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Reaction of Iodoform and Isopropyl Grignard Reagent Revisited

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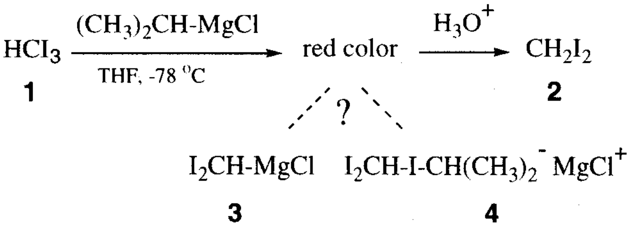
A new long-lived intermediate has been identified in the reaction of iodoform (**1**) with isopropylmagnesium chloride at −78 °C. The structure of the symmetrical iodine ate complex **7**, $I_2CH-I-CHI_2^-MgCl^+$, has been assigned to the deep red intermediate by NMR spectroscopic techniques, supported by calculations of $^1J_{C-H}$, $^2J_{C-C}$, and $^3J_{C-H}$ coupling constants.

Introduction

In 1973 Seyferth briefly described[1] the halogen/magnesium exchange reaction[2] between iodoform and isopropylmagnesium chloride. He noted the formation of an intense red color, which he ascribed to diiodomethylmagnesium chloride (**3**), because on protonation the red color disappeared and diiodomethane (**2**) was formed (Scheme 1).

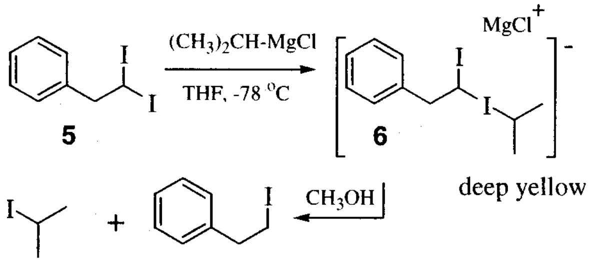
Scheme 1



We recently reported[3] that on reaction at −78 °C of the diiodoalkane **5** with isopropylmagnesium chloride the solution acquires an intense yellow color. Several lines of evidence suggested that the yellow color was caused by the iodine ate complex **6**, which has a half-life of up to 30 min at −78 °C in THF (Scheme 2).

This led us to speculate that the red color observed by Seyferth might have been caused by the iodine ate complex **4**,[4] rather than by the Grignard species **3**. We therefore reinvestigated the reaction between iodoform and isopropylmagnesium chloride to elucidate the nature of the intermediate which is responsible for the red color. Evidence is presented here which suggests that the red intermediate is neither the Grignard reagent **3** nor the ate complex **4** but a different ate complex, $I_2CH-I-CHI_2-MgCl^+$ (**7**).

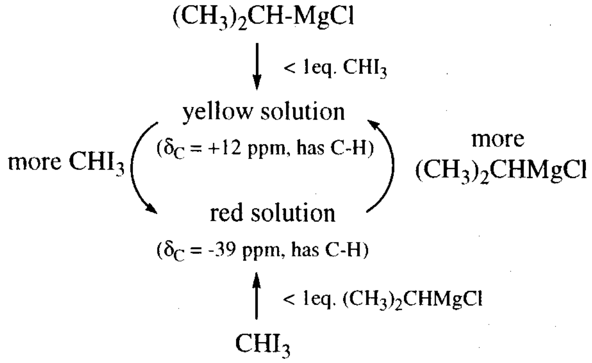
Scheme 2



Results and Discussion

Repetition of the experiments described by Seyferth showed them to be more complex in that sometimes the deep red color was observed and sometimes yellow solutions resulted. Eventually the following pattern emerged: when less than 1 equiv of iodoform was added to the Grignard reagent at −78 °C in THF, a yellow solution resulted. Further addition of iodoform caused the red color to appear. Likewise, if less than 1 equiv of Grignard was added to iodoform, the initially yellow solution turned red in less than 1 min. The color reverted to yellow upon addition of further Grignard reagent (Scheme 3).

