CO$_2$ Fixation

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The Elusive Cyanoformate: An Unusual Cyanide Shuttle

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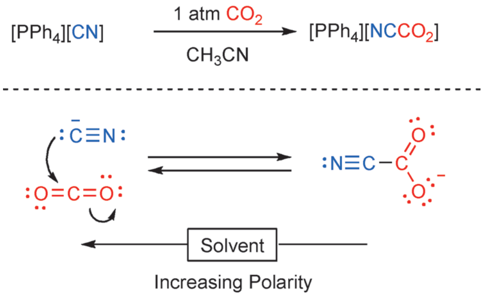
CO$_2$ makes up just 0.04 % of the earth's atmosphere and is essential for all life on earth. Nevertheless, it is the major anthropogenic greenhouse gas. Consequently, significant scientific effort has been devoted to establishing CO$_2$ as a cheap and readily available carbon feedstock. The electrophilic nature of CO$_2$ is exploited in its catalytic reduction to formates by either enzymes,[1] well-defined metal complexes, or metal oxides.[2] Nanoporous materials such as amine-grafted metal–organic frameworks (MOFs) can reversibly bind CO$_2$ and thus allow regeneration of the sorbent.[3] It comes as a surprise that CO$_2$ complexes with small nucleophilic anions, such as halides or pseudo-halides (e.g. OH$^-$, CN$^-$, OCN$^-$, SCN$^-$, and N$_3^-$) have not been thoroughly studied to date. The only well-characterized halide/pseudo-halide CO$_2$ species are hydrogen carbonate (old: bicarbonate) [HO-CO$_2$]$^-$ and fluorocarbonate [FCO$_2$]$^-$.[4] In this context, a recent report by Clybourne, Tuononen and co-workers on the preparation of the elusive cyanoformate anion warrants particular attention (Scheme 1).[5]

The synthesis of [NC-CO$_2$]$^-$ was realized by exposing a concentrated [PPh$_4$][CN] solution in CH$_3$CN to an atmosphere of CO$_2$. [PPh$_4$][NC-CO$_2$] precipitates as a colorless crystalline solid and its formation was confirmed by combined crystallographic, spectroscopic, and computational methods.



Scheme 1. Synthesis of the labile cyanoformate according to Clyburne et al. (top) and depiction of its breakdown into CO$_2$ and CN$^-$ depending on the polarity of the reaction medium (bottom).

As expected for a Lewis acid–base adduct, the C$_{CN}$–C$_{CO2}$ distance is 1.480(9) Å, whereas the C–N distance with 1.06(1) Å is relatively short, in the typical range of a triple bond. This view is supported by computational studies revealing the C–C bond to be predominantly a σ-type donor–acceptor interaction and hence, cyanide acts as a two-electron donor to CO$_2$. In contrast to CO$_2$, ketones are known to interact readily with cyanides to form cyanohydrins; this was reported first in Strecker's pioneering work in 1850.[6] However, the reaction of CO$_2$ with CN$^-$ is considerably less favorable for several reasons: 1) Distorting the linear CO$_2$ molecule is energetically not favorable (310 kJ mol^{-1});[7a] 2) the π bonds in CO$_2$ are considerably stronger than π bonds at sp^2-hybridized carbons;[7b] 3) the poor overall entropy is not compensated by the small enthalpic preference for cyanoformate formation. This situation is nicely reflected by the relatively large O-C-O angle of 133°, which indicates that CO$_2$ wants to escape this unfavorable situation. The stability of [NC-CO$_2$]$^-$ increases with decreasing solvent polarity (toluene). Thus, fragmentation into CO$_2$ and CN$^-$ is favored in polar reaction media. However, kinetics protects the anion from immediate breakdown as C–C bond scission has a relatively high activation barrier of ca. 40 kJ mol^{-1}. The authors carried out decomposition studies utilizing in situ generated [Bu$_4$N][NCCO$_2$] in an ionic liquid. This mixture was added to anhydrous toluene, tetrahydrofuran, and acetonitrile, respectively, to monitor the decay of the ν_{as}(CO$_2$) vibration in [NC-CO$_2$]$^-$ and determine the half-lives (toluene: 110 min; acetonitrile: 17 min). Traces of water led to immediate decomposition, as CN$^-$ is an excellent nucleophile and hydrogen carbonate is formed.

Besides hydrogen carbonate (**A**), fluorocarbonate is the only example of a stable halide/pseudo-halide adduct of CO$_2$ (Figure 1). Seppelt et al. reported the facile synthesis of [FCO$_2$]$^-$ (**B**) by exposing anhydrous solutions of ammonium fluoride salts to CO$_2$.[4] These salts are poorly soluble in common solvents and decompose when traces of water are present. The main hurdle for the preparation seems to be the low affinity of CO$_2$ towards F$^-$, which amounts to just -133 kJ mol^{-1}. [FCO$_2$]$^-$ is isoelectronic with [NO$_3$]$^-$; consequently neutral [NC-NO$_2$] (**C**) is the isoelectronic nitrogen congener of the cyanoformate anion. In a recent report Christe et al. described the challenging synthesis and comprehensive characterization of nitryl cyanide from NO$_2$BF$_4$ and *t*BuMe$_2$SiCN in nitromethane at -30 °C.[8] Fractional condensation yielded pure [NC-NO$_2$] which melted at -85 °C (boiling point 7 °C) and complete decomposition was ob-

