Syntheses, structural characterization and CO releasing properties of boranocarbonate $[H_3BCO_2H]^-$ derivatives†

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CO plays an important role in biological processes and molecules which release CO in a controllable way could therefore be used for medicinal purposes. Beside organometallic carbonyl complexes, boranocarbonate $[H_3BCO_2H]^-$ is one of the most promising candidates but releases CO too rapidly. In order to delay the CO release, we have prepared boranocarbamates $[H_3BCONH\text{-}R]^-$ from $[H_3BCO_2H]^-$ which comprise histamine, morpholine, aniline and ethylene-diamine bound *via* amides to the $\{H_3BCO\}$ moiety. The syntheses of the new derivatives is described together with their structural characterization. These compounds release CO at a much slower rate than the parent compound and are therefore potential CO releasing molecules for biological and medicinal application.

Introduction

Carbon monoxide (CO) is primarily known for its poisonous effects but biologists have lately discovered that this gaseous molecule possesses interesting signalling properties in mammalian organisms. In fact, in the past few years several scientific reports have corroborated that CO is an important cellular mediator and plays a regulatory role in physiological and biological processes. The biological significance of CO remained unexplored for several decades in spite of the discovery in the early seventies of its endogenous generation in the cell through the degradation of heme by constitutive (HO-2) and inducible (HO-1) heme oxygenase proteins.[1] It is now well documented that under certain pathophysiological conditions HO-1 is markedly up-regulated in tissues and consequently the production of CO is increased to a significant extent, thereby acting as an obligatory signalling molecule required for the adaptation of cells to stressful conditions.[2–4] Indeed, CO exhibits vasodilatory, *anti*-inflammatory and *anti*-apoptotic properties[5] and it is directly involved in the mitigation of pathological conditions including, among others, hypertension, ischemia-reperfusion injury and inflammatory disorders.[6] This unexpected pivotal role of CO in biology may find explanations in the evolution of this gas and its peculiar chemistry. In fact, it appears that CO played a significant role in the synthesis of the first amino and nucleic acids, the prehistoric time when the environment was rich in CO.[7]

In order to better understand the physiological effects of CO and to deliver this gas effectively to target tissues, research on compounds that could generate CO lately gained particular attention. The discovery and characterization of such compounds is extremely important because it opens new opportunities for the development of novel pharmaceutical agents that could facilitate the exploitation of CO therapy for clinical use. Intuitively, this approach would offer practical advantages since it may prevent the toxicity problems that arise with direct administration of CO gas. The development of transition metal carbonyls as first prototypic CO-releasing molecules (CO-RMs) aimed at controlling the delivery and action of CO in biological environment was a major step towards the realisation of CO-based pharmaceuticals.[6,8] The transition metal complexes, $[Mn_2(CO)_{10}]$, $[Fe(CO)_5]$, $[Ru(CO)_3Cl_2]_2$, $[Fe(CO)_3(\eta^4\text{-2-pyrone})]$ and $[Mn(CO)_3(tpm)]^+$ (tpm═tris(pyrazolyl)methane) are some examples of the CO-RMs that have been studied so far.[8–12] The complexes $[Mn_2(CO)_{10}]$ and $[Ru(CO)_3Cl_2]_2$ are of particular interest since they were the first to be pharmacologically relevant in exerting effects typical of CO gas, such as vessel relaxation, attenuation of coronary vasoconstriction and suppression of acute hypertension.[8] Even though these complexes gave promising results, they had several drawbacks like poor solubility in water, the requirement of a physical or chemical stimuli for the release of CO and the presence of a transition metal which could lead to increased cytotoxicity. Therefore, the need to increase solubility in water arose, which led to the synthesis of the first water-soluble compound of this class $[Ru(CO)_3Cl(glycinate)]$ or CORM-3, which releases CO ($t_{1/2}$ = >1 min) *in vivo*, *ex vivo* and *in vitro* biological models.[6] Several investigations on the medical applications of this compound revealed that $[Ru(CO)_3Cl(glycinate)]$ protects myocardial tissues against ischemia-reperfusion injury both *ex vivo*[13] and *in vivo*[14] and prolongs the survival of cardiac allografts in mice.[13] Since then more water-soluble transition metal CO-RMs have been produced and their bioactive properties reported.[15] These studies showed that transition metal carbonyls act as CO carriers and helped in elucidating some of the biological roles of CO *in vivo*.

