Coordinated Ketyl Radicals

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Gas-Phase Formation of the Gomberg–Bachmann Magnesium Ketyl[**]

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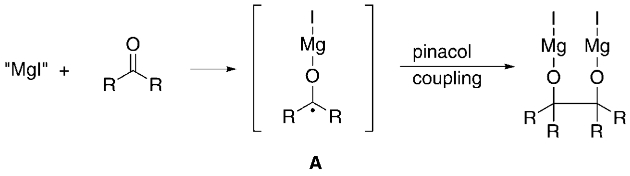
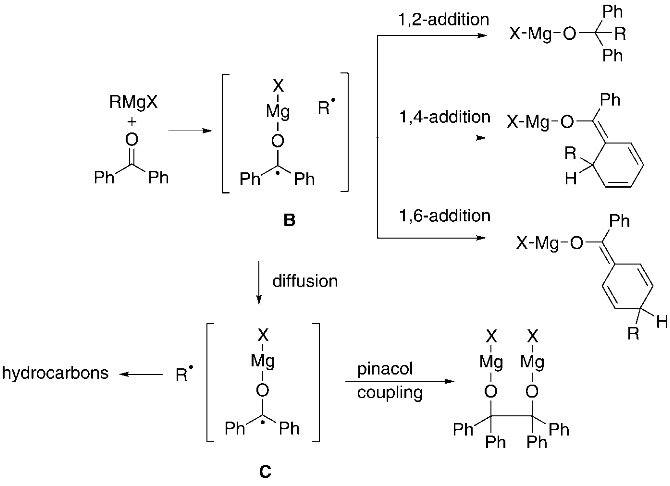
Dedicated to Professor Tony Wedd on the occasion of his 65th birthday

Ketyl radical anions have a rich history beginning in 1836, when Laurent noted a deep blue coloration of a solution of benzil upon addition of potassium hydroxide.[1,2] Since then, ketyl radical anions have been shown to be key intermediates in several important reactions.[3] When metal reagents are used to reduce carbonyl compounds through single electron transfer (SET), the resultant coordinated ketyl radical can undergo important C–C bond coupling reactions. An early example is the Gomberg–Bachmann pinacol synthesis (Scheme 1), which involves reducing a ketone with a Mg/MgI_2 mixture.[4] The subvalent magnesium iodide, $MgI^\bullet$, was proposed as the reductant, and the key intermediate is the magnesium ketyl **A**.[4,5]



Scheme 1. Pinacol synthesis according to Gomberg and Bachmann.

Inspired by Gomberg's work, in 1929 Blicke and Powers proposed the now generally accepted SET mechanism for Grignard reactions (Scheme 2).[6,7] Thus a Grignard reagent (simplified as RMgX[8]) can react with a ketone such as benzophenone to form a coordinated ketyl radical anion–radical pair **B**, which then either couples with the radical, $R^\bullet$, through 1,2, 1,4, and 1,6 pathways or undergoes diffusion to **C** and $R^\bullet$, which can undergo other competing reactions such as pinacol formation.



Scheme 2. SET pathway for the Grignard reaction (adapted from reference [7]).

As part of an ongoing series of studies aimed at examining organometallic reactions in the pristine gas-phase environment, it occurred to us that the decarboxylation strategy,[9] previously exploited to form organomagnesate anions, $RMgCl_2^-$,[9b] could provide suitable precursors to examine the gas-phase chemistry of coordinated ketyl anions directly related to **A** and **C**. Herein we describe the use of a combination of multistage mass spectrometry experiments (MS^n) in a quadrupole ion-trap (QIT) mass spectrometer[10,11] and DFT calculations[12] to demonstrate that the Mg^I anion, $MgCl_2^{\bullet-}$,[5] readily reacts with ketones, such as butanone, to form a coordinated ketyl radical anion[13] which undergoes simple β-radical cleavage, consistent with the condensed and gas-phase chemistry of "bare" ketyl radical anions.[3,14]

A survey of over ten carboxylates $[RCO_2MgCl_2]^-$ revealed that the phenylacetate system is the most suitable precursor to generate the desired $MgCl_2^{\bullet-}$ reagent in high yields. Thus the decarboxylation reaction yields the dominant organomagnesate fragment ion [Eq. (1a)] in the first stage of the CID (an MS^2 experiment) on $[PhCH_2CO_2MgCl_2]^-$ (Figure 1a).[15] This is consistent with the thermochemistry predicted by DFT calculations for this and the other potential competing fragmentation channels [Eqs. (1b) and (1c),[16] Table S1 in the Supporting Information).

