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Theoretical Investigation of the Mechanism of the Hock rearrangement with InCl_3 as Catalyst

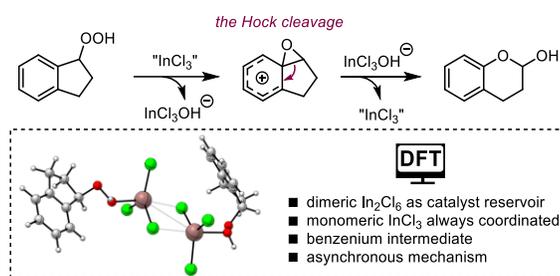
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KEYWORDS. Peroxides, Oxidative cleavage, Rearrangement, Oxacycles, DFT study.



ABSTRACT: The Hock rearrangement is an acid catalyzed reaction involving organic hydroperoxides and resulting in an oxidative cleavage of adjacent C–C bonds. It has significant industrial applications, like the production of phenol (cumene process), but it remains scarcely used in organic synthesis. In addition, its detailed mechanism has never been studied. Thus, we report herein a theoretical study of the Hock rearrangement, using InCl_3 as a Lewis acid catalyst. The aim of this work was to fully understand the mechanism of this fundamental reaction, and to rationalize the influence of the substrate electronic properties on the reaction outcome. Furthermore, the structure of the active indium(III) catalyst interacting with the peroxide substrate was investigated, showing the superiority of a coordinated monomeric form of the Lewis acid as the active catalytic species, compared to dimeric species. However, we show that In_2Cl_6 species coordinated to the substrate are central in this catalytic cycle, serving as a reservoir of active monomeric species.

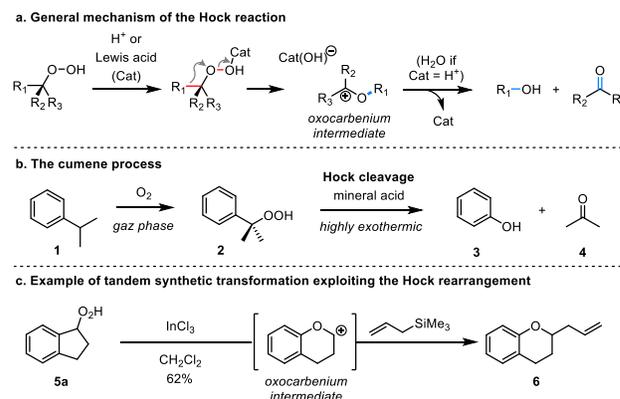
INTRODUCTION

The Hock rearrangement is the acid-catalyzed reaction of an organic hydroperoxide leading to the oxidative cleavage of a C–C bond.¹ This cleavage involves the migration of one of the adjacent carbons onto the closest oxygen of the hydroperoxide, concomitantly to the heterolytic cleavage of the O–O bond. The resulting oxocarbenium species usually reacts with water, leading to hydrolysis and to the straightforward formation of oxygenated products (Scheme 1a).

Since the discovery of the cumene (**1**) process by Hock and Lang,¹ this reaction has played a crucial role in the production of millions of tons of phenol (**3**) and acetone (**4**) from cumene hydroperoxide (**2**) each year (Scheme 1b).² Moreover, this rearrangement has recently been used to produce artemisinin, an antimalarial drug.³ However, harnessing its potential to develop new synthetic transformations remains a real challenge for organic chemists. Indeed, there have only been limited systematic studies on the selectivity

of the Hock cleavage,^{4–6} the effect of substituents,^{7–9} the catalyst scope^{10,11} or synthetic applications.^{12–20}

Scheme 1. The Hock rearrangement of organic hydroperoxides: (a) General mechanism; (b) The cumene process; (c) Example of tandem process exploiting the oxocarbenium intermediate.²¹



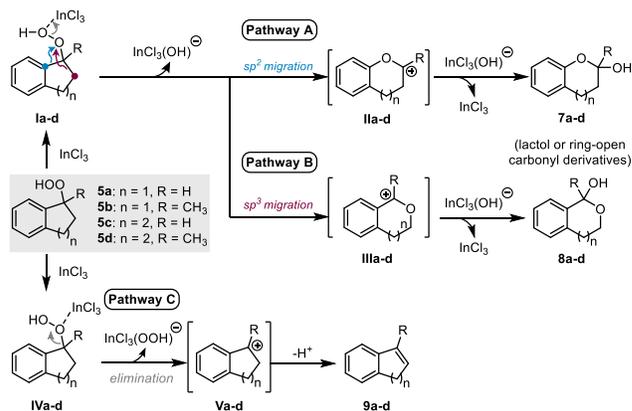
In a joint study, we recently demonstrated the potential of this reaction to synthesize benzoxacycles (e.g. chromane **6**) through tandem processes under InCl_3 catalysis (Scheme 1c).^{21,22} Indeed, by taking advantage of the electrophilic oxocarbenium intermediate generated during the Hock cleavage of indane (e.g. **5a**) or tetralin hydroperoxides, the usual hydrolytic process of the reaction could be bypassed by adding nucleophilic species. This work also established that InCl_3 is a mild and versatile catalyst to promote the Hock cleavage step.