Scheme 3



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† Fachbereich Chemie der Philipps Universität Marburg.
‡ University of Auckland.
§ Slovak Academy of Sciences.

[1] Seyferth, D.; Lambert, R. L., Jr. *J. Organomet. Chem* **1973**, *54*, 123−130.

[2] Villiéras, J. *Organomet. Chem. Rev. A* **1971**, *7*, 81−94.

[3] Schulze, V.; Brönstrup, M.; Böhm, V. P. W.; Schwerdtfeger, P.; Schimeczek, M.; Hoffmann, R. W. *Angew. Chem.* **1998**, *110*, 869−871; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 824−826.

[4] Iodine ate complexes as 10-X-2 species have been postulated as intermediates in iodine−metal exchange reactions,[5] evidence regarding their formation has been accrued,[6] and calculations supporting their stability have been reported.[7,8]

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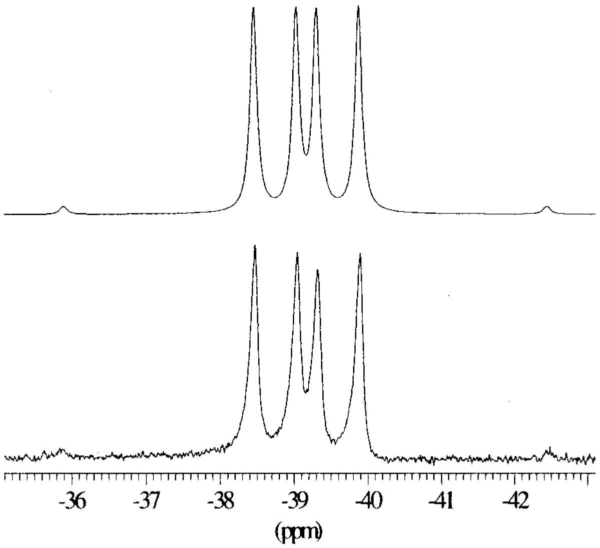
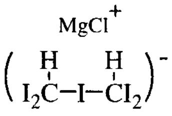


Figure 1. Gated decoupled ^{13}C NMR signals of **7**: (top) simulated with the coupling constants given in the text; (bottom) experimental spectrum.

To gain more insight into the nature of the species involved, the reaction was repeated with ^{13}C-labeled iodoform and the reaction mixtures were analyzed by ^{13}C NMR spectroscopy. This showed that in the yellow solution a species is present with δ_C 12 ppm, whereas the red solution is characterized by the presence of a species with δ_C −39 ppm. Depending on the preparation of the sample, both species may coexist; a red color dominates when the δ_C −39 ppm species is present. An "attached proton test"[9] showed that both species have a single hydrogen atom attached to the carbon atom. The key to the nature of the δ −39 ppm species came from a "gated decoupling" experiment. The δ −39 ppm signal appeared as a higher order multiplet (cf. Figure 1) of the AA′XX′ type. The splitting pattern could be simulated with the coupling constants $J_{AA'} = 315.9$ Hz, $J_{AX} = 138.7$ Hz, $J_{AX'} = 4.4$ Hz, and $J_{XX'} < 1$ Hz (Chart 1).

Chart 1



$$\mathrm{MgCl}^{+}\ \left(\mathrm{I_2\overset{H}{C}{-}I{-}\overset{H}{C}I_2}\right)^{-}$$

7

Coupling constants (Hz):

Observed:	Calculated (ab initio):
$^1J_{C\text{-}H} = 138.7$	$^1J_{C\text{-}H} = 121$
$^2J_{C\text{-}C} = 315.9$	$^2J_{C\text{-}C} = 433$
$^3J_{C\text{-}H} = 4.4$	$^3J_{C\text{-}H} = 12$
$^4J_{H\text{-}H} = < 1$	$^4J_{H\text{-}H} = < 1$

