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Fries Rearrangement of Aryl Formates: A Mechanistic Study by Means of ^{1}H, ^{2}H, and ^{11}B NMR Spectroscopy and DFT Calculations

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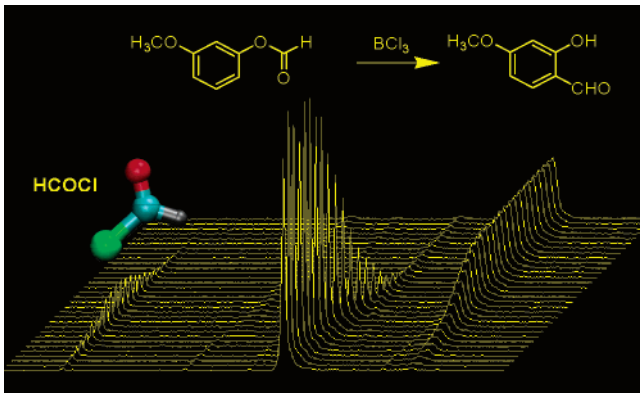

^{1}H, ^{2}H, and ^{11}B NMR spectroscopy has been used to study the mechanism of the Fries rearrangement of aryl formates promoted by boron trichloride by monitoring both the substrate and the Lewis acid. DFT calculations were employed to investigate the energetics of several reaction paths and to calculate NMR chemical shifts of key intermediates and products. After the formation of a 1:1 substrate−Lewis acid adduct, the rearrangement proceeds in two steps, beginning with the cleavage of the ester bond and the release of formyl chloride in situ, which, in turn, acts as a formylating agent, introducing an aldehydic functionality into the aromatic ring. The high regioselectivity (only the ortho product is obtained) is also accounted for by the proposed intermolecular, Lewis acid-assisted mechanism.

Introduction

The Fries rearrangement transforms an aryl ester into a mixture of *o*- and *p*-hydroxycarbonyl compounds, the ratio strongly depending on the reaction conditions, such as temperature, medium, and, most importantly, Lewis acid catalyst used.[1] In many cases, complete regioselectivity can be attained with a careful choice of the catalyst and of its molar ratio with the substrate.[2] Thus, a variety of catalysts such as polyphosphoric acid,[3] methanesulfonic acid/$POCl_3$,[4] montmorillonite clays,[5] hafnium trifluoromethanesulfonate,[6] scandium trifluoromethanesulfonate,[7] zirconium tetrachloride,[8] and titanium tetrachloride[9] have all been used to induce the rearrangement. More recently, heteropoly acids[10] and metal triflates, particularly yttrium and

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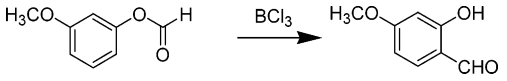
SCHEME 1. Fries Rearrangement of 3-Methoxyphenyl Formate



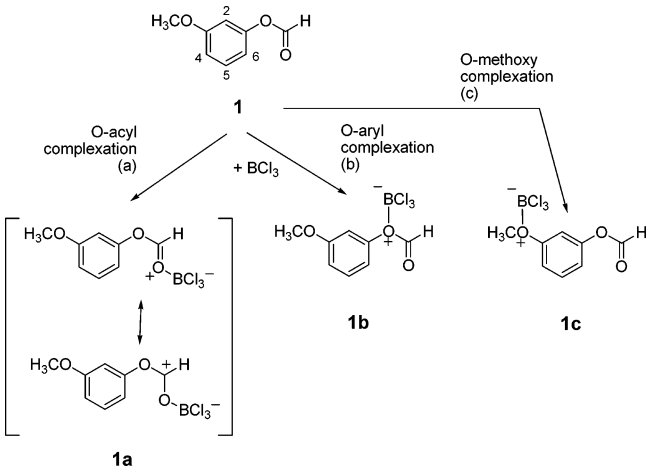
copper(II), together with methanesulfonic acid,[11] have been found to be efficient catalysts. Novel reaction methodologies have also been applied; Fries rearrangements have also been performed under microwave irradiation[12] or in ionic liquids.[13]