In spite of this potential, unlike the Baeyer-Villiger rearrangement involving Criegee perester intermediates,^{23–29} to the best of our knowledge the Hock reaction has never been theoretically studied. Furthermore, the above-mentioned synthetic work also raises fundamental issues. The relationship between the structure of the hydroperoxide substrate and the efficiency of the reaction remains underinvestigated. The active form of the Lewis acid catalyst InCl_3 is another point of interest, as it can potentially act in a monomeric or dimeric form,^{30–33} or as a cationic InCl_2^+ species,³⁴ which raises the question of its superelectrophilicity.³⁵ Herein, we wish to fill these gaps by reporting the first computational study of the Hock rearrangement at the DFT level. The aim was to fully assess this reaction mechanism and thus provide a clear understanding of the observed reactivity. This study also highlights the role and structure of the Lewis acid catalyst InCl_3 , which has already found numerous applications in organic synthesis.^{30–32,36}

RESULTS AND DISCUSSION

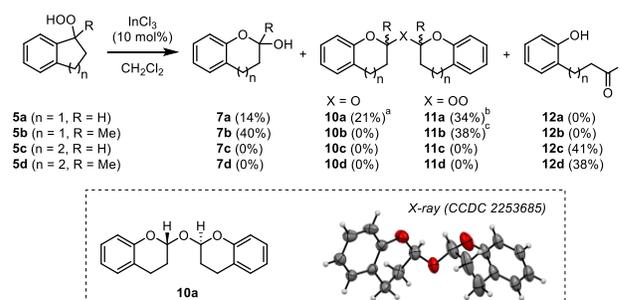
In accordance with our recent synthetic work,³⁷ this theoretical study focuses on the InCl_3 -catalyzed Hock rearrangement of indane (**5a** and **5b**) and tetralin (**5c** and **5d**) hydroperoxides, leading to chromane and benzoxepane products. Experimental observations^{4,37} allow to anticipate several possible reactions from those reactants in presence of a Lewis acid, depending on the coordination site of the catalyst or on the migratory group (Scheme 2). Firstly, during the expected Hock rearrangement from **Ia-d**, two oxocarbenium species could be formed depending on the migration of the sp^2 (giving **IIa-d**, Pathway A) or of the sp^3 carbons (giving **IIIa-d**, Pathway B), respectively resulting in isomeric benzoxacycle derivatives **7a-d** or **8a-d**, the second one being yet never observed in our experiments. Secondly, the elimination of the peroxide group could occur (Pathway C through **IVa-d**), leading to a benzylic carbocation **Va-d** and resulting in alkene **9a-d** upon proton elimination. All these reaction paths have been considered and computationally studied hereafter.

Scheme 2. Anticipation of the outcome of the Hock rearrangement stemming from substrates 5a-d



To complement the previous work,²¹ an experimental study was performed with substrates **5a-d** to assess their reactivity in presence of InCl_3 (Scheme 3). Pathway A shown in Scheme 2, consisting in the migration of the aryl sp^2 carbon, appeared to be predominant for all substrates. Indane peroxides gave lactols **7a/7b**, and dimeric derivatives like 2,2'-oxydichromane **10a** (*anti* isomer, giving suitable crystals for crystallography, Scheme 3) or 2,2'-peroxydichromanes **11a/11b** (presence of two diastereoisomers; structure confirmed by HRMS). These two peroxyacetals indicated the release of hydrogen peroxide during the reaction (Scheme 2, Pathway C). However, indene **9a**, an apolar volatile product, was not identified during the isolation process. Conversely, tetralin peroxides afforded acyclic phenolic derivatives **12c** and **12d** (resulting from transient benzoxepane lactols **7c** and **7d**). Neither the regioisomeric isochromanes or 2-benzoxepanes (**8a-d**) resulting from Pathway B or the elimination products (**9a-d**) from Pathway C were observed during this experiment. In the absence of an additional nucleophile, the reaction mixture was however more complex than that of our previous study,³⁷ probably due to numerous side-reactions occurring on such electrophilic products.

