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Brief communication

On the mechanism of a new dihalocyclopropane-dihalomethyl vinyl rearrangement

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Abstract. A tentative mechanism for a new dihalocyclopropane-dihalomethyl vinyl rearrangement is discussed following some isotopic labelling and substituted cyclohexene studies on fused cyclohexene-cyclopropane (norcarane) compounds.

1. Introduction

In our continued studies of unusual rearrangements of some *gem*-dihalocyclopropanes, we have reported on the synthesis of the dihalomethyl vinylic compounds of the Hiyama-type reaction for the dihalocyclopropane precursor [1]. The Hiyama reagent Cr^{+2} is formed *in situ* by reduction of Cr^{+3} in DMF with $LiAlH_4$, and is typically used to perform the allene synthesis from some specific exocyclic double bonds [2–4]. The combined action of the Lewis acid and the red–ox conditions of this reaction were studied for a limited number of substrates, and a rearrangement toward the dihalomethylvinyl was observed in some cases. Some allene derivatives and reduced allene products were also reported, as were rearranged homo-Makosza products [5–7]. In the polyene system, the exo and endo double bonds present on the same cyclic molecule reacted differently, but in the expected directions. However, the mechanism of the reaction was not elucidated (Scheme 1).

Because of the significant biological impact of carbenes as precursors to cyclopropanes, to cyclopropane intermediates, and to allenes and activated cyclopropanes, we would like to report on some additional experiments that we performed to further clarify the mechanism of this interesting reaction.

The formation of the dihalomethylvinyl by-product in this reaction was rigorously proven by its hydrolysis to the corresponding aldehyde or acid. Usually the *gem*-dihydroxy intermediate is involved in

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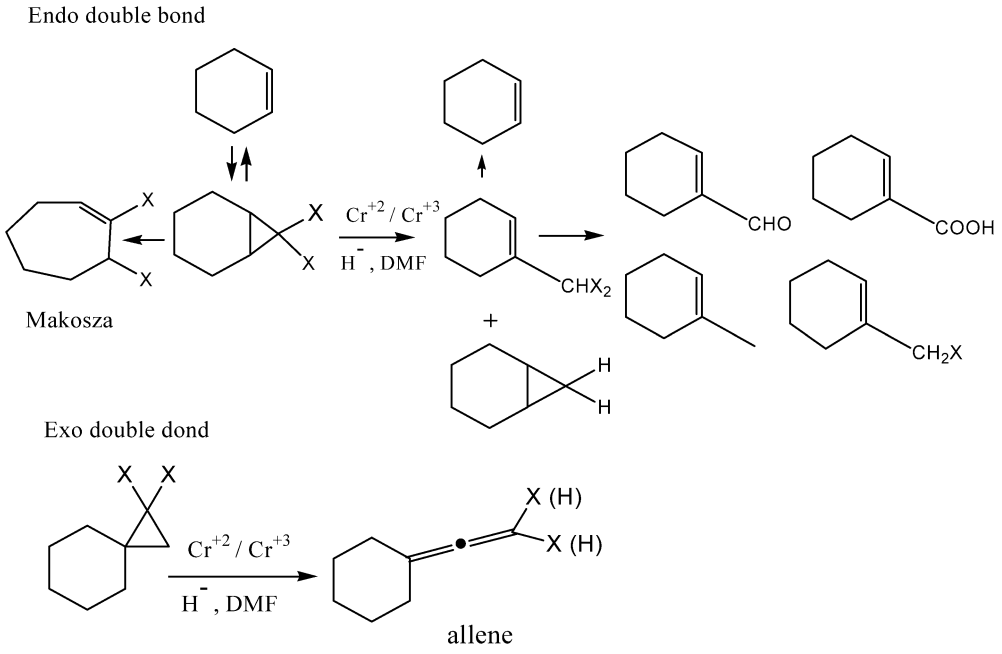


Scheme 1.

such a reaction, and its dehydration, and the subsequent oxidation of the resulting aldehyde group, leads to the unsaturated carboxylic acid. Our interest in this rearrangement reaction is whether it is ionic or radical, and if it is ionic, to specify the nature of the ionic intermediate.

