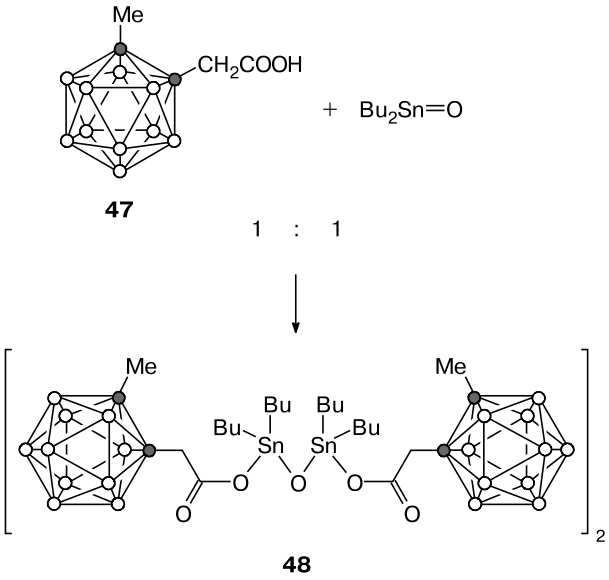
Dose /mg kg^{-1}	Average body weight/g			MST[a] /day	T/C[b] (%)	LTS[c]
	1 day	5 days	7 days			
7	25.6	23.4	25.3	14	140	1/6
10	25.4	21.1	14.5	14.5	145	0/6
14	24.6	20.7	20.4	5	50	0/6
Control	25.1	25.9	27.4	10	100	0/9

[a] MST is the median survival time.
[b] T/C is the treated/control ratio (the survival time of treated/control mice).
[c] LTS refers to long-term survivors.

Scheme 14



Scheme 15

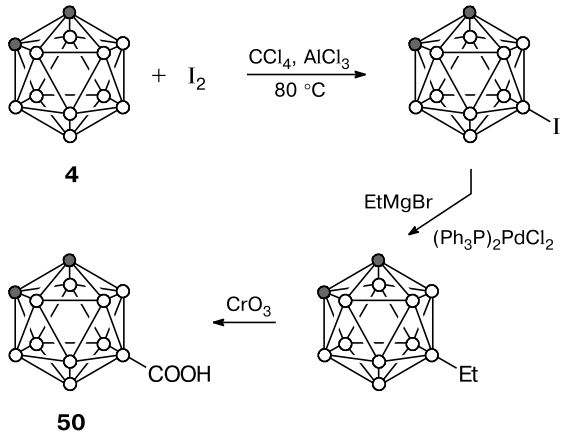


position 9 by heating *o*-carborane with iodine in CCl_4 in the presence of $AlCl_3$.[36] The reaction of the resulting iodacarborane with alkylmagnesium halides catalyzed by palladium triphenylphosphine complexes produced carboranes containing an alkyl substituent at position 9.[37] Oxidation of 9-alkyl-*o*-carborane with CrO_3 afforded *o*-carborane-9-carboxylic acid (**50**)[38] (see Scheme 16).

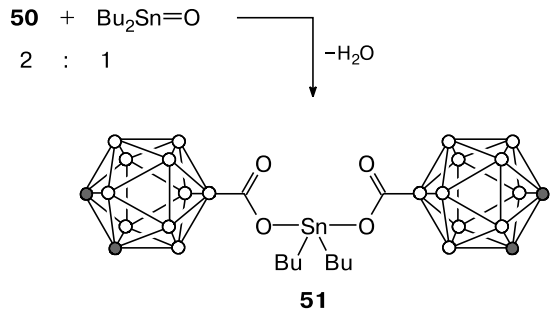
The reaction of dibutyltin(IV) oxide with *o*-carborane-9-carboxylic acid **50** in a ratio of 1 : 2 yielded the first carborane-containing tin derivative (1,2-$C_2B_{10}H_{11}$-9-COO)$_2SnBu_2$ (**51**), in which the carborane cage is bound to the carboxy fragment through the boron atom (Scheme 17).[39]

Tin derivatives containing three organic substituents and having the general formula R´C(O)OSnR_3 are rather well known as bactericides and fungicides. In this con-

Scheme 16



Scheme 17



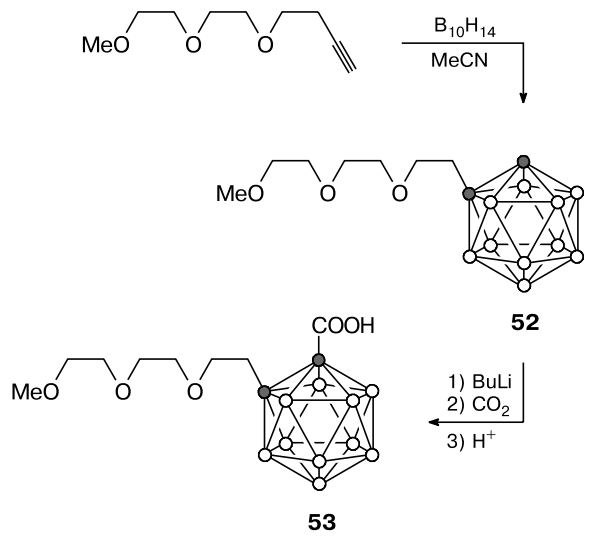
nection, these compounds were tested for antitumor activity. Some of these compounds showed rather good results.[40] At the same time, lipophilic/hydrophilic characteristics of these compounds are of importance. The lipophilic properties of these compounds play an important role in penetration through cell membranes. The hydrophilic character is necessary for solubility in an aqueous medium of cells. To increase solubility in water, a carborane derivative of tin containing a polyoxaalkyl chain bound to the carborane fragment was synthesized. Carboxylation of the corresponding carborane **52**, which was derived from alkyne and decaborane in acetonitrile[41] (Scheme 18), afforded 1-carboxy-2-(3′,6′,9′-trioxadecyl)-*o*-carborane 1-HOOC-2-Me(OCH_2CH_2)$_3$-1,2-$C_2B_{10}H_{10}$ (**53**).