Thus, the δ −39 ppm species is a symmetrical molecule which has two I_2CH groups, in which each proton is coupled to a carbon atom across the symmetry element (plane or axis). This led us to postulate that the δ −39 ppm species is the symmetrical iodine ate complex **7**.[10] This assignment would require, however, that a $^2J_{C-C}$ coupling constant across iodine could be as large as 316 Hz and that a three-bond coupling across iodine could give rise to a $^3J_{C-H}$ coupling constant as large as 4.4 Hz. There is precedent for such coupling across copper or zinc showing $^2J_{C-C}$ values around 15−20 Hz and $^3J_{C-H}$ constants around 1 Hz.[12] The lack of better models for **7** induced us to estimate the magnitude of the relevant coupling constants and also of the ^{13}C chemical shift by ab initio calculations.

To this end, geometries for a series of iodine-containing compounds were calculated at the B3LYP level of theory. Frequency analyses were carried out in order to show that all structures are minima. Excited-state calculations were carried out using the CIS, CASSCF, CASMP2, and TDB3LYP methods at the optimized geometries. Gaussian 98 was used for all calculations. The geometries attained were then used to calculate the ^{13}C NMR chemical shifts using the SOS-DFT approach of Malkin and Malkina.[13] The basis sets used are as follows: C, (12s7p2d) → (7s6p2d) derived from Ahlrich's TZB;[14] H, (10s2p) → (8s2p); Mg, (11s6p1d) → (7s4p1d); I, scalar relativistic Stuttgart pseudo-potential with valence (8s8p3d) → (7s7p3t) set.[15] The CAS space was selected from the list of the most important configurations obtained in the CIS procedure. For molecules with more than two iodine atoms CRSMP2 calculations were not carried out, due to the fact that the selection of configurations for the correlated treatment was not sufficient in Gaussian. The results of the chemical shift calculations are compiled in Table 1.

Table 1. Calculated and Experimental ^{13}C NMR Chemical Shifts (in ppm relative to Me_4Si) for Polyiodinated Alkanes

	δ_C	
compd	calcd	exptl
CH_4	−12.6	−2[a]
CH_3I	−40.4	−21[b]
CH_2I_2	−70.5	−62[b]
CHI_3	−135.6	−147[b]
CI_4	−275	−292[b]
CH_3CHI_2	−36.4	−39[c]
$I_2CHICHI_2$ (**7**)	−15.6	−39[d]

[a] In $CDCl_3$.[16] [b] In THF.[17] [c] In $CDCl_3$.[18] [d] This work.

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(5) Wittig, G.; Schöllkopf, U. *Tetrahedron* **1958**, *3*, 91−93.

(6) (a) Reich, H. J.; Phillips, N. H.; Reich, I. L. *J. Am. Chem. Soc.* **1985**, *107*, 4101−4103. (b) Farnham, W. B.; Calabrese, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2449−2451. (c) Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1989**, *111*, 3444−3445. (d) Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 1414−1416. (e) Reich, H. J.; Sanders, A. W.; Sikorski, W. H. *Abstracts of Papers*, 219th Annual Meeting of the American Chemical Society; American Chemical Society: Washington, DC, 2000; ORGN 20.

(7) (a) Cioslowski, J.; Piskorz, P.; Schimeczek, M.; Boche, G. *J. Am. Chem. Soc.* **1998**, *120*, 2612−2615. (b) Boche, G.; Schimeczek, M.; Cioslowski, J.; Piskorz, P. *Eur. J. Org. Chem.* **1998**, 1851−1860.

(8) Wiberg, K.; Sklenak, S.; Bailey, W. F. *J. Org. Chem.* **2000**, *65*, 2014−2021.

(9) Patt, S. L.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535−539.

(10) A related species, $F_2CH{-}I{-}CHF_2^-$, has recently been calculated to enjoy substantial stabilization;[8] cf. also the observations reported in ref 11.

(11) (a) Johncock, P. *J. Organomet. Chem.* **1969**, *19*, 257−265. (b) Uno, H.; Okada, S.-I.; Ono, T.; Shiraishi, Y.; Suzuki, H. *J. Org. Chem.* **1992**, *57*, 1504−1513.