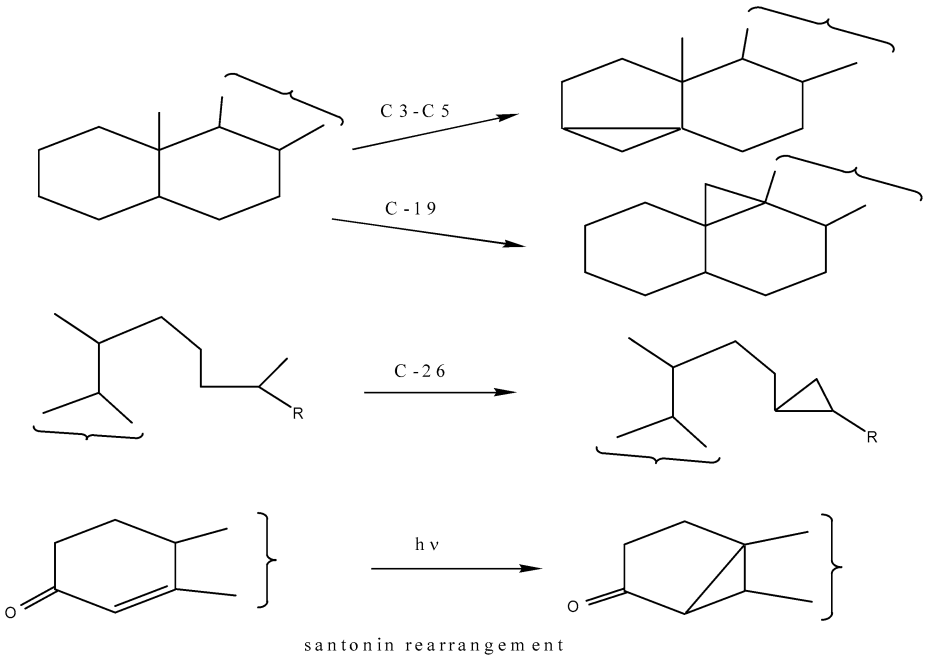
To this end, we studied the mechanism of the rearrangement of the *gem*-dihalocyclopropane cyclohexane 7,7-dichloro-bicyclo(4,1,0)heptane (7,7-dichloronorcarane) into 1-(dichloromethyl)-cyclohexene. This was done using a series of compounds in which each was a dihalocyclopropane fused to the cyclohexene substituted on the double bond with one or two substituents. Different Lewis acids were also tested, including those which have two neighboured oxidation states and those which do not.

Finally, we chose to study the mechanism using a more formal approach, consisting of isotopic labelling experiments in which the hydride was replaced by the deuteride and, during the post-reaction work-up, heavy water was added to deuterate the intermediate.

2. Biological importance of reaction of activated cyclopropanes

Several cyclopropane-containing natural products have been isolated, most of them from plants [8]. Although this strained-ring system has often been suggested to form part of a complex metabolic pathway, its role and reactivity are poorly known and insufficiently studied [9]. Among other things, its degradation and rearrangement remain a constant source of inspiration for the design of new drugs, by far surpassing (for instance) the use of the methylene cyclopropane carbon as a source of methyl in biological transformations [10] (Scheme 2).

Spontaneous and forced cleavages and rearrangements of the cyclopropane ring are an even more important question in the field of biologically-important products, because of the presence of an extensive family of *gem*-dihalocyclopropane derivatives currently available from the addition of carbenes to the double bonds and their hydrolysis to cyclopropanones.



Scheme 2. Some selected cyclopropanation in steroidal field (C3–C5, C-19, C-26, photochemical).