The incessant search continued in order to find a compound that could be safely used in biological systems. Promising features were found in sodium boranocarbonate $Na[H_3BCO_2H]$ (Na[**1**]), synthesised for the first time in the early sixties. It received its non-IUPAC name from the fact that the first pK_1 value is comparable to that of carbonate, although pK_2 could not exactly be determined due to decomposition under CO release.[16,17] It is

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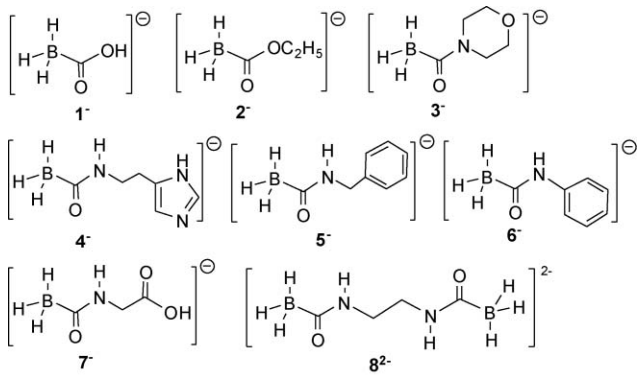
water-soluble and releases CO spontaneously in aqueous solutions under physiological conditions.[18,19] In addition, Na[**1**] does not contain a transition metal but boron instead, which is chemically more inert and less toxic. When dissolved in buffer, [**1**]$^-$ releases CO at a much slower rate ($t_{1/2}$ = 21 min, pH = 7.4, r.t.) than the other metal-containing CO-RMs and its pharmacological activities are dictated by the kinetic of CO release.[18] At this stage it would be extremely important to have boranocarbonate derivatives possessing different kinetics of CO release to identify the rate of CO required to maximize the therapeutic potential of these compounds. Thus, we strove to modify the parent compound [**1**]$^-$ so that we could tune the rate of CO release. We activated [**1**]$^-$ by its conversion to an ester and reacted it further with a range of amines to form the corresponding carbamates. In this article, we report the synthesis, structure and CO-releasing properties of derivatives of Na[**1**] which are shown in Scheme 1.



Scheme 1 Boranocarbamate derivatives of Na[H_3BCO_2H] Na[**1**].

Results and Discussion

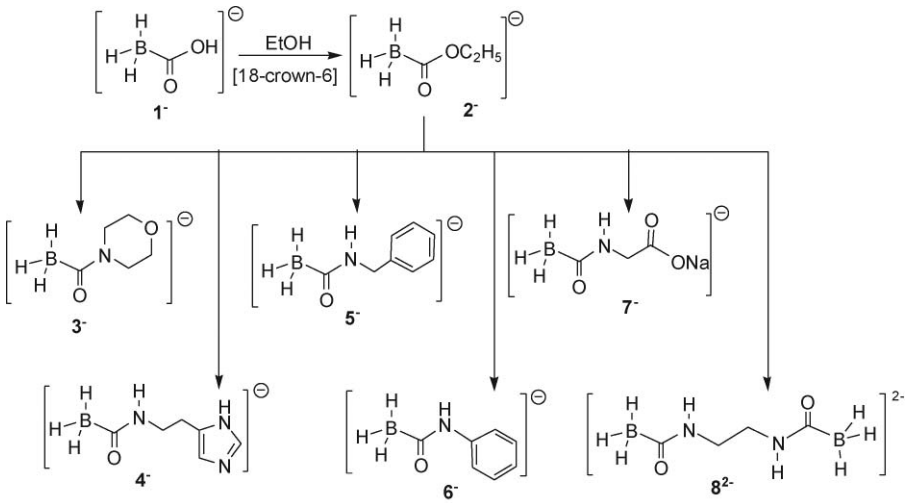
Synthesis

The synthesis of the parent compound Na[**1**] is mainly used for the preparation of ^{99m}Tc-carbonyl complexes for radiopharmaceutical purposes and has been described earlier.[20] During the synthesis, $H_3B{\cdot}THF$ is converted to H_3B-CO which forms [$H_3BCOOEt$]$^-$ upon bubbling the H_3B-CO gas stream through alkaline ethanol. Strong and long heating of this very basic solution in the presence of NaOH causes the ester to hydrolyze and compound Na[**1**] precipitates from the solution. [$H_3BCOOEt$]$^-$ cannot be isolated directly from the alkaline EtOH due to the presence of large amounts of NaOH and impurities. It would be a convenient starting material for the attempted boranocarbonate-amides derivatives since the ester group can be converted to an amide in the presence of the desired amines. Attempts to activate **1**$^-$ with *e.g.* pentafluoro-phenol failed since the acidic hydroxy function lead to protonation of the hydrides and decomposition of [**1**]$^-$. We found that prolonged stirring of [**1**]$^-$ in ethanol in the presence of 18-crown-6 as the phase transfer catalyst gave [Na(18-crown-6)][$H_3BCOOEt$] ([Na(18-crown-6)][**2**]) in good yield as the only product (Scheme 2).