(12) (a) Mobley, T. A.; Müller, F.; Berger, S. *J. Am. Chem. Soc.* **1999**, *120*, 1333−1334. (b) Mobley, A. T.; Berger, S. *Angew. Chem.* **1999**, *111*, 3256−3258; *Angew. Chem., Int. Ed.* **1999**, *38*, 3070−3072.

(13) Malkin, V. G.; Malkina, O. L.; Casida, M. E.; Salahub, D. R. *J. Am. Chem. Soc.* **1994**, *116*, 5898−5908.

(14) Schäfer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829−5835.

(15) Bergner, A.; Dolg, M.; Küchle, W.; Stoll, H.; Preuss, H. *Mol. Phys.* **1993**, *80*, 1431−1441.

(16) Gasteiger, J.; Suryanarayana, I. *Magn. Reson. Chem.* **1985**, *23*, 156−157.

(17) Seebach, D.; Siegel, H.; Gabriel, J.; Hässig, R. *Helv. Chim. Acta* **1980**, *63*, 2046−2053.

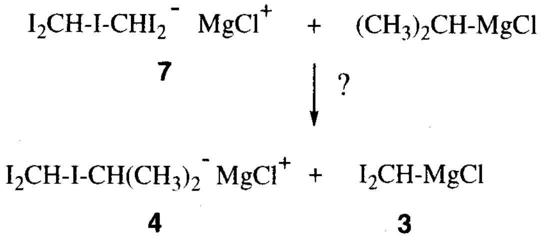
(18) Anson, C. E.; Sheppard, N.; Powell, D. P.; Norton, J. R.; Fischer, W.; Keiter, R. L.; Johnson, B. F. G.; Lewis, J.; Bhattacharrya, A. K.; Knox, S. A. R.; Turner, M. L. *J. Am. Chem. Soc.* **1994**, *116*, 3058−3062.

In the polyiodinated alkanes calculated “for calibration purposes” the agreement between the calculated and experimental chemical shifts is fair. Therefore, the difference between the calculated ^{13}C NMR shift for **7** (−15 ppm) and the experimental value assigned to **7** is not disturbing, given the fact that the role of the magnesium counterion is not taken into account in the calculations.

We then used the calculated geometries to calculate[13] the relevant coupling constants for structure **7** (see Chart 1). The fact that a remarkably large $^2J_{C-C}$ is reproduced in the calculations (433 Hz calculated vs 316 Hz experimental) further supports the structural assignment of **7**. The fair agreement between the experimental and calculated $^3J_{C-H}$ values also adds credence to this assignment.

At this point, the nature of the δ 12 ppm species had not been clarified. Is it the ate complex **4** or the Grignard reagent **3**? We favor the latter assignment because if the δ 12 ppm species were the ate complex **4**, the ^{13}C chemical shift might be expected to be dependent on the nature of the alkyl residue bound on the other side of the bridging iodine atom. However, treatment of the ^{13}C-labeled iodoform with ethyl- or phenylmagnesium chloride invariably showed a δ 12 ppm signal for the resulting yellow solution. Moreover, if the ate complex **4** were the yellow species, it is hard to see how and why it could be formed reversibly from the symmetrical ate complex **7** (Scheme 4) by addition of a Grignard reagent to the red solution. In this case we would expect to observe the generation of two ^{13}C NMR signals, that of **4** *and* that of **3,** but this was not observed.

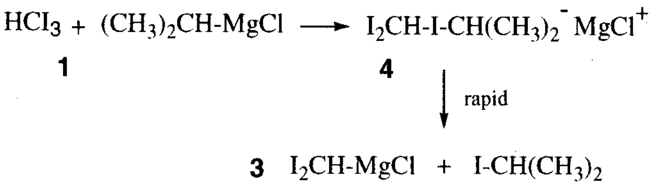
Scheme 4



While these arguments favor the assignment of the δ 12 ppm species as the Grignard compound **3**, this is not a clear-cut case. The chemical shift of **3** might also be expected to depend on whether the diiodomethyl anion is bound to Mg*Cl* or Mg^i*Pr*,[19] but on reaction of ^{13}C-labeled iodoform with diisopropylmagnesium the same chemical shift (12 ppm) was recorded as after reaction with isopropylmagnesium *chloride.*