The reaction of acid **53** with triphenyltin hydroxide produced a compound, which was isolated as triphenylstannate [(2-Me(OCH_2CH_2)$_3$-1,2-$C_2B_{10}H_{10}$-1-COO)$_2$$SnPh_3$]$^-$$Na^+$ (**54**) (Fig. 1), resulting in a further increase in its solubility in water (Scheme 19).[42]

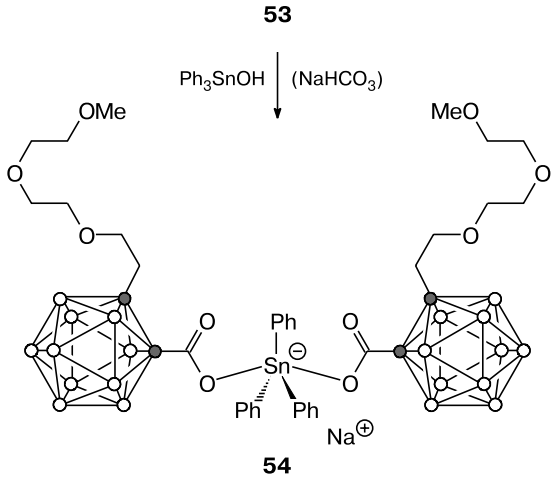
Compounds **46**, **48**, **49**, **51**, and **54** were tested for *in vitro* antitumor activity against seven types of human cancer cells. The results of assays are given in Table 6.

The compounds under study are much more active compared to the clinically used 5-fluorouracil, cisplatin,

Scheme 18



Scheme 19



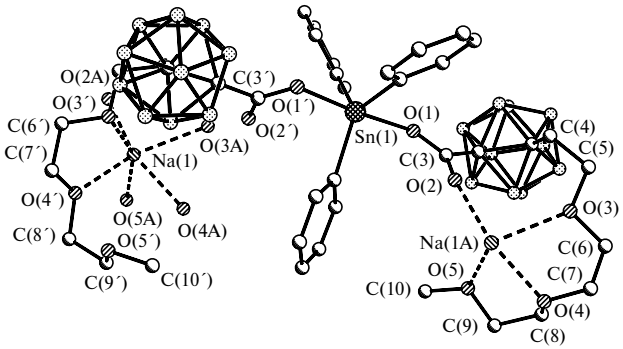


Fig. 1. Crystal structure of sodium bis[2-(3′,6′,9′-trioxadecyl)-1,2-dicarba-*closo*-dodecaborane-1-carboxylato]triphenylstannate, [(2-Me(OCH_2CH_2)$_3$-1,2-$C_2B_{10}H_{10}$-1-COO)$_2$$SnPh_3$]$^-$$Na^+$ (**54**).

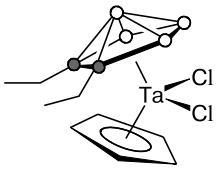
Table 6. *In vitro* antitumor activity IC_{50} (ng mL^{-1}) of compounds **46**, **48**, **49**, **51**, and **54** against the cell lines MCF-7 and EVSA-T (two types of breast cancers), IGROV (ovarian cancer), M19 MEL (skin cancer, melanoma), A498 (renal cancer), and H226 (lung cancer) compared to clinically used drugs and 2-phenyl-*o*-carborane-1-carboxylic acid 2-Ph-1,2-$C_2B_{10}H_{10}$-1-COOH (**45**)

Compound	MCF-7	EVSA-T	WiDr	IGROV	M19MEL	A498	H226
45[33]	56500	1750	45100	42400	58300	>60000	55000
46[33]	138	164	514	169	220	301	338
48[33]	74	140	283	102	172	182	246
49[35]	45	38	290	110	110	140	
51[39]	146	142	439	139	174	195	291
54[42]	44	38	37	39	39	45	41
Carboplatin	10500	4500	3500	2400	5500	1800	25000
Cisplatin	1400	920	1550	230	780	1200	3158
5-Fluorouracil	350	720	440	850	310	340	5300
Methotrexate	15	26	7	20	18	16	70
Doxorubicin	25	13	18	150	21	55	180

and carboplatin and are slightly less active than methotrexate and doxorubicin. Triphenylstannate **54** exhibits highest cytotoxicity due, apparently, to higher solubility in water because of the presence of polyoxide substituents and because it exists in the anionic form.

Activity of carboranyl derivatives of other metals

Numerous studies of metallocene sandwich complexes, both of the neutral complexes $(\eta^5\text{-}C_5H_5)_2MX_2$ and salts with the ferrocenyl-type ion $\{[(\eta^5\text{-}C_5H_5)_2Fe^+]X^-\}$, showed that many of these compounds exhibit antitumor activity against a number of cancer cells.[43—45]



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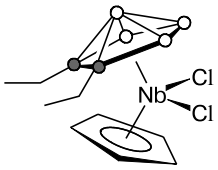

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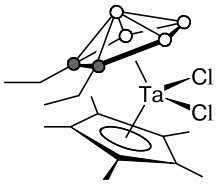

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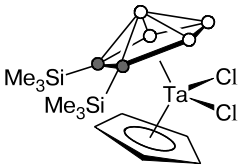

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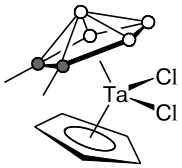


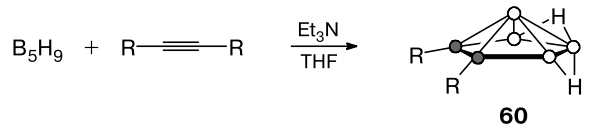
59

The pentagonal-pyramidal carborane ligand *nido*-$R_2C_2B_4H_4^{2-}$ is comparable in size and isoelectronic to the $\eta^5\text{-}C_5H_5^-$ ligand.[46—48]

Metallacarboranes **55—59** containing this ligand are potentially cytotoxic agents against some tumors inducing cancer cell death.[48]

Carborane *nido*-2,3-$R_2C_2B_4H_6$ (**60**), which is required for the construction of these metallacarboranes, can be synthesized by the reaction of B_5H_9 with alkynes[46] (Scheme 20).

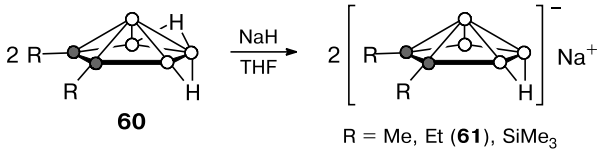
Scheme 20



60

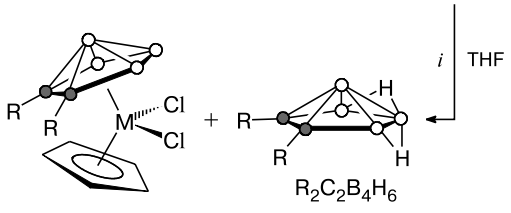
R = Me, Et, $SiMe_3$

Scheme 21



60

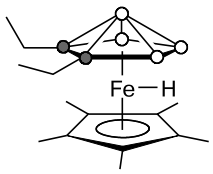
R = Me, Et (**61**), $SiMe_3$



$R_2C_2B_4H_6$

55—59

i. $CpMCl_4$ or Cp^*MCl_4.