$$[PhCH_2CO_2MgCl_2]^- \rightarrow [PhCH_2MgCl_2]^- + CO_2 \quad E_{act} = 48.0\ \text{kcal mol}^{-1} \tag{1a}$$

$$\rightarrow PhCH_2CO_2^- + MgCl_2 \quad \Delta H = 73.6\ \text{kcal mol}^{-1} \tag{1b}$$

$$\rightarrow Cl^- + PhCH_2CO_2MgCl \quad \Delta H = 56.2\ \text{kcal mol}^{-1} \tag{1c}$$

When the organomagnesate is mass-selected and subjected to CID in an MS^3 experiment, the bond-homolysis

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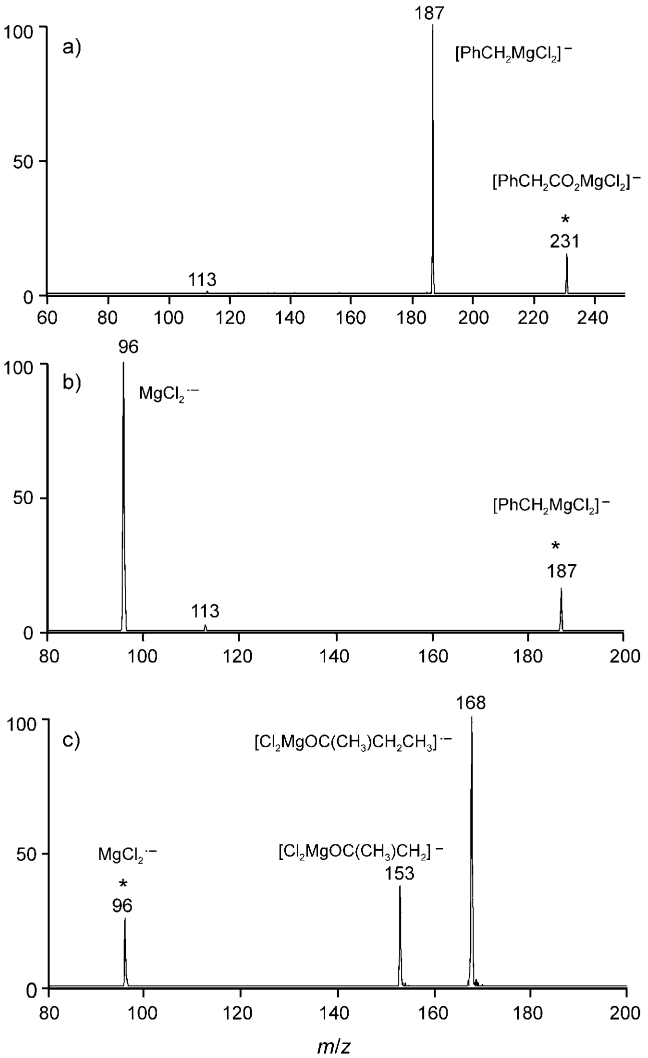

Figure 1. Mass spectra for the stepwise synthesis of $MgCl_2^{\bullet-}$ and its reactions: a) Collisional activation of $[PhCH_2CO_2MgCl_2]^-$ (*m*/*z* 231) to give $[PhCH_2MgCl_2]^-$ (*m*/*z* 187) and neutral CO_2; b) collisional activation of $[PhCH_2MgCl_2]^-$ (*m*/*z* 187) to give $MgCl_2^{\bullet-}$ (*m*/*z* 96) and $PhCH_2^{\bullet}$ through Mg–C bond homolysis; and c) ion–molecule reaction of mass-selected $MgCl_2^{\bullet-}$ (*m*/*z* 96) with butanone ($c \approx 3.6 \times 10^9$ molecules per cm^3, reaction time = 300 ms) to give the coordinated ketyl radical anion (*m*/*z* 168) and its β-methyl radical fragmentation product (*m*/*z* 153). The mass-selected precursor ion is marked with an * in each case. The peak at *m*/*z* 113 corresponds to $[HOMgCl_2]^-$, which arises from ion–molecule reactions between $[PhCH_2MgCl_2]^-$ and background water.[9b]