The direct result of this addition, the dihalocyclopropane ring, is much more susceptible to chemically-induced modifications, proceeding generally through carbocationic or radical mechanisms, internal nucleophilic substitution (often metal-assisted), and photochemical or microwave-assisted transformations [11–23]. As a result, a new class of biological products, metabolites, and intermediates has been created. The *gem*-dihalo group is an evident source of carbonyl via a hydrolytic pathway, and the *gem*-dihalo strained cyclopropane represents an easy target for a variety of elimination reactions, as the system is very reactive.

The biosynthetic implications of the cyclopropane intermediates were recently reviewed by Wessjohann et al. [8]. The cyclopropane opening, in particular, is a source of methyl group on polycyclic compounds such as steroids [11] or modified steroids, e.g.: bridged, seco or i-steroids. For example, the C-18 angular methyl synthesis for [8], the 5,10 seco for [12], and the 4,10-bounded bicyclic ring system for i-C-18 nor-steroids [13] are typical transformations involving cyclopropane in this family of biologically-important compounds. These rings are also present in the transformation of naturally-occurring sugars and sugar derivatives [14], aromatic compounds in the naphthalene series in particular [15], alpha-ketocyclopropane reactions [16], and vinylcyclopropane rearrangements to bicyclic benzocyclopropanes [17], as well as in many other terpenes and terpenoids, where this structure is much more frequently present and much more often involved in rearrangements [2,18]. Finally, in the field of heterocyclic compounds, N-, O-, S-, and P-containing rings (both aromatic and alicyclic) were obtained as a result of cyclopropane or dihalocyclopropane products [8,19].

In view of the importance of a better understanding of cyclopropane and activated cyclopropane reactions, we undertook a systematic study of the rearrangement of dihalocyclopropane, so as to be able to identify if the character of the reaction is ionic or radical (and whether biradical or mixed radical-ion species are present). Then, for the ionic pathway, the carbocationic or the carbanionic nature of the intermediates involved, was studied, followed by the role of Lewis acids, which are usually used in the

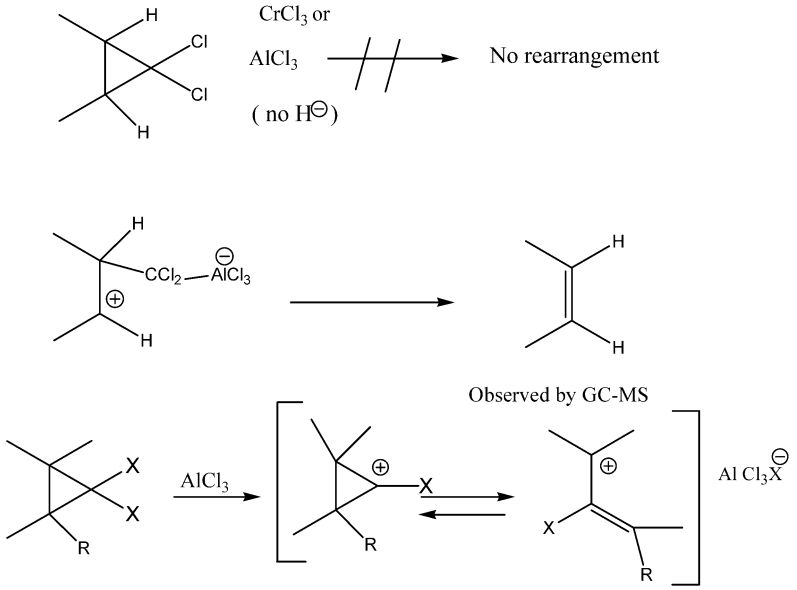
metal-assisted reaction, and the red–ox character of the rearrangement if a two-oxidation-state Lewis acid is involved.