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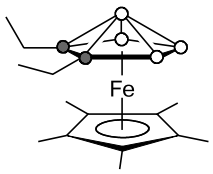

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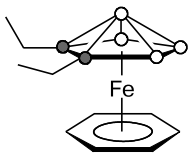

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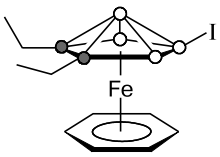

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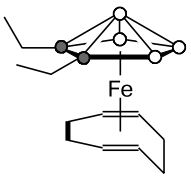

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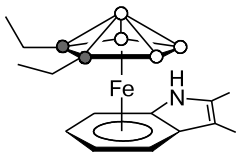

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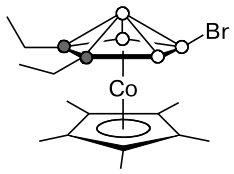

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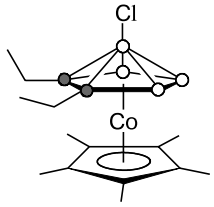

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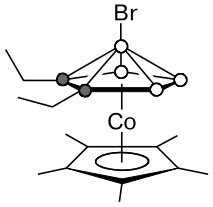


70

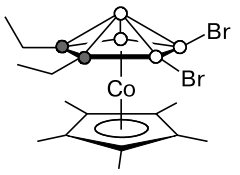
Disproportionation of two equivalents of the *nido*-carborane monoanions $[R_2C_2B_4H_5]^-$ with the corresponding $CpMCl_4$ or Cp^*MCl_4 complexes[49] affords compounds **55—59** (Scheme 21).

Metallacarboranes **55—59** proved to be efficient in growth termination of L1210 (mouse leukemia); all compounds, except for **59**, against P388 (mouse lymphoid leukemia). The human leukemia cell growth is inhibited under the action of **55—58** on the cell lines $Tmolt_3$; **55—57** and **59**, on $Tmolt_4$; and **55**, **56**, and **59**, on HI-60. These compounds proved to be cytotoxic toward lymphoma HuT-8, acute monocytic leukemia THP-1, and uterina carcinoma HeLa-S^3. Some complexes cause cell growth retardation of melanoma Sk-2 and breast cancer MCF-7. Studies on the lymphoid leukemia cell line P388 showed that these compounds also inhibit the purine synthesis, and this inhibition slows down the DNA and RNA synthesis.

More recently, the range of metal derivatives of small carboranes was extended.[50]

Compound **62** was synthesized by the reaction of the pentamethylcyclopentadienyl anion $C_5Me_5^-$ with anhydrous iron chloride and the $[Et_2C_2B_4H_5]^-$ anion (**61**) in tetrahydrofuran. After purification on silica gel, orange air-stable crystals were obtained in high yield. After storage in a solution of tetramethylethylenediamine (TMEDA) in THF in air (or in HCl—Et_2O in air), compound **62** was virtually quantitatively transformed into brown-green paramagnetic compound **63** (Scheme 22).[51]

The reaction of the $Et_2C_2B_4H_5^-$ anion (**61**) with iron chloride and the $C_8H_8^{2-}$ anion produced complex **66** in rather high yield. Refluxing of **66** with $AlCl_3$ in anhydrous benzene afforded complex **64**.[52] The reaction of the latter with *N*-iodosuccinimide gave complex **65** in high yield[53] (Scheme 23).



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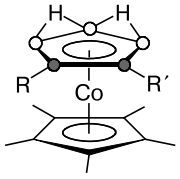

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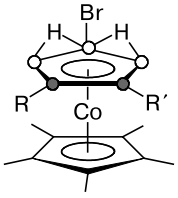

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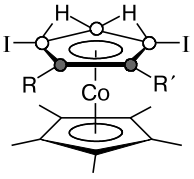

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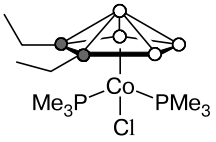

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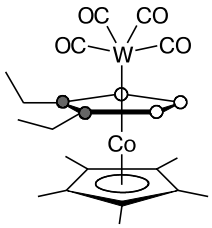

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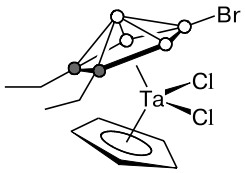

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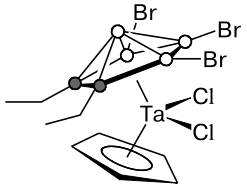

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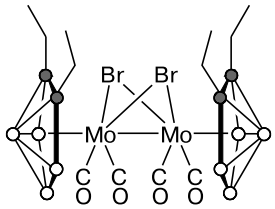

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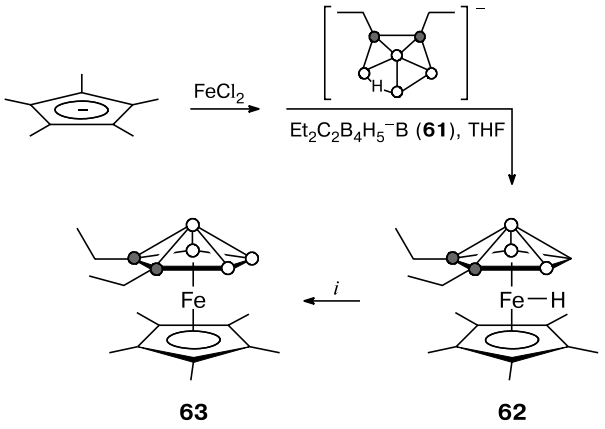
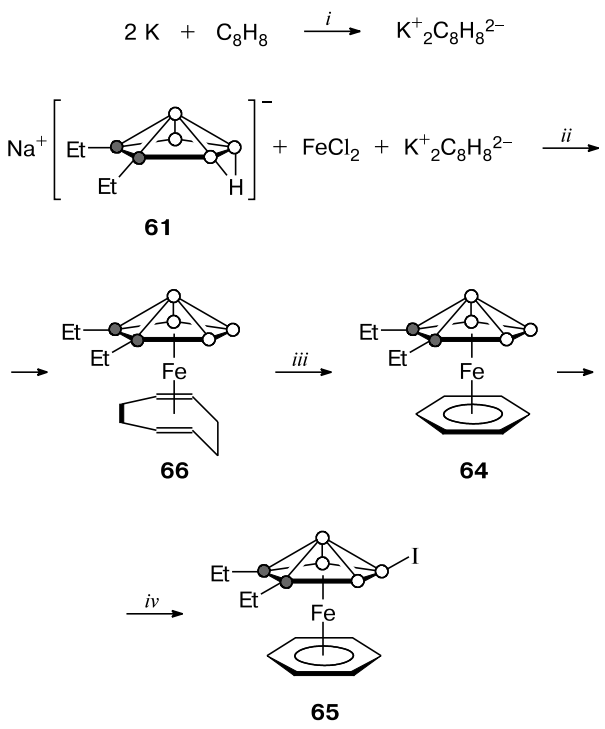
Scheme 22



i. TMEDA in air.