The ester [Na(18-crown-6)][**2**] is a stable white powder and soluble in organic solvents as well as in water. The ^{11}B NMR spectrum showed one single signal at –21 ppm and the ^{1}H NMR a quartet centred at 0.59 ppm in CD_3CN with ^{1}H,^{11}B coupling constants of 83 Hz. Compound **2**$^-$ was reacted with primary and secondary amines to readily yield the corresponding carbamate-derivatives of [**1**]$^-$, namely, Na[$H_3BCOmor$] (Na[**3**]) with morpholine (mor), [Na(18-crown-6)][$H_3BCOhist$] ([Na(18-crown-6)][**4**]) with histamine (hist), [Na(18-crown-6)][$H_3BCObza$] ([Na(18-crown-6)][**5**]) and [Na(18-crown-6)][$H_3BCOani$] ([Na(18-crown-6)][**6**]), with benzylamine (bza) and aniline (ani), respectively (Scheme 2).

The reaction of [Na(18-crown-6)][**2**] with amines comprising additional functionalities in their side chains was possible as well. Compound [**4**]$^-$ has an imidazole group and the reaction with glycine (gly) lead to the corresponding Na_2[$H_3BCOgly$] compound Na_2[**7**], which precipitated as the di-sodium salt. It was even possible to attach two boranocarbonato groups to ethylene-diamine (en) to yield [Na(18-crown-6)]$_2$[$(H_3BCO)_2$en] ([Na(18-crown-6)]$_2$[**8**]) in good yield (Scheme 2).

These examples reveal a general synthetic strategy for introducing the CO-releasing boranocarbonate group in different molecules by a simple ester to amide conversion. The compounds



Scheme 2 Synthetic scheme to boranocarbamates [**3**]$^-$–[**8**]$^{2-}$ from [**1**]$^-$ and [**2**]$^-$ respectively.

Table 1 Selected bond lengths [Å] and angles [°] of the boranocarbamate units for [Na(18-crown-6)][**3**], [K(18-crown-6)][**4**], [K(18-crown-6)][**6**]·$\frac{1}{2}$($C_6H_5NH_2$) and [K(18-crown-6)]$_2$[**8**]

	BH_3–C [Å]	C═O [Å]	C–N [Å]	BH_3–C═O [°]	BH_3–C–N [°]	O═C–N [°]
[Na(18-crown-6)][**3**]	1.620(4)	1.242(3)	1.373(3)	124.0(2)	119.3(2)	116.7(2)
[K(18-crown-6)][**4**]	1.606(4)	1.266(3)	1.341(2)	123.53(19)	119.2(2)	117.2(2)
[K(18-crown-6)][**6**]·$\frac{1}{2}$($C_6H_5NH_2$)	1.610(5)	1.232(4)	1.385(4)	126.2(3)	115.0(3)	118.8(3)
[K(18-crown-6)]$_2$[**8**]	1.611(4)	1.242(3)	1.365(3)	125.2(2)	117.0(2)	117.8(2)

[**3**]$^-$–[**8**]$^{2-}$ are models for biomolecules, which could carry the CORM to specific sites in an organism. All compounds were fully characterized (see experimental part) and show distinct ^{11}B NMR signals around –30 ppm.

Structural characterization. It was possible to grow X-ray quality crystals for compounds [Na(18-crown-6)][**2**], [Na(18-crown-6)][**3**], [K(18-crown-6)][**4**] and [K(18-crown-6)][**6**] and [K(18-crown-6)]$_2$[**8**] to establish their authenticity. Compounds [Na(18-crown-6)][**2**] and [Na(18-crown-6)][**3**] crystallized directly as the [Na(18-crown-6)]$^+$ salts from solution whereas [K(18-crown-6)][**4**], [K(18-crown-6)][**6**]·$\frac{1}{2}$($C_6H_5NH_2$) and [K(18-crown-6)]$_2$[**8**] crystallized only after addition of K^+ to the crystallization solution. [Na(18-crown-6]$^+$ in coordinating solvent is involved in the equilibrium with free Na^+ and 18-crown-6 which affected the crystallization of the corresponding salts. The ligand 18-crown-6 has a much stronger affinity for K^+ than for Na^+ in water (log K_1 0.82 (Na^+) *vs.* 2.05 (K^+)).[21] Hence, K^+ replaced Na^+ and thereby facilitated crystallization. The structure of [K(18-crown-6)][**6**]·$\frac{1}{2}$($C_6H_5NH_2$) contains half an aniline molecule as a solvate. Its centre sits on the crystallographic two-fold rotational axis. ORTEP presentations of the anions [**3**]$^-$, [**4**]$^-$, [**6**]$^-$ and [**8**]$^{2-}$ are given in Fig. 1, important bond lengths and angles in Table 1 and general crystallographic data in the supporting information.