Scheme 3. Experimental study of the Hock rearrangement of indane and tetralin peroxides, and X-ray structure of 10a.



^a Exclusively isolated as the *anti* diastereoisomer. ^b Two separable diastereoisomers in 20 and 14% yields (undifferentiated). ^c Unseparable diastereoisomers in a 2:1 ratio.

Our DFT study started with 1-indanyl hydroperoxide **5a** interacting with a single InCl_3 molecule (Figure 1). At first, the coordination of InCl_3 to the peroxide group provides two potential intermediates, **Ia** and **IVa**, depending on the oxygen involved. Both coordinations are exergonic, respectively by 21.0 and 20.8 kcal/mol. Transition state **TS_{Ia-IVa}**, with an energy barrier of ~ 2.8 kcal/mol, enables easy

interconversion between the two intermediates. We first considered the elimination reaction originating from the coordination of the internal oxygen through intermediate **IVa** (see also Scheme 1, Pathway C). The formation of carbocation **Va** along with $\text{InCl}_3(\text{OOH})^-$ is endergonic by 25.5 kcal/mol. Since the dissociation of $\text{InCl}_3(\text{OOH})^-$ is more difficult than that of InCl_3 , this reaction pathway (C) is therefore disfavoured from **5a**, in agreement with the experimental results.

Alternatively, the coordination of InCl_3 on the external oxygen of **5a** (**1a**) can result in two possible intermediates, **VIa**

through **TS_{Ia-VIa}** (migration of the adjacent aryl sp^2 carbon) or **VIIa** through **TS_{Ia-VIIa}** (migration of the adjacent alkyl sp^3 carbon). Both transition states involve a Hock rearrangement. However, the energy barrier of **TS_{Ia-VIa}** (referred to as ΔG^{Hock} in Figure 1, blue path) is favored by 9.7 kcal/mol compared to **TS_{Ia-VIIa}**, and by 16.7 kcal/mol compared to formation of **Va**. It strongly suggests that only the Hock rearrangement involving the sp^2 carbon can occur, as observed experimentally since the products stemming from **TS_{Ia-VIa}** (**7a**, **10a**, **11a**) were the only one identified (total yield of 69% for the Hock cleavage, Scheme 3).

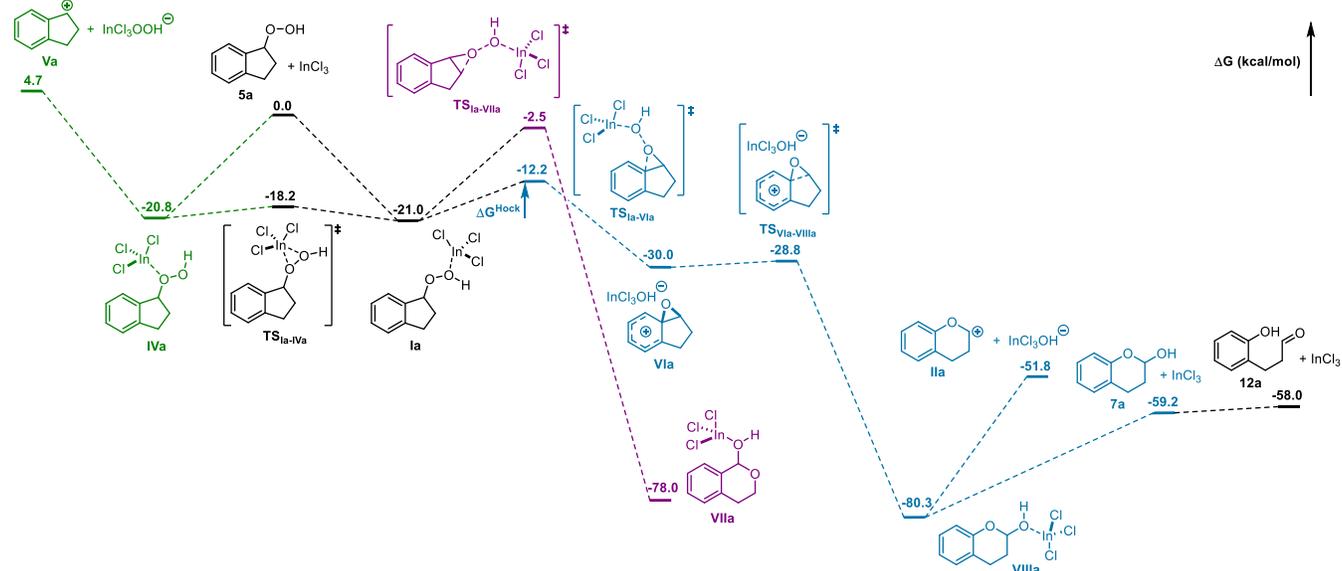


Figure 1. Free-energy profile of the InCl_3 -catalyzed Hock reaction of 1-indanyl hydroperoxide (**5a**) and other possible secondary reactions.