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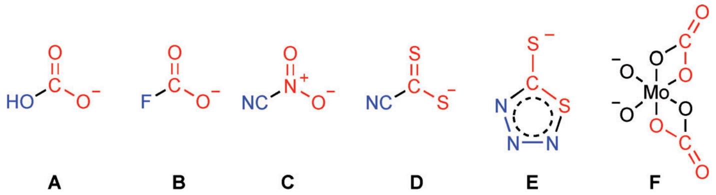

Figure 1. Structures of known halide/pseudo-halide (blue) adducts of CO_2/CS_2 (red) (A–D) and binding of two CO_2 molecules to MoO_4^{2-}.

served upon heating to 140 °C for several hours. The C_{CN}-N_{NO2} distance amounts to 1.42 Å and is shorter than that in the cyanoformate anion. The heavier congener of CO_2, CS_2, was shown to cleanly react with NaCN to afford sodium cyanodithioformate Na[NC-CS_2] (**D**) as early as 1955 by Bähr and Schleitzer.[9] In contrast to $[NC\text{-}CO_2]^-$, cyanodithioformate is stable even in aqueous media and is oxidized in polar solvents ($CHCl_3$) at elevated temperatures to afford tetracyanodithiin. Along these lines it is noteworthy that Sommer first prepared cyclic azidodithiocarbonates in 1915 by treatment of CS_2 with NaN_3.[10a] In contrast to the accumulation of negative charge at the oxygen atoms in $[NC\text{-}CO_2]^-$, the molecular structure of $[CS_2N_3]^-$ (**E**) reveals a five-membered heterocycle, which is planar with a delocalized negative charge,and thus, this anion can be regarded as a pseudo-halide. The corresponding dipseudo-halogen was prepared by Klapötke and co-workers by oxidative coupling of the anion with XeF_2.[10b] In contrast, there are no reports concerned with the synthesis of acyclic azidoformate or cyclic azidocarbonate anions. In analogy to the reversible binding of CO_2 to CN^- the Cummins group has shown just recently that molybdate anions can take up two molecules CO_2 (**F**), whereas the second molecule binds reversibly, and hence these results clearly show the potential of anions to act as CO_2 shuttles.[11] The electrophilic nature of CO_2 is also exploited to access polarity-switchable solvent systems, in which CO_2 forms high-polarity adducts with amines or alcohols and amines, and a switch back to low polarity is achieved by CO_2 removal.[12]

Clybourne, Tuononen, and co-workers propose that nature uses CO_2 as a Lewis acidic masking molecule in order to shuttle away CN^- from the active site of the enzyme ACC oxidase (E C 1.14.17.4). ACC oxidase catalyzes the synthesis of ethylene from 1-aminocyclopropane-1-carboxylic acid along with the putative cyanoformate.[13,14] Interestingly, in the key catalytic step water is absent from the active site, which results in a very low dielectric constant at the substrate binding site. This effect stabilizes cyanoformate within the active site and thus protects the iron center within the enzyme from immediate complexation with cyanide. Cyanoformate is subsequently released from the substrate binding site and exposed to the surrounding aqueous media with a higher dielectric constant, causing rapid decomposition into CN^- and CO_2. Formed CN^- still causes enzyme inhibition, but to a significantly lower degree. Apart from the masking concept of CN^- with CO_2, such a controlled cyanide release is also known in nature for the enzyme family of hydroxynitrile lyases, HNLs (E.C. 4.1.2.X).[15] These plant enzymes catalyze the cleavage of cyanohydrins to a corresponding carbonyl compound and toxic hydrogen cyanide (HCN), which then acts against herbivores and microorganisms. However, within this defense mechanism the cyanohydrin is originally stabilized as a nontoxic cyanogenic glycoside that prevents damage to the plant under normal conditions. During an attack, the plant releases the cyanogenic glycoside, which is converted by a glycosidase to the corresponding cyanohydrin and then cleaved by HNLs to form hydrogen cyanide. Interestingly, HNLs can also be used in reverse for the highly enantioselective synthesis of cyanohydrins. *R*- as well as *S*-selective hydroxylnitrile lyases are commercially available and widely used for the synthesis of various highly relevant intermediates of pharmaceuticals and agrochemicals, for example, (*S*)-3-phenoxybenzaldehyde cyanohydrin, which is a precursor of various synthetic pyrethroids, and (*R*)-2-hydroxy-4-phenylbutyronitrile for the synthesis of various ACE-inhibitors.[16] Important examples include the *R*-selective HNL from *Prunus amygdalus* (*Pa*HNL, bitter almond) and the *S*-selective HNL from *Hevea brasiliensis* (*Hb*HNL, rubber tree). Fortunately, these enzymes do not contain a central iron within the active site and are therefore not sensitive to high cyanide concentrations.

Finally, the results highlighted here are breakthroughs in small-molecule and enzyme chemistry and will serve as inspiration in synthesis as well as in the design and understanding of enzymes in biocatalytic processes. Needless to say, this concept might be applied to save people from cyanide poisoning: Grigori Rasputin[17] demonstrated this unintentionally when his would-be assassins gave him poisoned sweeties.

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