In the crystal structures, all carbonyl oxygen atoms are coordinated to the alkali cation. In the case of [Na(18-crown-6)][H_3BCOmor] [Na(18-crown-6)][**3**], the oxygen of the morpholine also coordinated to a neighbouring sodium, thereby forming an infinite chain. The carbonyl carbon atom is almost always perfectly planar (sum of the angles 359.53–360°). The bond lengths of the boranocarbamates are comparable with other compounds.[22]

CO releasing properties. The parent compound [**1**]$^-$ releases CO in aqueous solution. The rate of CO release is strongly pH dependent and the half-life time, $t_{1/2}$ at physiological pH and 37° C was found to be about 21 min.[5] The rate increased steeply with decreasing pH and $t_{1/2}$ was 3.3 min at pH = 6.5. On the other hand, the rate of CO release decreased with increasing pH value and [**1**]$^-$ was stable over an extended time period at pH > 8.5. For *in vivo* application, [**1**]$^-$ must be derivatised in a way to yield compounds, which maintain their CO releasing properties but at tuneable half life times. Thus, the carboxylate group attached to the {H_3B} moiety was altered for influencing the rates of CO release. The conversion of the carboxylate group to amides is attractive since amines are frequent motives in targeting biomolecules. From a mechanistic point of view, CO cleavage is initiated by the protonation of [**1**]$^-$ and the subsequent release of water (Scheme 3). The thereby generated H_3B–CO rapidly hydrolyses to CO and unidentified mixed boron-hydride-hydroxy compounds. Since the

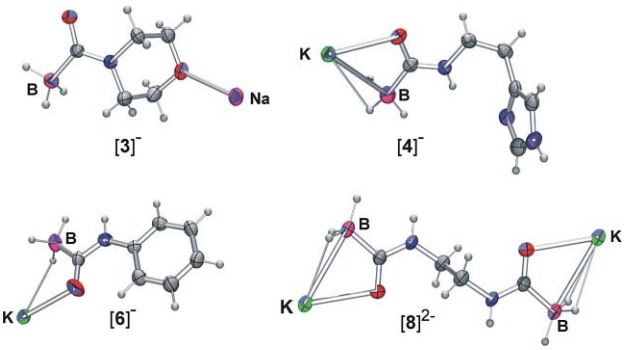
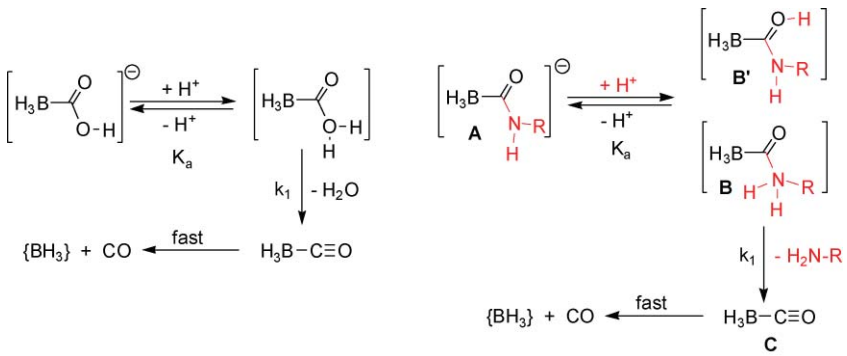


Fig. 1 ORTEPs of the structures of the boranocarbamate anions [H_3BCOmor]$^-$ [**3**]$^-$, [H_3BCOhist]$^-$ [**4**]$^-$, [H_3BCOani]$^-$ [**6**]$^-$, and [$(H_3BCO)_2$en]$^{2-}$ [**8**]$^{2-}$ and connectivities to the respective alkaline cations. Where applicable, the crown ethers have been omitted for clarity. Ellipsoids are drawn on the 50% probability level. For bond lengths and angles, see supplementary information.



Scheme 3 Assumed mechanisms of CO release from compound **1**$^-$ (left) and [**3**]$^-$–[**8**]$^{2-}$ (right). Protonation of the carboxylate or the amide group is followed by water or amine cleavage. The resulting, neutral H_3B–CO molecule releases CO rapidly.

protonation of an amide is more difficult than of the formal –COOH group, the CO release should be decelerated.