3. Lewis acid influence on the rearrangement

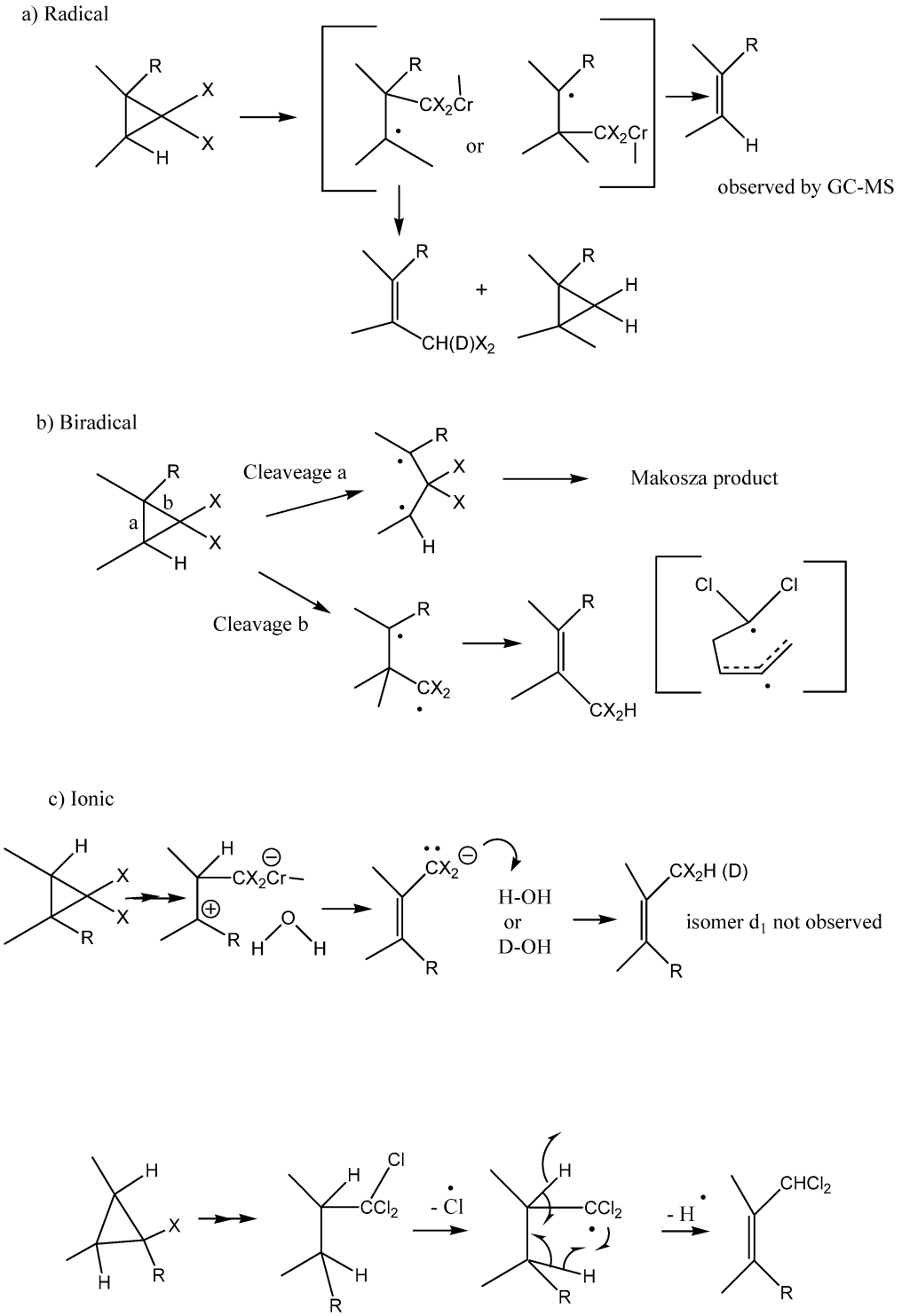
The Cr^{+2} used in this reaction was obtained directly from a commercial source (for example, Aldrich), or formed *in situ* (from Cr^{+3}/H^{-}). The rearrangement product is observed only in the latter case. The presence of the complete two cationic species seems to be necessary to perform this reaction. The use of Cr^{+3} alone, however, does not lead to any rearrangement. The same reaction in the presence of $AlCl_3$ (anh.) or B_2F_6 does not give any rearranged products, not even Makosza-like cyclic compounds (Scheme 3); however, the beginning of olefin formation was observed, and is enhanced by further addition of Lewis acid during the reaction (probably due to the change of solvent polarity from DMF to THF). In all these reactions the dihalocyclopropane is also reduced to cyclopropane (as detected by GC-MS).