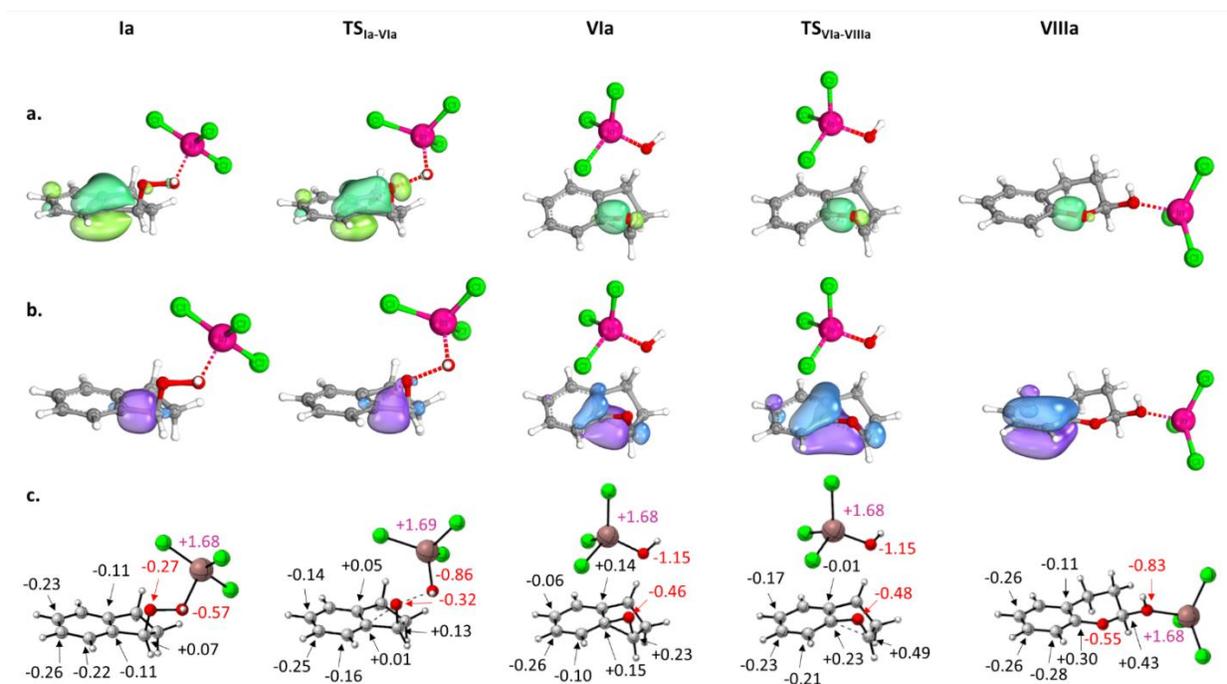


Figure 2. Changes in the electronic structure during the Hock rearrangement. Computation of IBO pathway (a and b) and NBO charges (c) from **Ia** to **VIIa**.

In fact, this transition state (**TS_{Ia-VIa}**) first leads to Wheland intermediate **VIa** (benzenium), which connects to **VIIIa** through **TS_{VIa-VIIIa}**. To shed light on the electronic structure changes along this preferred reaction path, the intrinsic bond orbitals (IBO)³⁸⁻⁴⁰ and the atomic charges in the framework of the natural bond orbital⁴¹ (NBO) analyses were computed (Figure 2). IBO enables to visually follow the orbital relocation during a molecular transformation. It showed that the cleavage occurs with an asynchronous movement of two pairs of electrons. From **Ia** to **VIa**, part of the aryl π cloud is transferred to the closest oxygen of the hydroperoxide (Figure 2a), enabling the formation of the C-O bond and the cleavage of the hydroperoxide O-O bond. From **VIa** to **VIIIa**, the cleavage of the C-C bond is associated with an electronic transfer from this σ -bond back to the aryl group (Figure 2b). Furthermore, NBO analysis underlines the same phenomenon. The charge carried by the benzenium cycle in *ortho* and *para* of the reactive center are less negative in **TS_{Ia-VIa}** and **VIa** than in the coordinated compound **Ia**. For example, the charge carried by the *para* carbon passes from -0.23 to -0.06 e, that is a loss of 0.17 e (Figure 2c). Following **TS_{VIa-VIIIa}**, formation of **VIIIa** enables the carbon atoms of the aromatic cycle to retrieve their original charge. Notably, the charges carried by the carbon atoms in *meta* are the same along the reaction path, which is consistent with the classical mesomeric forms drawing of the pentadienyl cation moiety of **VIa**.⁴² This electron transfer also suggests that the Hock rearrangement is favored by electron-rich aryl rings.