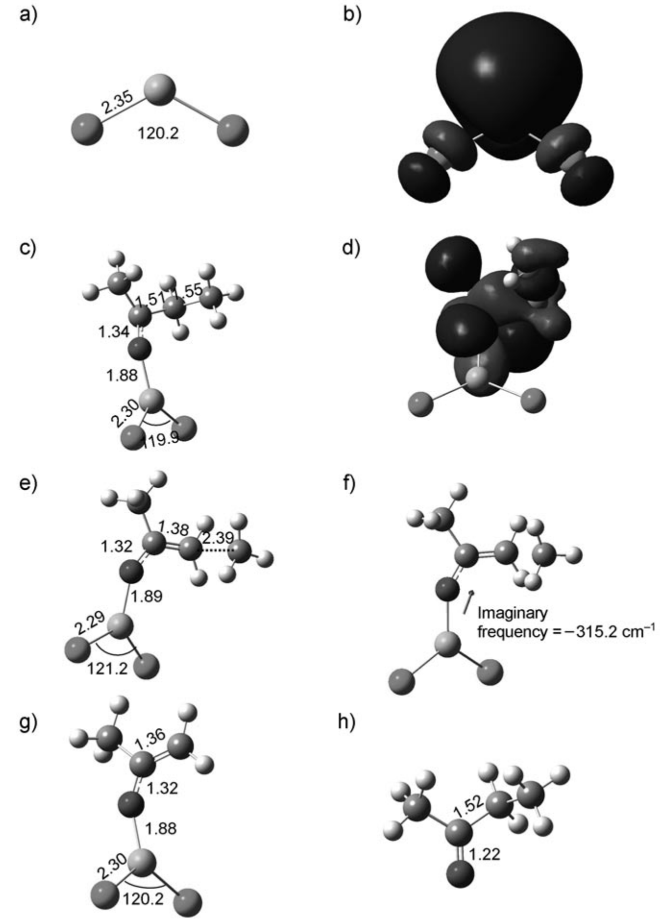

Figure 2. DFT B3LYP/6-31+G(d) calculations on $MgCl_2^{\bullet-}$ and structures relevant to its reaction with butanone: a) optimized structure of $MgCl_2^{\bullet-}$; b) SOMO of $MgCl_2^{\bullet-}$; c) optimized structure of the $MgCl_2$-coordinated butanone ketyl radical; d) SOMO of the $MgCl_2$-coordinated butanone ketyl radical; e) and f) transition state for the loss of CH_3; g) magnesium enolate; h) butanone.

$$[PhCH_2MgCl_2]^- \rightarrow MgCl_2^{\bullet-} + PhCH_2^{\bullet} \quad \Delta H = 54.9\ kcal\,mol^{-1} \tag{2a}$$

$$\rightarrow PhCH_2^- + MgCl_2 \quad \Delta H = 65.5\ kcal\,mol^{-1} \tag{2b}$$

$$\rightarrow Cl^- + PhCH_2MgCl \quad \Delta H = 58.2\ kcal\,mol^{-1} \tag{2c}$$

product, $MgCl_2^{\bullet-}$, is formed in good yield [Eq. (2a)] (Figure 1b). Heterolytic pathways such as those shown in Equations (2b) and (2c)[16] are insignificant, consistent with the theoretically predicted thermochemistry. Unlike the parent neutral $MgCl_2$, which is linear, $MgCl_2^{\bullet-}$ has—according to the calculations—a bent structure (Figure 2a), and an examination of the singly occupied molecular orbital (SOMO) reveals that it is metal-based (Figure 2b). The predicted adiabatic electron affinity (EA) of $MgCl_2$ is 1.3 eV, consistent with $MgCl_2^{\bullet-}$ being a bound anion and thus observable in the QIT.[17]

We have surveyed the reactions of $MgCl_2^{\bullet-}$ with a range of ketones, and since butanone is a representative example, it is discussed in detail. When butanone is introduced into the QIT and allowed to react with $MgCl_2^{\bullet-}$ in an MS^4 experiment, an adduct is rapidly formed, which is either collisionally stabilized [Eq. (3a), Figure 1c, *m*/*z* 168] or undergoes C–C bond cleavage through β cleavage ($CH_3^{\bullet}$ loss, Eq. (3b), Figure 1c, *m*/*z* 153) to form a coordinated magnesium enolate anion. When the adduct formed in Equation (3a) is mass-selected and subjected to CID in an MS^5 experiment, it fragments exclusively through $CH_3^{\bullet}$ loss (data not shown).