Scheme 3 shows the mechanisms which have been proposed for CO release from $[\mathbf{1}]^-$ and the derivatives $[\mathbf{3}]^-$–$[\mathbf{8}]^{2-}$. The amides of the (negatively charged) compounds $[\mathbf{3}]^-$–$[\mathbf{8}]^{2-}$ (**A**) are protonated in a rapid, amide pK_a-dependent equilibrium. Protonation can occur directly at the amide nitrogen to yield **B** or at the delocalised negative charge on the oxygen of the amide (**B′**). The rate-limiting step for this mechanism is the elimination of the amine (k_1) yielding H_3BCO (**C**), which in turn decomposes rapidly to release CO. This mechanistic model results in a rate law, which depends on K_a and k_1 according to the following formula.

$$A = H^+ \overset{K_a}{\rightleftharpoons} B \xrightarrow{k_1} C$$

$$\frac{dCO}{dt} = \frac{[H^+]K_a k_1[A]}{1+[H^+]K_a} k_{obs} = \frac{[H^+]K_a k_1}{1+[H^+]K_a}$$

Alternatively, the amides $[\mathbf{3}]^-$–$[\mathbf{8}]^{2-}$ can be hydrolysed to $[\mathbf{1}]^-$, which subsequently enters the normal CO releasing pathway, protonation of the carboxylate, cleavage of water and release of CO. The rate law would be the same as for $[\mathbf{3}]^-$–$[\mathbf{8}]^{2-}$ and the pK_a that of the parent $[\mathbf{1}]^-$. In our experiments, both pathways were observed. ^{11}B and ^{1}H NMR inspection of a solution of $[\mathbf{3}]^-$ for instance showed two signals, one for the amides and the other for $[\mathbf{1}]^-$ (see ESI†).

The rate of CO release by the various amides at constant pH and temperature in buffered solution was recorded by GC measurements. At a given pH, the curves could be fitted to a pseudo first order kinetics, which gave k_{obs} values and $t_{1/2}$ for compounds $[\mathbf{3}]^-$–$[\mathbf{8}]^{2-}$. The CO release from the morpholine amide derivative $[\mathbf{3}]^-$ at various pH values is given in Fig. 2.

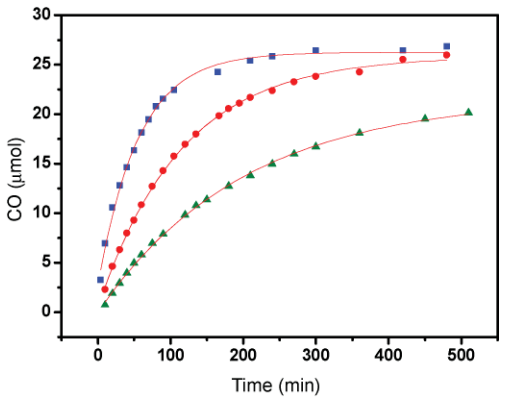


Fig. 2 CO release from $[\mathbf{3}]^-$ at pH = 6.7 (■), 7.4 (▼) and 8.0 (▲) and 37° C together with the mono-exponentially fitted curves.

The CO release from the ethyl ester $[\mathbf{2}]^-$ at room temperature was too rapid and complete within a couple of minutes. This indicated direct protonation and cleavage of ethanol in $[\mathbf{2}]^-$, without intermediate formation of substantial amounts of $[\mathbf{1}]^-$; otherwise the release of CO from $[\mathbf{2}]^-$ should show the same rate as that of $[\mathbf{1}]^-$. This behaviour clearly showed that ester derivatives of $[\mathbf{1}]^-$ are not suitable as CO-releasing molecules since CO release was too fast for application and difficult to control. Although the data for CO release from the amides do not allow a detailed kinetic and mechanistic analysis, it is evident that CO release slows down for $[\mathbf{3}]^-$–$[\mathbf{8}]^{2-}$ as compared to $[\mathbf{1}]^-$ and $[\mathbf{2}]^-$. At physiological pH and 37° C, compounds $[\mathbf{3}]^-$, $[\mathbf{4}]^-$ and $[\mathbf{7}]^-$ released CO with $t_{1/2} \approx 90$ min, $[\mathbf{6}]^-$ with ≈ 40 min and $[\mathbf{8}]^{2-}$ with ≈100 min, which indicates that the transformation of the acid in $[\mathbf{1}]^-$ to amides in $[\mathbf{3}]^-$–$[\mathbf{8}]^{2-}$ slows down the rates of CO release by factors between 5 and 10 as compared to $[\mathbf{1}]^-$ (21 min at 37° C). With these derivatizations, the half-life times are shifted to a range where the compounds have reasonable CO releasing properties for *in vitro* and *in vivo* application. It is obvious that derivatizations thus enable fine-tuning of the CO-releasing properties. The amides with primary or secondary amine groups ($[\mathbf{3}]^-$, $[\mathbf{4}]^-$ and $[\mathbf{7}]^-$) are slower than the anilide compound $[\mathbf{6}]^-$, which releases CO almost as fast as $[\mathbf{1}]^-$. Since the sp^2 nitrogen in aniline does not form strong amides, hydrolysis to $[\mathbf{1}]^-$ or the direct release of aniline form **B** is likely to be very fast. A steep increase of $\tau_{1/2}$ over the investigated pH range was observed and the trends are almost the same for all compounds. We found that the rate of CO release was about 4 times slower at pH = 8 than at 6.7 and showed a similar trend for all compounds. A selection of half life times for the different compounds are given in Table 2.