The use of samarium or cerium does not lead to any rearranged products; both lead to the formation of the vinylic products used for the preparation of the dihalocyclopropane derivatives. This fact was originally misinterpreted due to the possible presence of the starting vinylic compound in the reaction mixture. The role of the Lewis acid seems to be confirmed as being of dual nature – in its lower oxidation state (for example, Cr^{+2}), it is involved in the red–ox and is implicated in the chromo-organic compound, and in the higher oxidation state (for example, Cr^{+3}), it facilitates the rearrangement. Both Cr^{+2} and Cr^{+3} are Lewis acids, and either one can satisfy this second requirement and create the vinylic compound (Schemes 3, 4).

We conclude that a two-oxidation-state Lewis-acid reagent is necessary to perform the rearrangement reaction, in order to obtain either the allene Hiyama analogue or the dihalomethyl vinyl compound.



Scheme 3.



Scheme 4. Two step radical elimination of HCl from CCl_3 adduct.

The concurrent Lewis-acid-assisted pathway (Scheme 3) leads to the stable alpha halovinyl cation [20–23], for which, however, the formation of specific addition or hydrolysis products was not observed. As already mentioned, the presence of the hydride anion is necessary to maintain the Cr^{+2} formation. This supports an appealing alternative explanation, such as the further reduction of the dihalomethylvinyl obtained, but does not explain the numerous other products observed. However, the hydrolysis of the intermediate cation should lead to the carbonyl group formation. This does not explain the formation of any monohalogenated products, except those coming from the reduction with the hydride, as successfully proven by the isotopic labelling experiments.

If the quantity of hydride is reduced, the yield of the reaction decreases. The efficient production of the dihalomethylvinyl derivative then depends on the presence of Cr^{+2} ion. The increase in the quantity of hydride, conversely, strongly favours the formation of fully-dehalogenated fused cyclopropane–cyclohexane, instead of any rearranged products.

4. Radical or ionic mechanism of rearrangement?

Two distinct mechanistic pathways could lead to the formation of dihalomethyl vinyls from the starting dihalocyclopropane compounds (Schemes 3, 4). The first follows a carbocationic pathway (Schemes 3, 4), and can involve a dihalocarbanion formed prior to the hydrolysis of the resulting organometallic ion. When the work-up is performed at the end of the reaction with D_2O instead of with H_2O, not even traces of deuteration of the dihalomethyl species were observed for the 7,7-dichloronorcarane series of experiments with a complete Hiyama-reagent system. This isotopic labelling experiment indicated that the carbanionic hypothesis of the intermediate should be discarded.

Metallo-carbocationic species could be easily observed in the series of reactions involving chromium ions, and were often postulated as intermediates [24,25]. The presence of radicals (Scheme 4a), however, should be considered of equal probability, following the reaction conditions and the nature of the compounds involved. The radical pathway of this mechanism was not confirmed when the reaction was performed with, for example, trans-2-butene, a common quencher for radicals: the addition of the radical to the vinyl bond of the quencher was not detected. However, the one-electron rearrangement mechanism involving a Cr-organic intermediate should be privileged (as suggested by Wang [25]).

From the ionic perspective, the Lewis-acid-assisted reaction should follow the carbocation stability rule. In principle, if the tertiary carbocation is formed from the rearrangement of the dihalocyclopropane, it should be privileged over the secondary structure: for example, the rearrangements of limonene to bicyclo(3,1,0)hexene and to carene both proceed this way. The intermediate homoconjugated double bond or homoallyl closure is responsible for this rearrangement [2,20]. The second important question is the carbanionic species assisted by the presence of metal. Under aerobic conditions as mild as atmospheric oxygen, the Cr^{+2} necessary to the formation of the carbanionic intermediate can be further oxidized, leading to the formation of an organometallic radical; this would favour the cyclopropane formation rather than its rearrangement [21].