Despite the wide use of the Fries rearrangement in organic synthesis, also for preparation of intermediates in manufacturing fine and specialty chemicals as well as pharmaceuticals,[14] the details of the mechanism are still unclear. In some cases an intermolecular mechanism has been proposed;[15] in others, an intramolecular one has been put forward, at least for the ortho isomer;[16,17] for polymeric substrates, both mechanisms have been suggested.[18] In some cases, a mechanism that can be still regarded as intramolecular has been proposed also for the formation of the para isomer.[19] A mechanistic investigation of the rearrangement of phenyl benzoate promoted by $AlBr_3$ was reported by Hart and coworkers,[20] where an active participation of $AlBr_4^-$ was observed. Such a variety of proposals partly reflects also the large number of substrates, media, and Lewis acids used. Nevertheless, some general mechanistic features appear to be widely accepted and they involve the initial formation of a 1:1 complex between substrate and Lewis acid (but in some cases a 1:2 complex has been invoked[21]) which then undergoes a dissociation with formation of an acylium ion; this finally acts as the acylating agent.[2]

Recently, an extension of the Fries rearrangement to aryl formates has been presented,[22] which allows the introduction of an aldehydic functionality into an aromatic ring (see Scheme 1).

A preliminary mechanistic study of the model systems phenyl formate and 3-methoxyphenyl formate has been already reported.[23] DFT calculations of reaction paths of phenyl formate allowed us to exclude some possible routes, like a direct intramolecular rearrangement, and suggested that the formation of formyl chloride as an intermediate is not prohibited on the basis of the calculated energy barrier. On the other hand, ^{11}B NMR spectra recorded at low-temperature just after mixing and on the reaction mixture at the endpoint were not conclusive concerning the nature of the postulated intermediates and products.[23] In this work we report on a systematic NMR study, at various temperatures, of the reaction mechanism by monitoring the substrate transformation via ^1H and ^2H NMR and through ^{11}B NMR spectroscopy from the standpoint of the Lewis acid. DFT calculations have identified a viable route to the final product, and calculated ^1H and ^{11}B chemical shifts of substrate, intermediates, and final products agree very well with the observed resonances.

SCHEME 2. 3-Methoxyphenyl Formate (1) and Its Possible Coordination Modes with BCl_3 (1a, 1b, and 1c)[a]



[a] The resonance structure with a formal charge separation in **1a** accounts for the deshielding of the formyl carbon and proton upon complexation.

Results and Discussion

Structure of the Initial Formate Ester−BCl_3 Adduct. As a first step we have investigated the nature of the initial adduct formed when an excess (ca. 20%) of BCl_3 is added to a solution of 3-methoxyphenyl formate (see Scheme 2).

Three different coordination modes of the Lewis acid to the formyl group can be conceived according to whether the electron-deficient boron atom interacts with the acyl oxygen (*O*-acyl, **1a**), with the aryl ester oxygen (*O*-aryl, **1b**), or with the methoxy oxygen (*O*-methoxy, **1c**). The optimized geometry, for the three complexes, features a boron−oxygen distance and dihedral B−Cl−Cl−Cl angle of 1.591 Å and 29.0° for **1a**, 3.054 Å and 1.7° for **1b**, and 1.646 Å and 27.9° for **1c**. The geometrical parameters indicate that a relatively strong interaction occurs for complexes **1a** and **1c**. The interaction energies, without BSSE correction, at the DFT level, are −7.1, −1.7, and −0.9 kcal/mol, for **1a**, **1b**, and **1c**, respectively. We also note that the inclusion of the BSSE correction dramatically changes the results (see Table S2 of Supporting Information) still favoring complex **1a** over **1c**, while **1b** appears very little stabilized compared to free substrate and BCl_3. Indeed, since the geometry of BCl_3 in the complexes **1a** and **1c** changes significantly with respect to the free molecule, most of the stabilization obtained including the BSSE correction is a spurious outcome of the counterpoise method, while in the case

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of the **1b** complex the BSSE correction appears more justified. Thermal corrections (see the QM Calculations part of the Experimental Section) amount to about 14 kcal/mol of destabilization for **1a** and **1c** and about 8 kcal/mol of destabilization for **1b**. On the other hand, single-point calculations at the MP2 level, using the DFT-optimized geometries, provide a significantly different picture: the electronic energy is largely in favor of the complexes formation, particularly **1c**, likely because of dispersive interactions between chlorine atoms of BCl_3 and the aromatic ring. These data indicate that the energetics of this complexation is very sensitive to the method used and would be properly addressed only by recourse to very high levels of theory for optimization and frequency calculation. However, this is not strictly necessary for the purposes of this work, because conclusive information can be obtained by analyzing trends in NMR spectra, as follows.