Table 2 Selected half life times of CO release in buffered solution. Corresponding [CO] *vs.* time profiles can be found in the SI

	pH = 6.8	pH = 7.4	pH = 8.0
$[H_3BCOmor]^-$ $[\mathbf{3}]^-$	53 min	90 min	152 min
$[H_3BCOhist]^-$ $[\mathbf{4}]^-$	39 min	80 min	139 min
$[H_3BCOani]^-$ $[\mathbf{6}]^-$	—	46 min	—
$[H_3BCOgly]^-$ $[\mathbf{7}]^-$	41 min	80 min	142 min
$[(H_3BCO)_2en]^{2-}$ $[\mathbf{8}]^{2-}$	63 min	95 min	155 min

The reactions undergone by residual $\{BH_3\}$ fragment after CO release were difficult to assess. The ^{11}B NMR during and after the reactions showed, besides the sharp signal of the respective starting compound, just broad and unresolved signals and even ^{1}H NMR did not exhibit distinct signals assignable to single and specific species. It is likely that the $\{BH_3\}$ residue hydrolyses to mixtures of mixed and multinuclear borohydride-hydroxide species.

Conclusions

We have synthesized and fully characterized a number of boranocarbamate derivatives. These derivatizations were able to tune the rate of CO release observed upon dissolution of the compounds in water. We found a decrease in the rate of CO formation by factors between 5 and 10, in addition to a strong pH dependence. It can, thus, be concluded that the introduction of functionalities to the borano-carbonate framework $[\mathbf{1}]^-$ allows for an adequate tuning of CO release. Furthermore, instead of the model amines selected in this work, targeting molecules such as peptides could be coupled along the same synthetic strategy, which will produce site specific CO releasing molecules.

Experimental Section

Materials and methods

All reactions were carried out under a nitrogen atmosphere and all the chemicals, purchased from commercial sources, were used without further purification. Water was doubly distilled before use in the preparation of the standard buffers. IR spectra were recorded on a PE Spectrum BX FT-IR spectrophotometer. NMR

spectra were recorded on a Varian Gemini 300 MHz spectrometers in D_2O or CD_3CN. The chemical shifts values are in ppm *vs.* TMS and *vs.* BF_3·diethyl ether for ^1H and for ^{11}B, respectively. Elemental analyses were performed on a Leco CHNS-932 elemental analyser.

Gas chromatography

The gas chromatograms were recorded on a Varian CP-3800 gas chromatograph with helium as the carrier gas and a 3 m × 2 mm molecular sieve 13X 80-100. The gas flow was set to 20 μL min^{-1}. The oven was operated at 100° C. The 100 μL gas samples were injected using a Hamilton (1825 RN) gastight microlitre syringe. The CO was detected using a Thermal Conductivity Detector (TCD). Calibrations were performed by the injection of known quantities of pure CO diluted in a sealed vial containing the same volume of the buffer as used for the measurements.

X-Ray crystallography measurements

Crystallographic data were collected at 183(2) K either on a Stoe IPDS 2T diffractometer with Cu-Kα radiation (λ = 1.54186 Å) for [Na(18-crown-6)][**3**] or on an Oxford Diffraction Xcalibur system with a Ruby detector (Mo-Kα radiation, λ = 0.7107 Å) for [Na(18-crown-6)][**2**], [K(18-crown-6)][**4**] and [K(18-crown-6)][**6**]·$\frac{1}{2}(C_6H_5NH_2)$ and [K(18-crown-6)]$_2$[**8**]. Suitable crystals were covered with oil (Infineum V8512, formerly known as Paratone N), mounted on top of a glass fibre and immediately transferred to the diffractometer. In the case of the IPDS 2T, reflection data was processed with the help of the program X-Area.[23] Data were corrected for Lorentz and polarisation effects as well as for absorption (numerical). In case of the Oxford system, the program suite CrysAlis^{Pro} was used for data collection, semi-empirical absorption correction and data reduction.[24] Structures were solved with direct methods using SIR97[25] and were refined by full-matrix least-squares methods on F^2 with SHELXL-97.[26] The hydrogen atoms of the BH_3 groups were treated as follows: The isotropic thermal parameters were multiplied with 1.5 of the values of their corresponding boron atoms. The positions were freely refined in the cases of [K(18-crown-6)][**4**] and [K(18-crown-6)]$_2$[**8**]; for [K(18-crown-6)][**6**] $\frac{1}{2}(C_6H_5NH_2)$ in addition the B–H bond lengths were restraint to 1.1 Å. In the case of [Na(18-crown-6)][**2**] and [Na(18-crown-6)][**3**], the hydrogen atoms were forced to form a perfect tetrahedral boron atom with identical, but otherwise freely refined B–H bond lengths. The structures were checked for higher symmetry with help of the program Platon.[27] CCDC reference numbers 775354 [K(18-crown-6)][**4**], 775355 [K(18-crown-6)]$_2$[**8**], 775356 ([Na(18-crown-6)][**3**], 775357 [K(18-crown-6)][**6**] $\frac{1}{2}(C_6H_5NH_2)$, and 775358 [Na(18-crown-6)][**2**] can be received free of charge from The Cambridge Crystallographic Data Centre.