In the same pathway, the stable carbocation should also help any nucleophilic agent to form the halogenated double bond necessary for the rearrangement [22]. In our search for a reaction reasonably close to our proposed mechanism (for instance, the photochemical transformation of the *gem*-dihalocyclopropane), one should consider the biradical-dipole ion (Scheme 4b), an intermediate in which, after the demotion of the biradical structure (intersystem crossing T-S), the dipole ion leads the rearrangement of the dihalocyclopropane to the vinylic compound.

The most plausible reaction mechanism consistent with our findings was, however, the one observed from the deconjugated vinylcyclopropane cyclohexanes [23]. In this case, the biradical structure (Scheme 4b in one step or two steps) either

– cleaves the C-C bond of cyclopropane as by the Makosza pathway, or
– cleaves one of two C-CX_2 bonds, leading to our rearrangement compound.

A hydrogen radical shift from the activated dihalobiradical to either the isomeric cyclopropane carbon methane or methylene is, however, necessary to produce the vinyl dihalomethyl rearrangement. It seems that this pathway is also followed by the formation of the vinyl conjugated dihalocyclopropane, and finally gives the dihalocyclopentene derivatives.

5. Study of substituted cyclohexenes

The rearrangement of 7,7-dihalonorcarane toward the 1-dihalomethyl cyclohexene takes place with a relatively modest yield of 25%. Following the same reaction on closely-related alkylated derivatives, such as 1-alkyl-7,7-dihalonorcaranes and 1,2-dialkyl-7,7-dihalonorcaranes, we observed (with GC-MS monitoring) that, for the first one, the main reaction product was the 1-alkylcyclohexene together with the rearranged product. The yield of this product was, however, smaller (Scheme 3). This result could be related to the stability of the radical intermediate and the facile elimination of the dihaloorganochromium leaving group, followed by the hydrogen shift, consistent with the relative stability of these two intermediates.

The same reaction performed in the presence of sodium borodeuteride, instead of the lithium aluminium hydride, does not produce any increase in the yield of deuterated dihalomethyl radical, which means that neither the hydride nor the deuteride ion interferes with the formation of the double bond. The reduction of the dihalochromoethyl to the dihalomethyl therefore takes place subsequent to the double bond formation, by the elimination of the ring hydrogen (as hydride).

The difference in the nature of the leaving groups involved directs the formation of the double bond toward the rearrangement. To achieve that, it is necessary to have a minimum of one vinylic hydrogen available.

6. Isotopic labelling essays

When studying the rearrangement mechanism, it was important to perform the reaction with different sources of labelling agents, in order to observe the specific labellings. When $LiAlD_4$ was used instead of $LiAlH_4$ to induce the formation of Cr^{+2}, it was impossible to observe the same level of H-migration necessary to the dihalomethyl formation from various carbocations. We tried DMF-d_7 as a solvent; however, that did not play any role in the reaction, especially because it was replaced by THF in the procedure. Finally, D_2O was used as a potential source of D^+, to mark any carbanionic intermediate which might be formed.

We did not observe any labelling, in any of the cases. The rearranged product, when treated with $LiAlD_4$ in a separate reaction, exchanges the halogen against D to form the monohalogenated species, and finally reduces the second halogen to the dideuterated product (Scheme 4c).

In order to test that limitation and further clarify the scope of this rearrangement reaction, the dialkylated norcarene [26] was subjected to several different reaction conditions. These reactions did not produce any rearrangement, and instead led to an elimination, restoring the double bond. These results were monitored by GC-MS. This means that the presence of a minimum of one H on the 7,7-dihalonorcarene skeleton is necessary to produce the rearrangement (exchange with D_2O in this series, when water was applied on the work-up stage, was not observed). This also means that the rearrangement is completed prior to this step.