Upon addition of BCl_3 to **1**, the only significant change in the proton resonances is a large deshielding of the formyl proton from 8.31 ppm of pure **1** (at room temperature) to 8.87 ppm at room temperature and up to 9.15 ppm at −5 °C. The other resonances are also deshielded, compared to the pure substrate, but only by about 0.05−0.1 ppm, depending on the temperature (note that a systematic small shift of all resonances is observed simply as a solvent effect when the solution of BCl_3 in heptane is added to the solution of substrate in $CDCl_3$). The ^1H spectrum at three different temperatures after the addition of BCl_3 is shown in Figure S1 of the Supporting Information (except the methoxy signal at 3.85 ppm). The aromatic pattern of the adduct is the same as that of **1**, featuring, for increasing shielding, the triplet of proton H5, two doublets (H4 and H6), and the singlet of H2. The large changes that the formyl proton resonance undergoes upon addition of BCl_3, and its temperature dependence, indicate the formation of a complex involving the formyl moiety that can be attributed to the coordination of the Lewis acid to the acyl oxygen. The large deshielding of the formyl proton is consistent with a reduced electron density on the formyl group in **1a** (Scheme 2).

Strong support to this proposal is provided by DFT calculations of the relevant chemical shifts.[24] The calculated results for the free substrate are 8.36 ppm (formyl proton) and 3.77 ppm (methoxy protons), quite in good agreement with experiment. For the *O*-acyl complex **1a** the resonance of the formyl proton is calculated to be largely deshielded ($\Delta\delta = 1.02$ ppm), as observed experimentally, while the methoxy resonance is deshielded by only 0.06 ppm, also in very good agreement with experiments. In contrast, calculated chemical shift variations for **1b** and **1c** are totally in disagreement with experiments: for **1b** the formyl proton is slightly shielded ($\Delta\delta = -0.05$ ppm) and the methoxy protons are essentially unchanged ($\Delta\delta = -0.01$ ppm), while for **1c** the formyl proton is again slightly shielded ($\Delta\delta = -0.03$ ppm) and the methoxy protons significantly deshielded ($\Delta\delta = 0.62$ ppm).

A significant deshielding is also observed for the resonance of the formyl carbon (see Figures S3−S5 of Supporting Information), which is shifted from 159.2 ppm in the pure substrate to 173.6 ppm after the Lewis acid is added at −10 °C ($\Delta\delta = 14.4$ ppm), while the methoxy carbon changes only by 0.3 ppm (again a small solvent effect is expected). The corresponding calculated chemical shift variations are the following, for the formyl and methoxy carbons respectively: 18.7 and 0.6 ppm for **1a**, −1.6 and 0.1 ppm for **1b**, and −1.5 and 13.7 ppm for **1c**. As with the proton resonances, the calculated results for **1b** and **1c** are in complete disagreement with the experiment.

The ^{11}B spectrum of the initial adduct is also in agreement with *O*-acyl complexation. After mixing with **1**, the resonance of BCl_3 in heptane (46.5 ppm) disappears from the spectrum, which now consists of a single resonance at 27.3 ppm at 13 °C (25.6 ppm at −5 °C) (Figure S2). Since BCl_3 is in 20% excess, the presence of a single signal indicates that free BCl_3 and the initial adduct are in the fast exchange regime. A comparison with calculated ^{11}B chemical shifts is again useful: for BCl_3, $\delta(^{11}B) = 52.8$ ppm (the calculated value is too deshielded, compared to the experimental value, mainly because of the neglect of spin−orbit coupling[23]). The calculated ^{11}B chemical shifts of the initial adduct are, respectively, 18.8, 23.7, and 50.3 ppm for the *O*-acyl, *O*-methoxy, and *O*-aryl complex; the latter result is very close to that of free BCl_3, as expected. Therefore, the experimental value is somewhat higher than the expected chemical shift of the *O*-acyl complex. This is consistent with the rapid equilibrium of BCl_3 between the bound form and the free Lewis acid.

Thus, all available information consistently indicates that the substrate is converted to the *O*-acyl complex **1a** and that the latter is in fast equilibrium with excess BCl_3.

Kinetics of the Fries Rearrangement. The kinetics has been qualitatively studied by means of ^1H, ^2H and ^{11}B NMR spectroscopy at several temperatures. In Figure 1a−c we report the time evolution at +7 °C of the ^1H spectra, subdivided for clarity in three regions (aldehydic, methoxy, aromatic).

In the ^1H NMR spectra of Figure 1, three sets of signals can be clearly identified: those of the substrate which are decreasing to zero; those of a final product, which are increasing; and those of an intermediate, reaching a maximum concentration after about 4 h (at 7 °C). In ref 23 it was postulated that the Fries rearrangement of aryl formates promoted by BCl_3 proceeds through the formation of formyl chloride as an intermediate, followed by acylation of the aromatic ring in the ortho position.