Nevertheless, the ate complex **4** is a plausible intermediate in the conversion of iodoform into the Grignard reagent **3** (Scheme 5). If we do not observe any ^{13}C NMR signals that can be assigned to **4** (its chemical shift could be guessed to lie between 0 and −20 ppm[21]), it means that the stationary concentration of **4** remains too low, due to rapid transformation of **4** into **3** under the conditions applied.

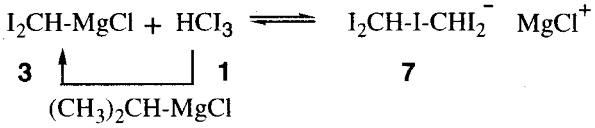
Scheme 5



This is not unreasonable, since we previously observed that the lifetime of the related iodine ate complex **6** depends strongly on the presence of excess Grignard reagent. The lifetime of **6** may become as low as seconds at −78 °C in the presence of excess Grignard reagent. Since in the present case the yellow color, i.e., the δ 12 ppm species, is only seen when there is an excess of the Grignard reagent, we deem it unlikely to be the ate complex **4**. We take all these arguments together to mean that the yellow species with δ +12 ppm is the Grignard reagent **3** and not the ate complex **4**.

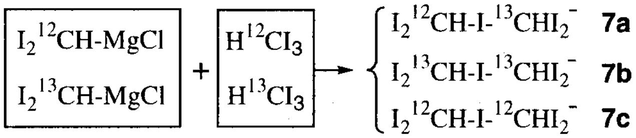
It is easy to postulate that the (diiodomethyl)magnesium reagent **3** associates with further iodoform to give the symmetrical ate complex **7** (Scheme 6). The formation constant must be <10, since the NMR signal of **3** (δ 12 ppm) is still observed with low intensity when free iodoform (δ −146 ppm) is present. Addition of Grignard reagent to the red solution of **7** should therefore trap the iodoform out of the equilibrium and transform it into **3**.

Scheme 6



The equilibration between the iodine ate complex **7** and its constituents is, however, a slow process, at least on the NMR time scale; otherwise, no AA′XX′ splitting pattern could result. This conclusion was further supported by an experiment in which a 1:1 mixture of H^{12}CI$_3$ and H^{13}CI$_3$ was treated with isopropyl Grignard reagent, giving rise to a mixture of the isotopically distinct ate complexes **7a**−**c** (Scheme 7).

Scheme 7



Of these, **7c** is ^{13}C NMR silent. **7a** should show a doublet and **7b** the higher order multiplet of Figure 1 in the ^{13}C NMR spectrum. We observe an overlay of a doublet and of the multiplet at −60 °C. If there were a rapid equilibration of these species, only a doublet would have been observed.

Let us reiterate the experimental facts: On reaction of isopropylmagnesium chloride with less than 1 equiv of iodoform a yellow solution results that displays the δ 12 ppm signal of **3**. When further iodoform is added, a red solution and a species with δ −39 ppm, **7**, arises.

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(19) Such a behavior has been noted with various (1-iodo-2-phenylethyl)magnesium species.[20]

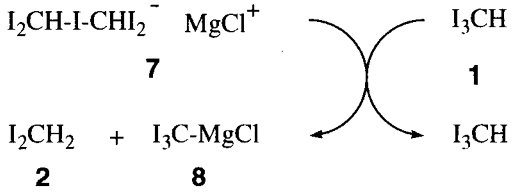
(20) Schulze, V.; Löwe, R.; Fau, S.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1998**, 463−465 and references quoted therein.

(21) The trend in the chemical shifts of PhCH$_2$CHI$_2$ (−23 ppm), PhCH$_2$CH(I)ICH(CH$_3$)$_2^-$MgCl$^+$ (33 ppm), and PhCH$_2$CH(I)MgX (41−48 ppm) can be taken to interpolate the value for **4** between that of CHI$_3$ (−146 ppm) and I$_2$CHMgX (**3**, +12 ppm).