Scheme 23

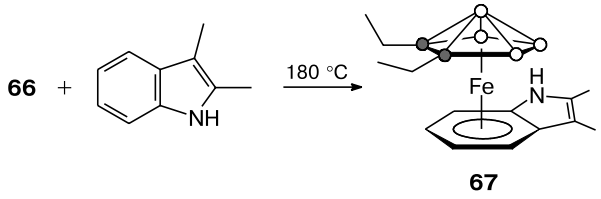


Reagents and conditions: *i*. THF, −30 °C, 2 h; *ii*. THF, −30 °C; *iii*. C_6H_6, $AlCl_3$, refluxing, 3 h; *iv*. *N*-iodosuccinimide, CH_2Cl_2.

The thermal reaction of compound **66** with 2,3-dimethylindole produces the air-stable complex (η^6-$HNMe_2C_8H_4$)$Fe(Et_2C_2B_4H_4)$ (**67**)[54] (Scheme 24).

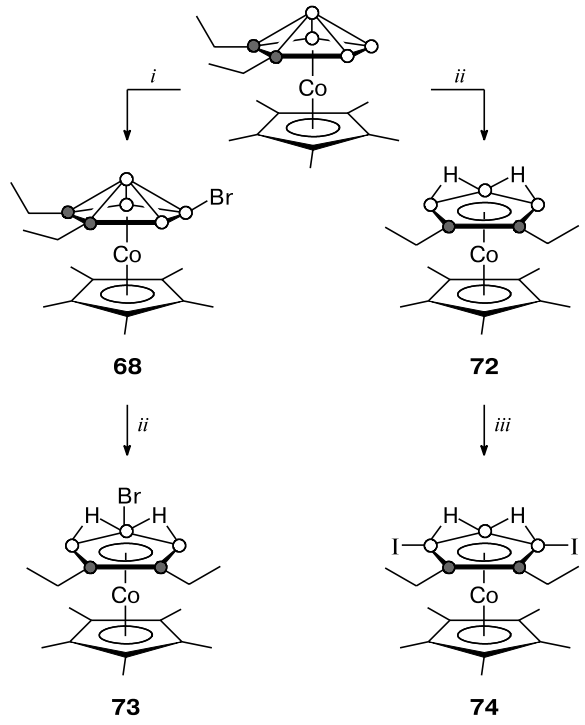
The reaction of the $Cp^*Co(Et_2C_2B_4H_4)$ complex with *N*-halosuccinimides in THF or dichloromethane affords the corresponding orange B(5)-monosubstituted complexes in high yields (if X = Br, compound **68** is formed)[55]

Scheme 24



(Scheme 25). The reactions with both substituted and unsubstituted complexes with TMEDA are accompanied by abstraction of the BH fragment from the cap to form air-stable complexes **72** and **73**.[56] The reaction of complex **72** with 2.5 equivalents of iodosuccinimide in THF gives complex **74** in quantitative yield (see Scheme 25).

Scheme 25

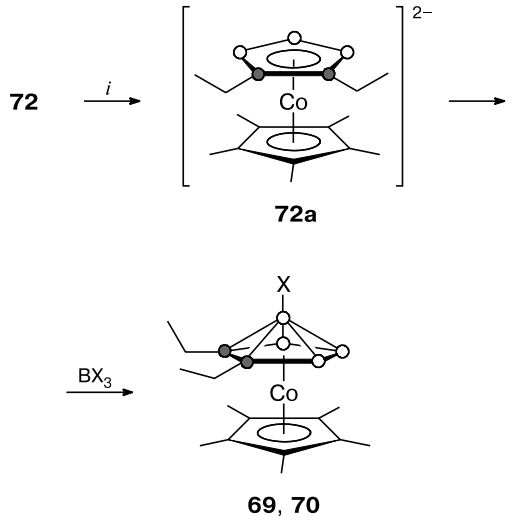


Reagents and conditions: *i*. *N*-bromosuccinimide, THF or CH_2Cl_2; *ii*. TMEDA/H_2O; *iii*. *N*-iodosuccinimide (2 equiv.), THF.

Deprotonation of complex **72** with two equivalents of *tert*-butyllithium in toluene at 0 °C affords orange dianion **72a**. The reaction of the latter with a 1.0 *M* BCl_3 solution in heptane produces the yellow air-stable $Cp^*Co(Et_2C_2B_4H_3$-7-Cl) complex (**69**). 7-Bromo derivative **70** was prepared analogously by the reaction of **72a** with BBr_3 (Scheme 26).[57]

The reaction of compound **72** with butyllithium is accompanied by hydrogen abstraction to form com-

Scheme 26

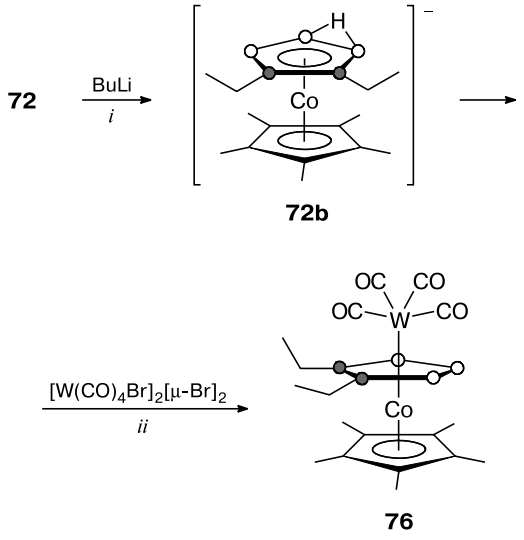


X = Cl (**69**), Br (**70**)

Reagents and conditions: *i*. Bu^{t}Li (2 equiv.), toluene, 0 °C.

plex **72b**, whose reaction with $[W(CO)_4Br]_2(\mu\text{-}Br)_2$ gives rise[58] to compound **76** (Scheme 27). Compound **79** was synthesized[58] according to Scheme 28.

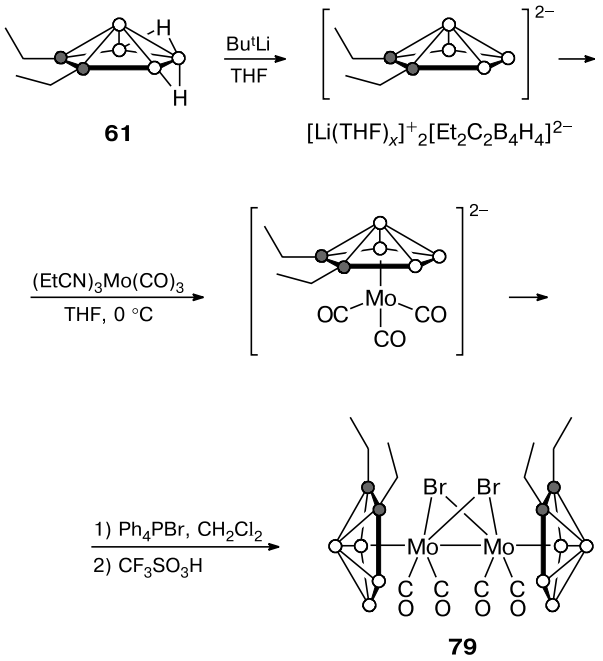
Scheme 27



Reagents and conditions: *i*. toluene, 0 °C; *ii*. toluene, 1) −78 °C, 2) 25 °C.