The calculation for *para*-substituted substrates confirmed that π -withdrawing (**5e**, **5f**) and π -donating (**5g**, **5h**) substituents respectively decrease and increase the energy barrier of the Hock rearrangement (ΔG^{Hock}), in good agreement with the electronic density flow analysis during the course of the reaction (Figure 3). Compound **5i**, with a π -donating methoxy group in *ortho*, shows a similar effect as **5h**. In addition, **5j** highlights that the *meta* position has no influence on the barrier of the rearrangement, in good agreement with the above analysis. These results are confirmed by experimental observations regarding the reactivity of substituted substrates³⁷: for example, the presence of a strongly π -donating group such as a OMe in *para* position induces an enhanced reactivity of the hydroperoxide substrate which no longer allows its isolation, whereas the reactivity is not modified when the same substituent is in the *meta* position.

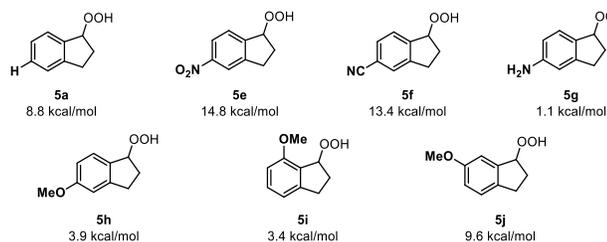


Figure 3. Energy barrier of the Hock rearrangement for substituted substrates (ΔG^{Hock} in kcal/mol).

Stemming from **VIIIa**, the release of $\text{InCl}_3(\text{OH})^-$ to form the oxocarbenium species **IIa** is endergonic by 28.5 kcal/mol. However, the release of the catalyst alone from **VIIIa** to generate **7a** is preferred as endergonic by only 21.1 kcal/mol.

This energy is close to the energy released by the coordination of InCl_3 to the reactant **5a** (21.0 kcal/mol), which suggests close coordination affinities of the catalyst for the starting material and the product. This proximity supports the turnover of catalytic InCl_3 and raises the question of the structure of the catalyst (*vide infra*).

To complete this work, the Hock rearrangement of tertiary hydroperoxide **5b** and that of tetralin hydroperoxides **5c** and **5d** was computationally studied, allowing comparison with the previous case (Table 1). Regarding tertiary hydroperoxide **5b**, a better stabilization of benzylic carbocation intermediates **Vb** is expected, favoring a competing elimination of the hydroperoxide over the Hock rearrangement. The formation of the tertiary carbocation **Vb** from **Ib** is easier than that of the secondary one (step **Ia** \rightarrow **Va**), being endergonic by only 19.3 kcal/mol (25.7 kcal/mol for **Va**). However, the Hock rearrangement remains consistently favored (**TS_{Ib-VIb}**), in agreement with experimental results in which no carbocation-derived compound was observed.³⁷ Furthermore, the Hock reaction is favored by ~ 2 kcal/mol (ΔG^{Hock}) when involving a tertiary hydroperoxide rather than a secondary one (Table 1, entry 4). Unlike **5a**, substrate **5b** first led to the formation of oxocarbenium intermediate **IIb**, before hydration leading to **7b** (Table 1, entries 6-7). Similar observations were made for **5c** and **5d**, while these rearrangements did not stop to the lactol products but to the thermodynamically favored open forms **12c** and **12d**, unlike substrate **5a** that led to the more stable lactol **7a**.

Table 1. Free energy of intermediates derived from **5a-d** in the InCl_3 -catalyzed Hock reaction.

Entry					
	5	0.0	0.0	0.0	0.0
0	5	0.0	0.0	0.0	0.0
1	IV	-20.8	-21.7	-28.8	-29.2
2	V	4.7	-2.9	0.3	-6.2
3	I	-21.0	-22.2	-26.2	-27.2
4	TS_{I-VI}	-12.2 (8.8) ^a	-15.5 (6.7) ^a	-18.1 (8.6) ^a	-20.8 (6.4) ^a
5	VIII	-80.3	-83.1	-80.0	-84.9
6	II	-51.8	-62.7	-51.1	-61.3
7	7	-59.2	-62.0	-49.7	-52.1
8	11	-58.0	-62.2	-56.4	-62.1

^a The value in parentheses corresponds to ΔG^{Hock} , the energy barrier of the Hock rearrangement in kcal/mol

A final question arose concerning the exact nature of the catalyst. Recent studies showed that the catalytically active species of Lewis acids of type AX_3 (A = Al, Ga, Fe, In and X = H, Cl) are in the dimeric form A_2X_6 , or in the form of a super-electrophile like $\text{X}_2\text{A-X-AX}_3$.^{33-35,43,44} The Hock rearrangement of **5a** was thus investigated in the presence of dimeric InCl_3 (Figure 4, not all intermediates are presented, see Supporting information for details).