Syntheses

The synthesis of Na[H_3BCO_2H] Na[**1**] was performed according to literature procedure.[17]

[Na(18-crown-6)] *O*-ethylboranocarbonate [Na(18-crown-6)][2]

18-Crown-6 (0.80 g, 3 mmol) was added to a suspension of Na[**1**] (0.25 g, 3 mmol) in 15 mL ethanol constant stirring. The mixture was allowed to stir overnight at r.t. and filtered to remove undissolved **1**. The filtrate was evaporated to dryness to yield a white solid, which was washed with Et_2O to remove unreacted 18-crown-6 and dried again. The residue was dissolved in acetonitrile, filtered and the filtrate evaporated to dryness to yield 650 mg of **2** (58%). X-ray quality crystals were obtained from the slow evaporation of **2** in acetonitrile. Elemental analysis: Found: C, 48.25; H, 8.81. Calcd for $C_{15}H_{32}BNaO_8$: C, 48.15; H, 8.62%. IR (KBr pellet) ν_{max}/cm^{-1}: 1634 (CO). δ_H (300 MHz, CD_3CN): 3.74 (2H, q, J = 7.1 Hz, CH_2CH_3), 3.57 (24H, s, crown-OCH_2), 1.07 (3H, t, J = 7.1 Hz, CH_2CH_3), 0.59 (3H, q, J = 83 Hz, BH_3) ppm. δ_C (75 MHz, CD_3CN): 15.89 (s, CH_3), 55.48 (s, CH_2), 71.17 (s, O–CH_2) ppm. δ_B (96 MHz, CD_3CN): –28.0 ppm.

[Na] morpholineboranocarbamate [Na(18-crown-6)][3]

Excess morpholine (0.080 g, 1 mmol) was added to a solution of [Na(18-crown-6)][**2**] (0.30 g, 0.8 mmol) in 10 ml acetonitrile with constant stirring. Stirring was continued overnight at r. t. and filtered. The filtrate was evaporated to give a white solid, which was washed with ether to remove unreacted morpholine and then dried under vacuum. The white solid was dissolved in a minimum amount of acetonitrile. Addition of excess ether with constant stirring caused precipitation of the desired amide product without crown ether after about 2 h. Filtration yielded 72 mg of analytically pure **3** (56%). X-ray quality crystals of the compound with $[Na(18\text{-crown-6})]^+$ as cation were obtained from the ether washings. Elemental Analysis: Found: C, 39.56; H, 7.28; N, 9.19. Calcd. for $C_5H_{11}BNNaO_2$: C, 39.78; H, 7.35; N, 9.28%. IR (KBr pellet) ν_{max}/cm^{-1}: 1595 (CO). δ_H (300 MHz, D_2O): 3.57 (24H, s, crown-OCH_2), 3.53 (4H, t, mor-*H*), 3.38 (4H, t, mor-*H*), 0.75 (3H, q, J = 82 Hz, BH_3) ppm. δ_B (96 MHz, D_2O): –31.4 ppm.

[Na(18-crown-6)] histamineboranocarbamate [Na(18-crown-6)][4]

Histamine (0.032 g, 0.28 mmol) was added to a solution of [Na(18-crown-6)][**2**] (0.10 g, 0.27 mmol) in 5 mL of dry acetonitrile and stirred overnight at r. t. The solution was filtered, the filtrate evaporated to dryness to obtain, after washing the residue with dry Et_2O, a pale yellow solid which was dried under vacuum. Yield: 47 mg (43%). Elemental Analysis: Found: C, 46.31; H, 8.10; N, 9.25. Calcd for $C_{18}H_{35}BN_3NaO_7$: C, 49.21; H, 8.03; N, 9.57%. δ_H (300 MHz, CD_3CN): 7.41 (1H, s, hist-H), 6.66 (1H, s, hist-H), 6.26 (1H, s, hist-H), 3.57 (24H, s, crown-OCH_2), 3.32 (2H, q, J = 6.6 Hz, hist-CH_2), 2.66 (2H, t, J = 7.0 Hz, hist-CH_2), 0.67 (3H, q, J = 82 Hz, BH_3) ppm. δ_B (96 MHz, CD_3CN): –25.91 ppm.