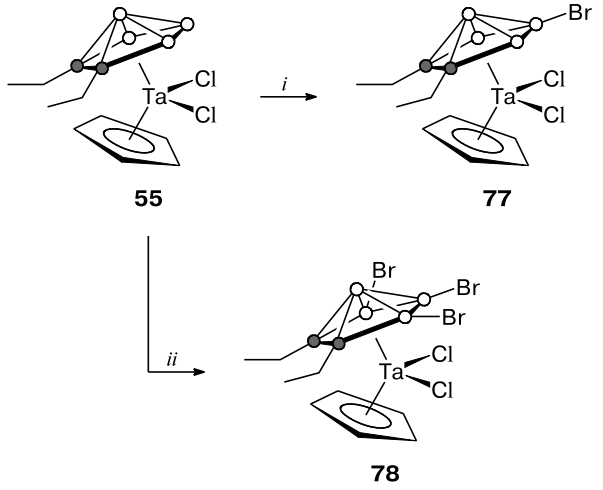
The reaction of complex **55** with 1 equiv. of Br_2 in CH_2Cl_2 for 8 h produces monobromo derivative **77** in virtually quantitative yield. However, it is more convenient to perform this transformation with the use of *N*-bromosuccinimide. Heating with an excess of Br_2

Scheme 28



in CCl_4 for 24 h afforded tribromo derivative **78** (Scheme 29).[59]

Scheme 29



Reagents and conditions: *i*. Br_2, CH_2Cl_2, or NBS, THF; *ii*. 10 Br_2, CCl_4, 60 °C, 24 h.

Complexes containing Fe, Co, Ta, Mo, or W coordinated by the C_2B_4 or C_2B_3 ligands proved to be cytotoxic against some mouse and human cancer cells. These complexes are most efficient against leukemias and lymphomas and, which is of interest, are active against growth of certain solid tumors.[50]

All compounds are efficient in the L1210 cell growth retardation. The ED_{50} concentration (the concentration causing inhibition of 50% cancer cell growth) of complexes **64**, **65**, and **71** is lower than 1 μg mL^{-1}. Complexes **68** and **71** proved to be most active against P388 (ED_{50} < 1 μg mL^{-1}). All compounds are active against $Tmolt_3$, whereas compounds **62**, **64—66**, **71**, **72**, **74**, and **75** are active only against $Tmolt_4$. The growth retardation of the human leukemia cells HL-60 is caused by all the complexes under study. Complexes **64** and **77** show the highest activity (ED_{50} < 1 μg mL^{-1}). Complex **75** is most active against THP-1 (monocytic leukemia); complexes **70** and **76**, against Hut-78 (lymphoma); complexes **69—72**, **76**, and **79**, against uterina carcinoma HeLa-S[3].

These compounds act more selectively on a cell line cultured from solid human tumors. For example, compound **64** is the only complex exhibiting activity against lung cancer A549. Compounds **64—67** and **72—79** are active against lung cancer MB9812. Complexes **65**, **66**, **74**, and **76** slow Sk-2 melanoma growth. Only compound **75** is active against skin epidermoid carcinoma cells A431 (cysts). None of the complexes under study are active against nasopharyngeal carcinoma KB. Types of cancer cells and complexes exhibiting activity are listed below: osteosarcoma, **68**, **75**, and **76**; glioma UM-86, **78**; adenocarcinoma of the colon SW480, **77** and **74—79**; ovarian cancer, **68** and **76—79**; and breast cancer MCF-7, **74**, **75**, and **78**. However, metallacarboranes **62—79** are inactive against adenocarcinoma of the ileum HCT-8. The antitumor activity of the compounds under study was attributed to inhibition of multistep nucleic acid metabolism characteristic of many other metal complexes.

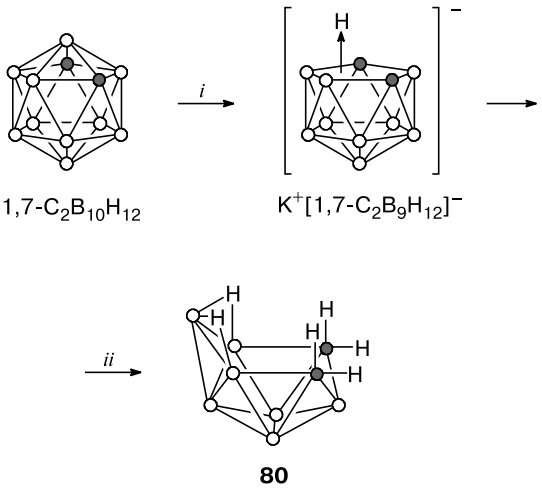
The tricarbadecaboranyl fragment *nido*-[6-Me-5,6,9-$C_3B_7H_9$], like the cyclopentadienyl ligand, can be coordinated to transition metals as a monoanionic six-electron donor to give the corresponding metallacaboranes.[60,61]

The coordination properties of the tricarbadecaboranyl anion (6-R-*nido*-5,6,9-$C_3B_7H_9^-$, R = Me or Ph) are in many aspects similar to those of the cyclopentadienyl anion ($C_5H_5^-$). However, metallatricarbadecaboranyl complexes exhibit higher oxidative, chemical, thermal, and hydrolytic stability than metallocenyl analogs.

The tricarbadecaboranyl anion can be synthesized according to the following scheme. The reaction of *m*-carborane 1,7-$C_2B_{10}H_{12}$ with an ethanolic alkaline solution produces the 1,7-dicarba-*nido*-dodecahydroundecaborate anion (1,7-$C_2B_9H_{12}^-$), and oxidation of the latter affords *arachno*-4,6-$C_2B_7H_{13}$ (**80**)[62] (Scheme 30).