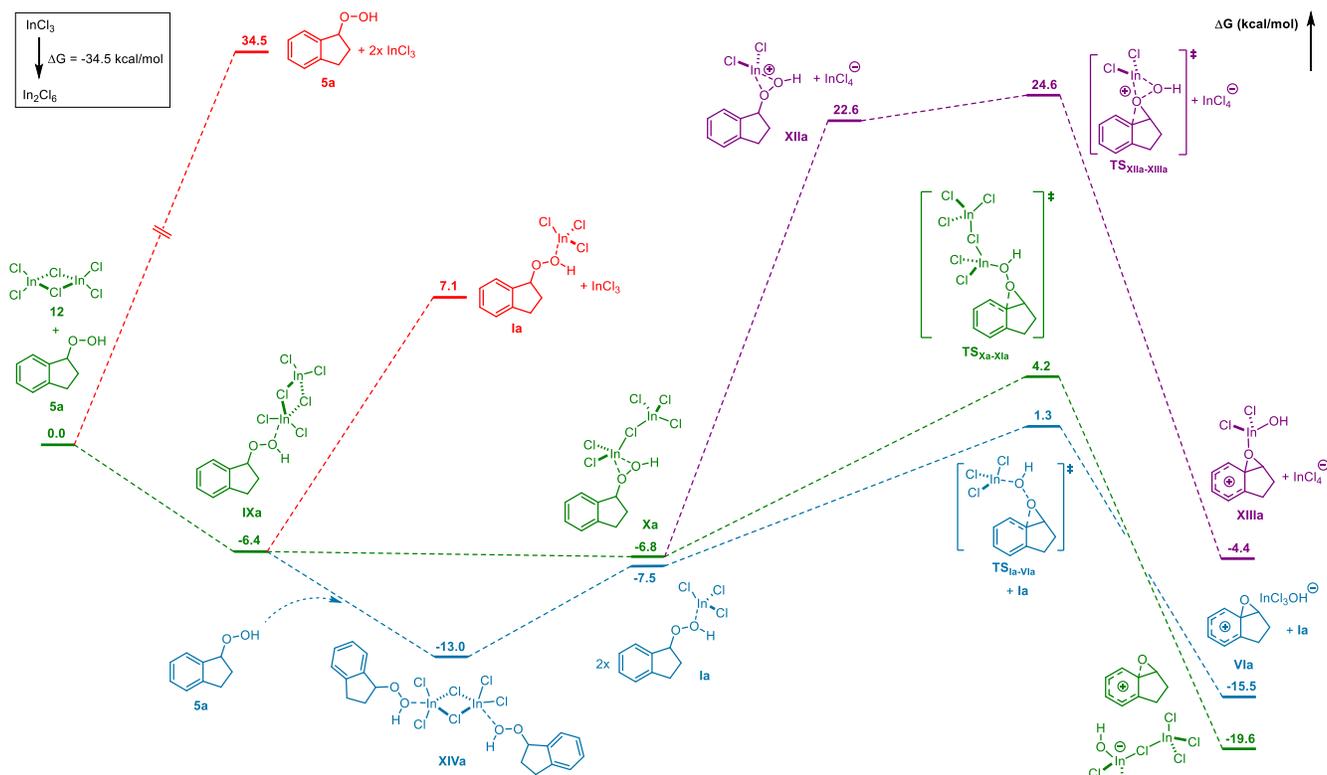


Figure 4. Free-energy profile of the Hock reaction of 1-indanyl hydroperoxide (**5a**) catalyzed by In_2Cl_6 versus InCl_3 and InCl_2^+ .