[Na(18-crown-6)] benzylamineboranocarbamate [Na(18-crown-6)][5]

Benzylamine (0.090 g, 0.84 mmol) was added to a solution of [Na(18-crown-6)][**2**] (0.30 g, 0.8 mmol) in 15 ml of dry acetonitrile with constant stirring. After 2 d, the reaction mixture was filtered, the filtrate evaporated to dryness and washed with ether to remove unreacted benzyl amine. The white solid product obtained was free of benzyl amine but hygroscopic. Yield: 50%. Elemental Analysis: Found: C, 53.84; H, 7.89; N, 3.60. Calcd for $C_{20}H_{35}BNNaO_7$: C, 55.18; H, 8.10; N, 3.22%. IR (KBr pellet) ν_{max}/cm^{-1}: 1571 (CO). δ_H (300 MHz, D_2O): 7.17–7.30 (5H, m, arom-H), 4.20 (24H, s,

crown-OCH_2), 0.73 (3H, q, J = 81 Hz, BH_3) ppm. δ_B (96 MHz, D_2O): –30.14 ppm.

[Na(18-crown-6)] anilineboranocarbamate [Na(18-crown-6)][6]

Aniline (0.06 g, 0.66 mmol) was added to a clear solution of [Na(18-crown-6)][**2**] (0.2 g, 0.55 mmol) in 7 ml of dry acetonitrile. The reaction mixture was stirred at 45 °C for 5 days. After filtration and evaporation of the filtrate to dryness, the white solid obtained was washed with ether to remove unreacted aniline. Some product went into the ether solution as evident from the X-ray quality crystals obtained from slow evaporation of ether. Yield: 190 mg (80%). Elemental Analysis: Found: C, 53.94; H, 3.49; N, 7.65. Calcd for $C_{19}H_{33}BNNaO_7$: C, 54.17; H, 3.32; N, 7.90%. δ_H (300 MHz, CD_3CN): 7.52 (d, J = 8 Hz, ani-H), 7.14 (t, J = 8 Hz, ani-H), 6.80 (t, J = 8 Hz, ani-H), 6.62 (d, J = 6 Hz, ani-H), 3.57 (24H, s, crown-OCH_2), 0.77 (3H, q, J = 82.6 Hz, BH_3) ppm.

Na_2[glycineboranocarbamate] Na_2[7]

Na[glycinate] (0.08 g, 0.84 mmol) was added to a solution of [Na(18-crown-6)][**2**] (0.30 g, 0.8 mmol) in 10 mL dry ethanol with constant stirring and was allowed to proceed for 2 d. The product precipitated as a white solid, which was filtered off and dried under vacuum. Adding excess sodium tetrafluoroborate to the filtrate and allowing the mixture to stir for about 3 h resulted in the precipitation of more product. Yield: 84 mg (65%). Elemental Analysis: Found: C, 22.47; H, 3.82; N, 8.60. Calcd for $C_3H_6BNNa_2O_3$: C, 22.40; H, 3.76; N, 8.71%. IR (KBr pellet) ν_{max}/cm^{-1}: 1598 (CO). δ_H (300 MHz, D_2O): δ = 3.57 (2H, s, –CH_2CH_3), 0.68 (3H, q, J = 81 Hz, –CH_2CH_3) ppm. δ_B (96 MHz, D_2O): –30.19 ppm.

[Na(18-crown-6)]$_2$[ethylenediamine-diboranocarbamate] [Na(18-crown-6)]$_2$[8]

Ethylenediamine (0.01 g, 0.15 mmol) was added to a solution of [Na(18-crown-6)][**2**] (0.1 g, 0.27 mmol) in 5 mL CH_3CN. The solution was allowed to stir overnight at r. t. The reaction mixture was filtered and the filtrate evaporated to dryness to give a white residue. The solid was washed with ether and dried under vacuum to give the ethylene diamide of sodium boranocarbonate. Yield: 67%. IR (KBr pellet) ν_{max}/cm^{-1}: 1577. δ_H (300 MHz, CD_3CN): 3.57 (24H, s, crown-OCH_2), 2.95 (4H, s, –CH_2CH_2-), 0.60 (3H, q, J = 81.8 Hz, BH_3) ppm. δ_B (96 MHz, CD_3CN): –25.74 ppm.

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