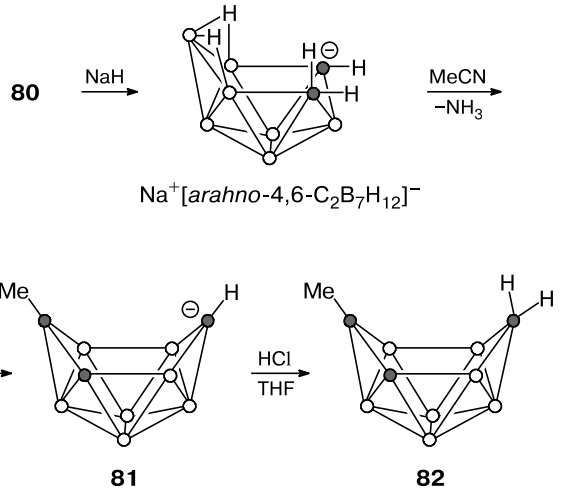
The reaction of **80** with NaH followed by the addition of acetonitrile gives rise to the 6-Me-*nido*-5,6,9-$C_3B_7H_9^-$ anion (**81**), and the treatment of the latter with hydrochloric acid affords carborane 6-Me-*nido*-5,6,9-$C_3B_7H_{10}$ (**82**)[60] (Scheme 31).

Scheme 30



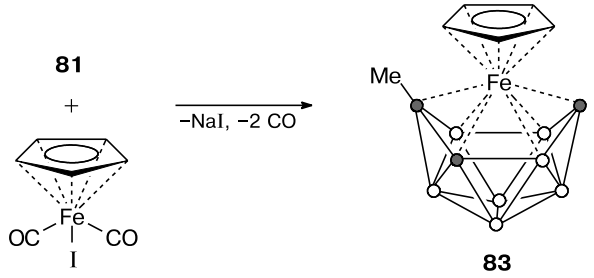
Reagents and conditions: *i*. KOH, EtOH, reflux, 40 h; *ii*. $Na_2Cr_2O_7$, H_2SO_4, CH_2Cl_2, 2 h.

Scheme 31



The reaction of anion **81** with the iron complex $[(\eta^5\text{-}C_5H_5)Fe(CO)_2I]$ produces a mixture of three complexes, *viz.*, 1-(η^5-C_5H_5)Fe-2-Me-2,3,4-$C_3B_7H_9$ (**83**)

Scheme 32



(the major product), 1-(η^5-C_5H_5)Fe-4-Me-2,3,4-$C_3B_7H_9$, and *commo*-Fe-(1-Fe-5-Me-2,3,5-$C_3B_7H_9$)-(1-Fe-4-Me-2,3,5-$C_3B_7H_9$). Major product **83** was isolated by fractional crystallization (Scheme 32).

Oxidation of compound **83** with silver ions affords the paramagnetic ferratricarbadecaboranyl cation in quantitative yield[63] (Scheme 33).

Scheme 33

83 + AgX ⟶ [1-(η^5-C_5H_5)Fe-2-Me-2,3,4-$C_3B_7H_9$][X]

X = AsF_6^-, SbF_6^-

The ferratricarbadecaboranyl salts [1-(η^5-C_5H_5)Fe-2-Me-2,3,4-$C_3B_7H_9$]$^+$ X^- (X^- = AsF_6^- or SbF_6^-), as well as neutral complex **83**, proved to be efficient cytotoxic agents causing the cell death of some cultures, for example, of L-1210 (leukemia), Tmolt3 (leukosis), HL-60 (leukosis), and HeLa-S^3 (uterina carcinoma). On the whole, these drugs are inactive against such solid types of cancer cells as KB (nasopharyngeal cancer), A431 (skin cancer), HCT-8 (ileocecal carcinoma), SW480 (colorectal cancer), osteosarcoma, and glioma. However, these salts cause growth retardation of bronchogenic lung cancer MB-9812.[15]

The tricarbadecaboranyl fragment *nido*-[6-R-5,6,9-$C_3B_7H_9$] (R = Me or Ph) forms stable vanadium and niobium monohalide complexes. Some of these complexes exhibit cytotoxic properties. For the synthesis of these complexes, lithium derivatives were initially prepared (Scheme 34).

Scheme 34

80 $\xrightarrow[2)\ RCN]{1)\ LiH}$ Li^+[6-R-*nido*-5,6,9-$C_3B_7H_9$]$^-$

84, **85**

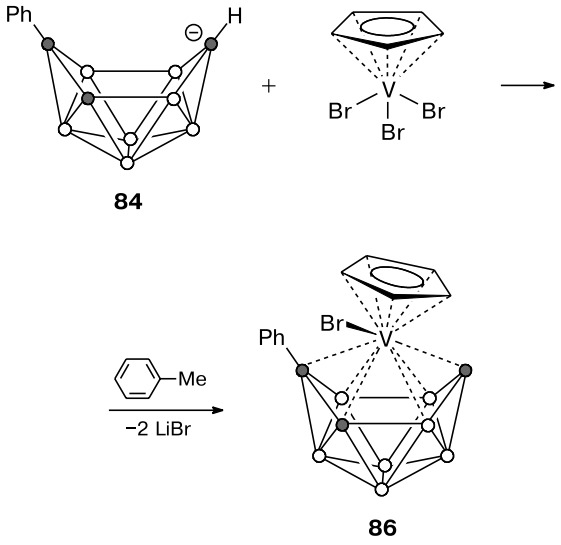
R = Ph (**84**), Me (**85**)

The reaction of **84** with (η^5-C_5H_5)VBr_3 (which was prepared by the reaction of (η^5-C_5H_5)$V(CO)_4$ with Br_2)[64] did not produce the expected dibromide complex; instead, the reaction gave the monobromide complex (η^5-C_5H_5)-1-Br-2-Ph-1,2,3,4-$VC_3B_7H_9$ (**86**),[65] in which vanadium formally has oxidation state +3 (Scheme 35).

The reaction of $NbCl_4(THF)_2$ with two equivalents of **85** afforded the monochloride complex *commo*-Nb-1-Cl-(4-Me-1,2,3,4-$NbC_3B_7H_9$)$_2$ (**87**), which was accompanied by a decrease in the oxidation state of niobium from +4 to +3 (Scheme 36).