The dimerization of InCl_3 gives rise to a stable homodimer (In_2Cl_6) favored by 34.5 kcal/mol. This dimer is bridged by two chlorine atoms and can coordinate to the peroxide, leading to complex **IXa**. As expected, this coordination is much less exergonic than that of monomeric InCl_3 (-6.4 vs -21.0 kcal/mol). Interestingly, **IXa** can reorganize to structure **Xa** bridged by a single chlorine atom between the two indium atoms, thus adopting the $\text{Cl}_2\text{In}-\text{Cl}-\text{InCl}_3$ scaffold. Unexpectedly, unlike Ga_2Cl_6 catalysis displaying gallium superelectrophilic species during the reorganization of 1,6 enynes³³ or the methylation of benzene,⁴⁴ the dimeric species $\text{Cl}_2\text{In}-\text{Cl}-\text{InCl}_3$ is not a superelectrophile able to promote the Hock rearrangement. Indeed, not only **Xa** is not significantly more stable than **IXa** (-0.4 kcal/mol), but more importantly the activating barrier for the Hock rearrangement is in this case higher (+11.0 kcal/mol from **Xa** to $\text{TS}_{\text{Xa-XIa}}$) than with monomeric InCl_3 (+8.8 kcal/mol from **Ia** to $\text{TS}_{\text{Ia-VIa}}$). NBO analysis underlines the fact that the In atom coordinated to the hydroperoxide group in **Xa** has a greater positive charge (+1.74 e) than the other In atom (+1.61 e). However, the In-Cl-In bonds show that the Cl atom is closer by 12 pm to the In atom coordinated to the peroxide (Figure 5).

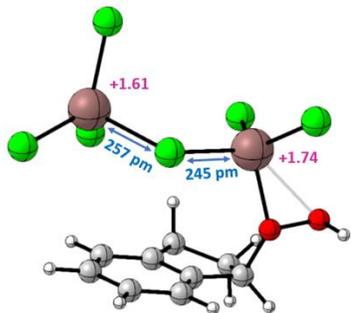


Figure 5: Structure, NBO charges and bond length of intermediate **Xa**.

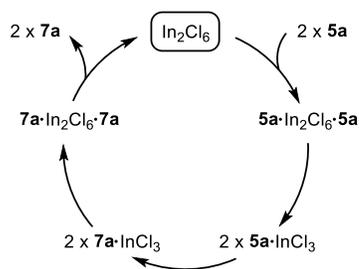
These structural and electronic differences in the two In atoms of **Xa** do not seem sufficient to allow a representation as $[\text{InCl}_2^+-\text{InCl}_4^-]$. Finally, further calculations demonstrated that InCl_2^+ can be a superelectrophilic catalyst for the Hock rearrangement, with an energy barrier reduced to +2.0 kcal/mol from the complex **5a-InCl}_2^+ (**XIIa**) to $\text{TS}_{\text{XIIa-XIIa}}$. However, the high endergonicity of the formation of this complex (+29.4 kcal/mol from **Xa**) precludes any possibility for InCl_2^+ to be the catalyst of this reaction.**

Finally, we investigated the possible coordination of In_2Cl_6 by two molecules of peroxide substrate (**5a**). It is first interesting to mention that the coordination of an In_2Cl_6 dimer on a single molecule of **5a** (formation of **Xa**: -6.8 kcal/mol) is almost as exergonic as the coordination of two InCl_3 monomers on two molecules of **5a** (formation of two **Ia**: -7.5 = +34.5 - 2 x 21.0 kcal/mol). The dissociation of the In_2Cl_6 dimer can neither occur before nor after its coordination to a single molecule of **5a**, because both processes lead to highly energetic intermediates (pathway in red Figure 4). However, a second molecule of **5a** can bind to **IXa**, leading to stable, symmetrical, dimeric intermediate **XIVa** (**5a-In}_2\text{Cl}_6\cdot\text{5a}**). This double coordination is consistent with the presence of an excess of substrate **5a** during the reaction. From **XIVa**, two possible pathways can be envisaged: (i) the reversible formation of **IXa** by releasing a molecule of hydroperoxide (endergonic by 6.6 kcal/mol), finally resulting in monobridged **Xa**, or (ii) the dissociation of dimeric **XIVa** releasing two molecules of monomeric complex **Ia**, associated to a cost of 5.5 kcal/mol. The latter should thus be the privileged pathway, leading to an InCl_3 -catalyzed rearrangement through $\text{TS}_{\text{Ia-VIa}}$, endergonic by 8.8 kcal/mol. The direct

In_2Cl_6 -mediated Hock rearrangement is more speculative as it goes through $\text{TS}_{\text{Xa-X1a}}$ which is located 2.9 kcal/mol higher than $\text{TS}_{\text{Ia-VIa}}$.

This study thus points out to monomeric InCl_3 as the active catalyst of the rearrangement. It is important to note however that this monomeric catalyst is generated from **XIVa** and only exists in a coordinated form. While InCl_3 has a strong and similar affinity for the substrate (**5a**) and the product (**7a**), its tendency to dimerize is even more exergonic. Consequently, free monomeric InCl_3 does not exist in solution, while the dimer In_2Cl_6 can be regenerated at the end of the reaction, finally explaining the turnover of this catalyst (Scheme 4).