When overall ca. 1.5 equiv of iodoform is added, its signal can be recorded at δ −146 ppm. In addition, we noted the formation of some diiodomethane with δ −63 ppm.

The formation of the diiodomethane was initially attributed to the presence of moisture, realizing that even crystallized iodoform tenaciously holds water, which may be seen by NMR spectroscopy after dissolution of the crystals. Reaction of scrupulously dried iodoform with isopropylmagnesium chloride led to solutions in which the CH_2I_2 signal at δ −63 ppm was initially very small. We noted, however, that this signal increased in intensity, typically by maintaining the THF solution at −50 °C, at the expense of the slowly decreasing signal at −39 ppm. It therefore appears that the symmetrical ate complex **7** is decomposing to give diiodomethane **2** (Scheme 8). The easiest way to account for this is to invoke a reaction in which iodoform serves as a proton source to protonate the ate complex **7** and thus takes the role of a catalyst for the decomposition of the ate complex.

Scheme 8



Rapid reaction with protons is one of the characteristic features we have noted for the ate complex **6**. It is conceivable that the C−H acidity of iodoform might be high enough to allow the protonation of **7** to proceed. In an alternate scenario, iodoform might protonate the (diiodomethyl)magnesium chloride, **3** being in equilibrium with the ate complex **7**. In either case, (triiodomethyl)magnesium chloride (**8**) should be the coproduct. We noted in some experiments that a broad and weak signal at δ −133 ppm arose concomitant with the formation of the diiodomethane signal at δ −63 ppm. The species responsible for this signal has only limited thermal stability, as its signal decays rapidly when the solution is warmed above −65 °C. At present, the assignment of the δ −133 ppm signal to **8** is tentative. The position of this signal is 13 ppm downfield from that of iodoform, corresponding to a small carbenoid downfield shift.[20] This appears not unreasonable in the absence of good reference data.

Conclusion

The present study has shown that Seyferth's reaction of isopropyl Grignard with iodoform proceeds to generate the Grignard species **3** while the ate complex **4** is not detected. Further addition of iodoform converts **3** into the symmetrical ate complex **7**, the red species observed by Seyferth. The latter species is transformed slowly (probably under catalysis by iodoform) to diiodomethane and (triiodomethyl)magnesium chloride.

Experimental Section

Iodoform-^{13}C. Aqueous sodium hydroxide (50%, 4.2 mL) was added at room temperature to a solution of acetophenone-*methyl*-^{13}C (500 mg, 4.13 mmol) in water (21 mL). An aqueous solution of iodine (10%) and potassium iodide (20%) (85 mL) was added dropwise until the color of iodine persisted. The resulting yellow precipitate was filtered, washed with water (5 mL), and recrystallized (methanol) to give 1.26 g (77%) of microcrystalline yellow iodoform-^{13}C with mp 120 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 4.87 (d, J_{HC} = 187.1 Hz, 1 H). ^{13}C NMR (100 MHz, THF-d_8): δ 146.

Typical Experiment. An NMR tube was heated under vacuum and allowed to cool under argon twice. After a septum was fitted, isopropylmagnesium chloride in THF-d_8 (165 μL, 97.4 μmol) was added, followed by THF-d_8 (350 μL). The NMR tube was kept under argon pressure via a needle through the septum and cooled to −98 °C. A solution of iodoform-^{13}C (63 mg, 160 μmol) in THF-d_8 (150 μL) was slowly added to the cold Grignard solution along the wall of the NMR tube. The NMR tube was removed from the cooling bath and inverted once to ensure complete mixture. The NMR tube was kept in the cooling bath until it was transferred (<15 s) to the NMR spectrometer, the probe of which was precooled to −90 °C. NMR spectra were taken at temperatures between −90 and −70 °C. The red species decomposes rapidly at temperatures above −65 °C.

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