The results of tests on cytotoxicity[66] of complexes **86** and **87** show that the activity of these complexes is very high, particularly against such types of murine and human

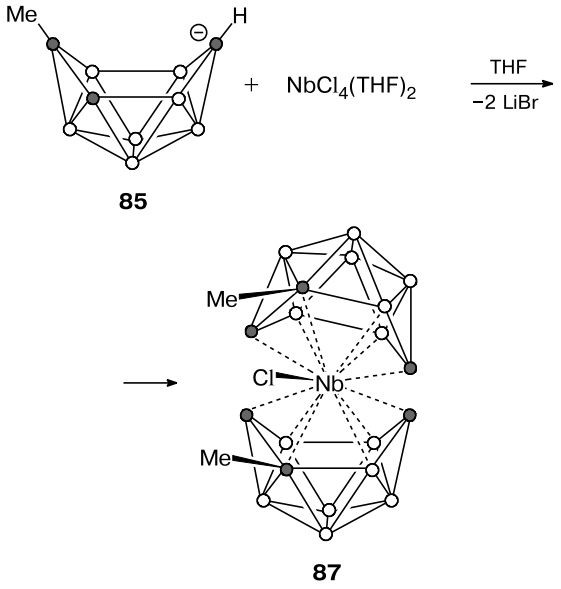
Scheme 35



84

86

Scheme 36



85

87

cells as leukemia and lymphoma as well as against uterina carcinoma cells HeLa-S^3 (Table 7). Complex **86** is active against growth of cells KB (nasopharyngeal carcinoma), Hepe-2 (liver cancer), and HCT-8 (ileocecal adenocarcinoma). Both complexes are active against 1-A9 (ovarian carcinoma). Complexes are inactive against A-549 (lung cancer), MCF-7 (breast cancer), U86 (glioma), PL (prostate), HSO (osteosarcoma), SK-2 (melanoma), and human fibroblasts. On the whole, the cytotoxicity of complexes **86** and **87** is similar to that of other metal complexes, when they are active against certain cancer cell and only against a few solid types of cancer cells.

Table 7. *In vitro* antitumor activity ED_{50} (mg mL^{-1}) of compounds **86** and **87** against a series of murine and human cell lines compared to the clinically used drugs 6-MP (mercaptopurine), Ara-C (cytarabine), VP-16 (etoposide), 5-FU (5-fluorouracil), and mitomycin

Cell type	**86**	**87**	6-MP	Ara-C	VP-16	5-Fu	Mitomycin
L1210	1.48	2.55	2.43	3.07	1.83	1.41	
P388	2.11	2.21	2.04	0.79	0.99	1.41	
HL-60	3.05	1.41	3.35	4.00	4.43	5.28	
$Tmolt_3$	2.59	3.33	1.62	2.67	1.00	2.14	
$Tmolt_4$	2.96	4.04	2.67	2.36	1.92	2.75	
THP-1	1.85	2.35	3.03	2.54	3.27	1.12	
HeLa-S^3	3.31	2.93	2.12	2.13	1.69	2.47	
KB	1.70	4.24	11.04	2.84	3.32	1.25	1.70
A-549	5.25	5.15	4.71	5.62	4.74	3.58	0.14
Hepe-2	2.17	4.60					
1-A9	3.79	2.29	6.64	5.39	6.24		
MCF-7	10.6	9.13	8.84	12.45	11.00	6.82	0.45
UM 87B	4.78	4.98	4.46	1.88	2.44	1.28	1.60
HCT-8	2.17	4.60	1.15	2.54	1.13	1.30	0.15
PL	8.12	14.4					
HSO	6.74	9.02	9.13	0.86	3.57	8.73	
SK-2	12.64	11.9	6.86	10.53	3.53	5.93	
Fibroblasts	7,92	6,94					

The compound is considered to be active when ED < 4 mg mL^{-1}.

The present review summarizes our results and data published in the literature on the synthesis and antitumor activity of metal-containing carboranes. Many of these compounds were demonstrated to exhibit high antitumor activity against some malignant tumors.

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References

1. B. Rosenberg, L. Van Camp, J. E. Trosko, and V. H. Mansour, *Nature*, 1969, **222**, 385.
2. P. J. Sadler, *Chem. Brit.*, 1982, **18**, 182.
3. *Metal-based Anti-tumour Drugs*, Ed. M. Gielen, Freund Publishing House Ltd, London, 1989, 272 p.
4. R. N. Grimes, *Carboranes*, Academic Press, New York, 1970.
5. V. I. Bregadze, *Chem. Rev.*, 1992, **92**, 209.
6. M. F. Hawthorne, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 950.
7. A. H. Soloway, W. Tjarks, B. A. Barnum, F.-G. Rong, R. F. Barth, I. M. Codogni, and J. G. Wilson, *Chem. Rev.*, 1998, **98**, 1515.
8. J. F. Valliant, K. J. Guenther, A. S. King, P. Morel, P. Schaffer, O. O. Sogbein, and K. A. Stephenson, *Coord. Chem. Rev.*, 2002, **232**, 173.
9. I. B. Sivaev and V. I. Bregadze, *Ros. Khim. Zh.*, 2004, **48**, 109 [*Mendeleev Chem. J.*, 2004, **48** (Engl. Transl.)].
10. V. I. Bregadze, I. B. Sivaev, and S. A. Glazun, *Anti-Cancer Agents in Medical Chemistry*, 2006, **6**, 75.
11. R. A. Watson-Clark, M. L. Banquerigo, K. Shelly, M. F. Hawthorne, and E. Brahn, *Proc. Natl. Acad. Sci. USA*, 1998, **95**, 2531.
12. K. Drechsel, C. S. Lee, E. W. Leung, R. R. Kane, and M. F. Hawthorne, *Tetrahedron Lett.*, 1994, **35**, 6217.
13. S. L. Woodhouse and L. M. Rendina, *Chem. Commun.*, 2001, 2464.
14. H. Ghaneolhosseini, W. Tjarks, and S. Sjöberg, *Tetrahedron*, 1997, **53**, 17519.
15. I. H. Hall, A. E. Warren, C. C. Lee, M. D. Wasczcak, and L. G. Sneddon, *Anticancer Res.*, 1998, **18**, 951.
16. W. D. McFadyen, L. P. G. Wakelin, I. A. G. Roos, and B. L. Hillcoat, *Biochem. J.*, 1986, **238**, 757.
17. W. D. McFadyen, L. P. G. Wakelin, I. A. G. Roos, and B. L. Hillcoat, *Biochem. J.*, 1987, **242**, 177.
18. L. I. Zakharkin and G. G. Zhigareva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1967, 1358 [*Bull. Acad. Sci USSR, Div. Chem. Sci.*, 1967, **16** (Engl. Transl.)].
19. C. Viñas, R. Benakki, F. Teixidor, and J. Casabo, *Inorg. Chem.*, 1995, **34**, 3844.
20. J. Plešek and S. Hermanek, *Collect. Czech. Chem. Commun.*, 1981, **46**, 687.
21. I. Ujváry and R. J. Nachman, *Tetrahedron Lett.*, 1999, 5147.
22. J. A. Todd, P. Turner, E. J. Ziolkowski, and L. M. Rendina, *Inorg. Chem.*, 2005, **44**, 6401.
23. J. A. Todd and L. M. Rendina, *Inorg. Chem.*, 2002, **41**, 3331.
24. R. Büchner, J. S. Field, R. J. Haines, C. T. Cunningham, and D. R. McMillin, *Inorg. Chem.*, 1997, **36**, 3952.
25. S. L. Woodhouse, E. J. Ziolkowski, and L. M. Rendina, *Dalton Trans.*, 2005, 2827.
26. M. Gielen, *Appl. Organomet. Chem.*, 2002, **16**, 481.
27. M. Gielen, M. Biesemans, and R. Willem, *Appl. Organomet. Chem.*, 2005, **19**, 440.