$$\begin{aligned} &\mathrm{MgCl_2^{\bullet-} + CH_3C(O)CH_2CH_3} \\ &\rightarrow \mathrm{[Cl_2MgOC(CH_3)CH_2CH_3]^{\bullet-}} \quad \Delta H = -27.6\ \mathrm{kcal\,mol^{-1}} \end{aligned} \tag{3a}$$

$$\rightarrow \mathrm{[Cl_2MgOC(CH_3)CH_2]^{-} + CH_3^{\bullet}} \quad \Delta H = -8.4\ \mathrm{kcal\,mol^{-1}} \tag{3b}$$

DFT calculations support the formation and subsequent fragmentation of the coordinated ketyl radical anion and are consistent with the reactions being observed under the near-thermal ion–molecule conditions of the QIT.[10] Thus the formation of both ionic products [Eqs. (3a) and (3b)] is predicted to be exothermic, and the energy for the transition state associated with the methyl radical loss pathway [Eq. (3b)] lies below that of the separated reactants. The radical anion adduct possesses a magnesium center which is three-coordinate (Figure 2c) and a SOMO which is no longer metal-based (Figure 2d). Selected bond lengths shown in the structures in Figure 2 are also consistent with the radical reactions observed. Thus, the C–O bond lengthens from 1.22 Å in butanone (Figure 2h) to 1.34 and 1.32 Å in the adduct and enolate, respectively (Figure 2c,g), consistent with the loss of C=O character. The C–C bond length undergoes little change from butanone (1.52 Å in Figure 2h) to the adduct (1.51 Å in Figure 2c), but drops significantly in the enolate (1.36 Å in Figure 2g), consistent with C=C bond formation in the final product [Eq. (3b)]. These bond length changes are also evident in the enolization transition state (Figure 2e), which possesses the correct imaginary frequency (Figure 2f).

The results presented herein are important since: 1) the Gomberg–Bachmann magnesium ketyl has been directly observed in the gas phase for the first time; 2) the outlined strategy represents a new way of forming gas-phase distonic-ate anions, which is complementary to Squires' method;[13] 3) the facile reactions of $\mathrm{MgCl_2^{\bullet-}}$ with carbonyl compounds accompanied by diagnostic radical-driven fragmentation reactions of the resultant coordinated ketyl radical anions suggest potential roles for $\mathrm{MgCl_2^{\bullet-}}$ as a reagent anion in analytical and bioanalytical mass spectrometry.[18,19]

Experimental Section

Mass spectrometry: All experiments were carried out using a Finnigan LCQ quadrupole ion-trap mass spectrometer equipped with electrospray ionization. The instrument has been modified to allow for ion–molecule reactions as described previously.[11] All reagents were used as received. Magnesium chloride and phenylacetic acid were dissolved in methanol in a 1:2 molar ratio, with typical concentrations of 0.2–1.0 mM. These solutions were pumped via a syringe into the electrospray source at a rate of 5 μL min^{-1}. Typical electrospray source conditions involved needle potentials of 3.5–4.5 kV. The heated-capillary temperature was ca. 160–180 °C. Extensive tuning of the electrospray conditions for signal optimization was often required due to low signal-to-noise ratio and/or low abundance of some species. Mass selection and collision-induced dissociation were carried out using standard isolation and excitation procedures within the "advanced scan" function of the LCQ software. The magnesium and chlorine isotope patterns (^{24}Mg 78.99 %, ^{25}Mg 10 %, and ^{26}Mg 11.01 %; ^{35}Cl 75.77 %, ^{37}Cl 24.23 %) were used to identify magnesium/chlorine containing species.

Calculations: DFT calculations were carried out at the B3LYP/6-31+G(d) level of theory[12a–c] using the Gaussian03 program.[12d] Species were characterized by frequency calculations, and zero-point energies were scaled by 0.9806[12e] for use in all thermochemical calculations. Structures and SOMOs of the radicals were visualized using Gaussview.[12f] Full data (Cartesian coordinates and energies) are given in the Supporting Information.

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[16] Due to the low mass cut-off of the LCQ spectrometer, Cl^- cannot be observed.

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