Scheme 4. Catalytic cycle of the InCl_3 -catalyzed Hock rearrangement.



CONCLUSION

In conclusion, this study of the InCl_3 -catalyzed Hock rearrangement elucidates for the first time the details of the electronic mechanism of this reaction. In particular, the demonstration that a key benzenium intermediate is involved in the reaction gives clues for better stabilization of this intermediate through the choice of appropriate substituents. This benzenium intermediate is a consequence of the migration of the aryl sp^2 *ipso*-carbon onto the internal peroxide oxygen, with concomitant cleavage of the O–O bond. The cleavage of the C–C bond appears to be consecutive to the benzenium formation, highlighting an asynchronous mechanism.

Furthermore, we propose that the catalysis of this reaction (Scheme 4) involves a monomeric complex of InCl_3 coordinated to one molecule of hydroperoxide substrate ($\text{InCl}_3 \cdot \text{ROOH}$), originating from the cleavage of the much more stable symmetrical homodimer $\text{In}_2\text{Cl}_6 \cdot (\text{ROOH})_2$. By decreasing the activation barrier of the Hock rearrangement, this coordinated InCl_3 monomer behaves as a better electrophile compared to the dimer that is significantly less activating (*e.g.* 8.8 kcal/mol vs. 11.0 kcal/mol for substrate **5a**). Therefore, unlike previous studies highlighting super-electrophilic dimeric species such as A_2X_6 or $\text{AX}_2^+ \text{AX}_4^-$ among the group 13 elements,^{33,35,44} our study shows the absence of superelectrophilicity for the dimeric In_2Cl_6 species during this Hock rearrangement. These species are however central in our catalytic cycle, serving as a reservoir of active monomeric catalytic species. Overall, while monomeric species are mostly considered in In(III)-based methodologies, we can reasonably suggest that homodimeric and other coordinated species should be given better attention as part of the catalytic cycle.

COMPUTATIONAL DETAILS

The calculations were performed using Gaussian 09 software. Geometry optimizations and transition states (TS) were obtained employing the 6-31G(d,p) basis set^{45,46} on all atoms except for indium which was modeled using LANL2DZ effective core potential and associated double-zeta valence basis,⁴⁷ in combination with B3LYP-D3 functional.^{48,49} This level of theory previously proved reliable to study the Baeyer-Villiger mechanism.⁵⁰ Both TS and geometry optimization were confirmed using frequency calculations at the same level of theory. Solvent effects were included in the calculations thanks to IEFPCM continuum solvation model⁵¹ using dichloromethane as solvent. For every TS found, intrinsic reaction coordinates (IRC)^{52,53} were calculated to ensure that the corresponding TS is connected to the proper reactant(s) and product(s). The energy obtained were improved thanks to single point calculation with the same method and aug-cc-pVTZ basis set⁵⁴ for all atoms except Indium. Indium was modeled using the multi electron fit fully relativistic effective core potential ECP28MDF⁵⁵ in combination with basis set aug-cc-pVTZ-PP. The three-dimensional optimized structures were prepared using CYLview20.⁵⁶ Intrinsic bond orbitals (IBO) analyses were performed using Iboview software^{38–40} on the optimized geometries with default method (PBE/def2-TZVP) to generate Kohn-Sham wave functions. IBO analyses enable to visually follow the movement of electrons during a molecular transformation thanks to the representation of localized molecular orbitals. NBO charges were computed using NBO6 software at the IEFPCM(CH_2Cl_2)-B3LYP-D3/6-31G(d,p) – LanL2DZ level. The Gibbs free energies presented in this article are IEFPCM(CH_2Cl_2)-B3LYP-D3/aug-cc-pVTZ(-PP) //IEFPCM(CH_2Cl_2)-B3LYP-D3/6-31G(d,p) – LanL2DZ electronic energies modified with thermal and entropy corrections from IEFPCM(CH_2Cl_2)-B3LYP-D3/6-31G(d,p) – LanL2DZ calculations. Due to the well-known errors associated with entropy calculations, we apply a scaling factor of 0.5 to the entropic contributions as recommended and successfully used in the literature.^{57–61}

ASSOCIATED CONTENT

Supporting Information. Experimental methods, copies of NMR spectra, additional computational details, cartesian coordinates of stationary points and CIF file. The crystallographic data of **10a** have been deposited on the Cambridge Crystallographic Data Center under the CCDC number 2253685. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

The manuscript was written through contributions of all authors.

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