7. Variable temperature and microwave studies

In order to clarify the possible radical nature of this reaction and further optimize the reaction conditions, several temperatures were tested for their effect on the hydride-induced Cr^{+2} formation in DMF. When the temperature was decreased to between -5 and -10° C, the reaction yield was reduced accordingly. Conversely, when the reaction was performed at higher than room temperature, at $+50^{\circ}$ C in particular, the yield of Makosza-like product was much higher, but no concomitant increase of our new rearranged product was observed. In fact, the higher temperature also led to the decomposition of the dihalocyclopropane derivative and its reduction to the corresponding cyclopropane. In this respect the hydride shift should then be either of radical or ionic nature, but originating from the intramolecular rearrangement. Similar observations on the influence of temperature and of the quantity of base increasing the likelihood of other possible rearrangements, e.g. toward the homo-cyclic products, have already been made for Makosza products [26,27]. The use of microwaves in DMF was not very successful, insofar as the reaction yield is concerned; however, the slow decomposition of the hydride under those conditions was much more pronounced than the formation of unsaturated products only (starting material and partially-reduced halocylopropane formation was observed). We concluded that the best conditions for this reaction were conveniently at room temperature.

8. Conclusion

The mechanism of this new Hiyama-like rearrangement is therefore suggested to be as per Scheme 3. In summary, we propose that the mechanism for this rearrangement proceeds *via* the biradical (or monoradical-metal $R-\dot{C}r-\overset{|}{\underset{|}{C}}-$) intermediates. Most of the structures of the products observed were successfully identified, and support this proposal.

Additional experiments performed in this series seem to indicate that the rearrangement follows the intramolecular H-shift in order to form the dihalomethylvinyl products which, as a next step, allowed us to obtain the intermediary *gem*-diol and then, depending on the hydrolytic conditions, the aldehyde and acid. Further experiments allowing us to unequivocally confirm the mechanism will, however, be costly and will demand several rigorously controlled experiments on 7,7-dichloronorcarene-1,2-d_2. Only such a double deuteration will finally clarify the origin of the H-shift observed in this rearrangement, as well as partially indicate the stereochemistry of the Makosza homo-rearranged product. Preliminary attempts with this substrate clearly showed the need for this, if only the poor isotopic labelling of this compound (as established from NMR and mass spectrometric measurements) is improved [28]. The use of perdeuterated cyclohexane, also costly, is inconclusive because of the many possible migrations of

deuterium. It could be also interesting to further study the two-solvent system and its influence on the rearrangement.

We also established that the hydrogen necessary to form the dihalomethylvinyl *via* the hydride shift should come from the vinylic H, not from the $LiAlH_4$ used to form the Cr^{+2} species. Therefore, it is necessary to have at least one H on the double bond to obtain this new rearrangement.

Finally, in this new red–ox rearrangement, both the presence of two neighbouring Lewis-acid cations and the formation of a less oxidized one are necessary to perform this reaction. The formation of this less oxidized Lewis acid cation can efficiently be done *in situ*. Despite testing several other Lewis acids, only the Cr^{+2}/Cr^{+3} pair produced this rearrangement with a reasonable yield.

Experimental notes

All additional GC-MS experiments described in this Note were performed on Riber 10-30 quadrupole mass spectrometer equipped with BP-1 capillary column (25 m, o 0.3 u). For experimental details see [2]. The dihalocyclopropane condensed to cyclohexane were prepared by phase transfer method as quoted in [1] and [2].

All cyclohexene products used in this study: cyclohexene, 1-methylcyclohexene, 1,2-dimethylcyclohexene and cyclohexene-d_{10} (Aldrich Chemicals), were successfully transformed into the corresponding dichlorocyclopropane derivatives. The cyclohexene-1,2-d_2 was obtained with low 40% deuterium labelling (total yield of 23%) from adipic dialdehyde-1,6-d_2 [28].

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