28. V. I. Bregadze, V. Ts. Kampel, and N. N. Godovikov, *J. Organomet. Chem.*, 1976, **112**, 249.
29. V. I. Bregadze, V. Ts. Kampel, and N. N. Godovikov, *J. Organomet. Chem.*, 1977, **136**, 281.
30. V. I. Bregadze, V. Ts. Kampel, and N. N. Godovikov, *J. Organomet. Chem.*, 1978, **157**, C1.
31. M. Gielen, F. Kayser, O. B. Zhidkova, V. Ts. Kampel, V. I. Bregadze, D. de Vos, M. Biesemans, B. Mahieu, and R. Willem, *Metal-Based Drugs*, 1995, **2**, 37.
32. L. I. Zakharkin, V. I. Stanko, A. I. Klimova, and Yu. A. Chapovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1963, 2236 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1963, **12** (Engl. Transl.)].
33. E. R. T. Tiekink, M. Gielen, A. Bouhdid, R. Willem, V. I. Bregadze, L. V. Ermanson, and S. A. Glazun, *Metal-Based Drugs*, 1997, **4**, 75.
34. L. I. Zakharkin and A. V. Grebennikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1967, 696 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1967, **16** (Engl. Transl.)].
35. M. Gielen, A. Bouhdid, R. Willem, V. I. Bregadze, L. V. Ermanson, and E. R. T. Tiekink, *J. Organomet. Chem.*, 1995, **501**, 277.
36. L. I. Zakharkin and V. N. Kalinin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1966, 575 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1966, **15** (Engl. Transl.)].
37. L. I. Zakharkin, A. I. Kovredov, V. A. Ol´shevskaya, and Zh. S. Shaugumbekova, *J. Organomet. Chem.*, 1982, **226**, 217.
38. L. I. Zakharkin, A. I. Kovredov, V. A. Ol´shevskaya, and V. A. Antonovich, *J. Organomet. Chem.*, 1984, **227**, 81.
39. V. I. Bregadze, S. A. Glazun, P. V. Petrovskii, Z. A. Starikova, V. Ya. Rochev, H. Dalil, M. Biesemans, R. Willem, M. Gielen, and D. de Vos, *Appl. Organomet. Chem.*, 2003, **17**, 453.
40. R. Willem, A. Bouhdid, B. Mahieu, L. Ghys, M. Biesemans, E. R. T. Tiekink, D. de Vos, and M. Gielen, *J. Organomet. Chem.*, 1997, **531**, 151.
41. A. A. Semioshkin, S. A. Glazun, G. M. Ptashits, V. V. Kachala, P. V. Petrovskii, and V. I. Bregadze, *Mendeleev Commun.*, 2000, 118.
42. V. I. Bregadze, S. A. Glazun, P. V. Petrovskii, Z. A. Starikova, A. G. Buyanovskaya, R. U. Takazova, M. Gielen, D. de Vos, M. Kemmer, M. Biesemans, and R. Willem, *Appl. Organomet. Chem.*, 2004, **18**, 191.
43. R. Köpf-Maier, H. Köpf, and E. W. Neuse, *Angew. Chem.*, 1984, **23**, 456.
44. E. W. Neuse and F. Kanzawa, *Appl. Organomet. Chem.*, 1990, **4**, 19.
45. A. Houlton, R. M. G. Roberts, and J. Silver, *J. Organomet. Chem.*, 1991, **418**, 107.
46. R. N. Grimes, *Chem. Rev.*, 1992, **92**, 251.
47. A. K. Saxena and N. S. Hosmane, *Chem. Rev.*, 1993, **93**, 1081.
48. I. H. Hall, C. E. Tolmie, B. J. Barnes, M. A. Curtis, J. M. Russel, and M. G. Finn, *Appl. Organomet. Chem.*, 2000, **14**, 108.
49. K. E. Stockman, K. L. Houseknecht, E. A. Boring, M. Sabat, M. G. Finn, and R. N. Grimes, *Organometallics*, 1995, **14**, 3014.
50. I. H. Hall, C. B. Lackey, T. D. Kidtler, R. W. Durha, Jr., J. M. Russel, and R. N. Grimes, *Anticancer Res.*, 2000, **20**, 2345.
51. M. Stephan, J. H. Davis, X. Meng, K. J. Chase, J. Hauss, U. Zenneck, H. Pritzkow, W. Siebert, and R. N. Grimes, *J. Am. Chem. Soc.*, 1992, **114**, 5214.
52. R. G. Swisher and R. N. Grimes, *Organomet. Synth.*, 1986, **3**, 104.
53. J. M. Russell, M. Sabat, and R. N. Grimes, *Organometallics*, 2002, **21**, 4113.
54. K. J. Chase and R. N. Grimes, *Inorg. Chem.*, 1991, **30**, 3957.
55. K. E. Stockman, D. L. Garrett, and R. N. Grimes, *Organometallics*, 1995, **14**, 4661.
56. J. H. Davis, Jr., E. Sinn, and R. N. Grimes, *J. Am. Chem. Soc.*, 1989, **111**, 4776.
57. M. A. Curtis, M. Sabat, and R. N. Grimes, *Inorg. Chem.*, 1996, **35**, 6703.
58. M. A. Curtis, E. J. Houser, M. Sabat, and R. N. Grimes, *Inorg. Chem.*, 1998, **37**, 102.
59. K. E. Stockman, E. A. Boring, M. Sabat, M. G. Finn, and R. N. Grimes, *Organometallics*, 2000, **19**, 2200.
60. C. A. Plumb, P. J. Carroll, and L. G. Sneddon, *Organometallics*, 1992, **11**, 1665.
61. C. A. Plumb, P. J. Carroll, and L. G. Sneddon, *Organometallics*, 1992, **11**, 1672.
62. P. M. Garrett, T. A. George, and M. F. Hawthorne, *Inorg. Chem.*, 1969, **8**, 2008.
63. M. D. Wasczak, C. C. Lee, I. H. Hall, P. J. Carroll, and L. G. Sneddon, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2228.
64. M. S. Hammer and L. Messerle, *Inorg. Chem.*, 1990, **29**, 1780.
65. B. M. Ramachandran, Y. Wang, Sang Ook Kang, P. J. Carroll, and L. G. Sneddon, *Organometallics*, 2004, **23**, 2989.
66. I. H. Hall, R. W. Durham Jr., M. Tram, S. Mueller, B. M. Ramachandran, and L. G. Sneddon, *J. Inorg. Biochem.*, 2003, **93**, 125.

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