The transient signal that appears at 9.70 ppm in the ^1H NMR spectra (Figure 1a) can indeed be attributed to formyl chloride. In fact, a DFT calculation of the proton chemical shift of formyl chloride gives a value of 9.82 ppm, in very close agreement with experiment. However, the existence of the proposed intermediate needs to be further supported.

Formyl chloride has been isolated and characterized at low temperature.[25] It has been found to decompose into CO and HCl[26] and its lifetime has been found to range from tens or hundreds of minutes in the gas phase[27] to less than a millisecond in water.[26] Recent ab initio calculations suggest a strong catalytic effect of water on the decomposition reaction and indicate that at least four water molecules are necessary to increase the rate of decomposition in water with respect to the gas phase.[28] The

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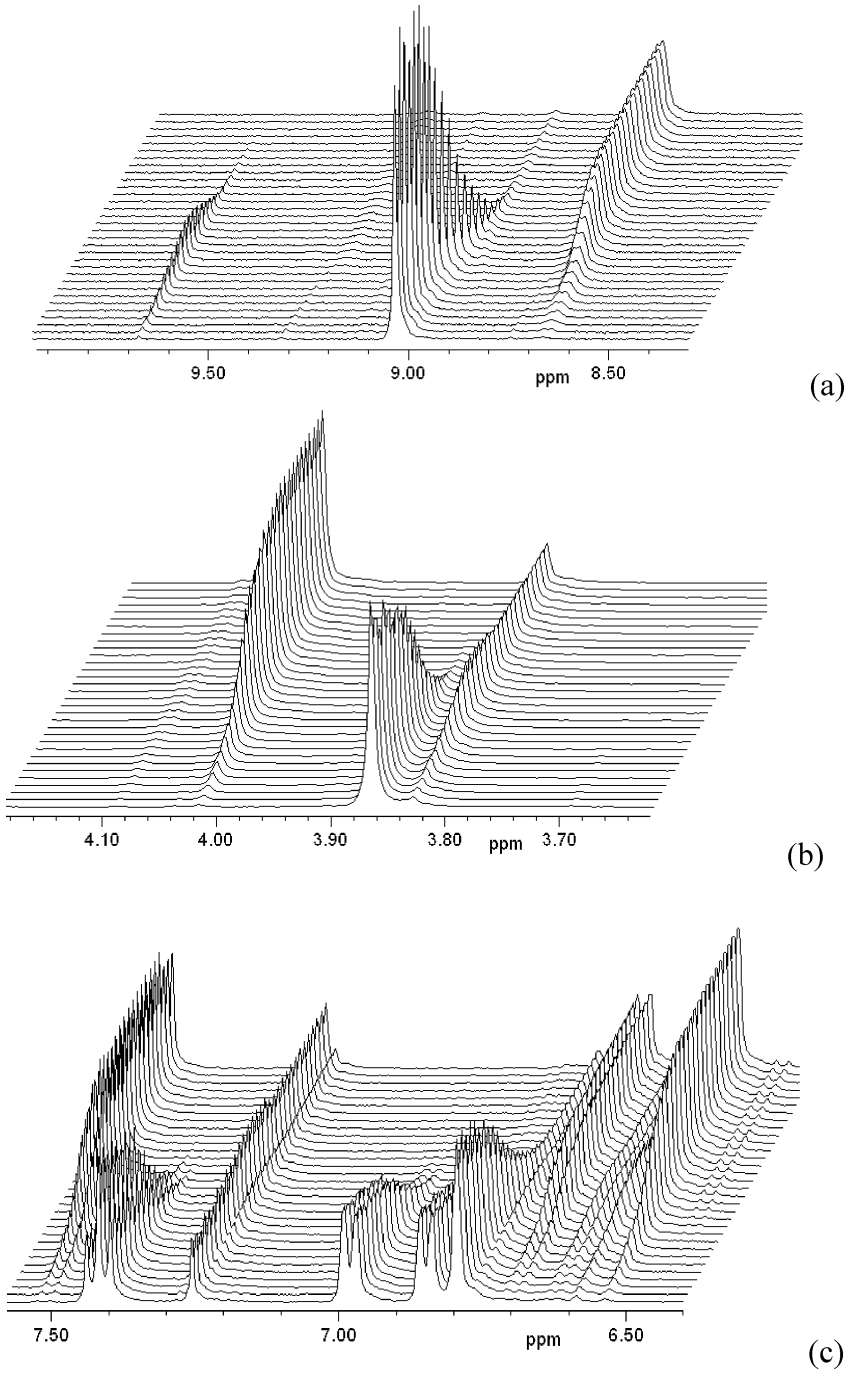

FIGURE 1. Time evolution over 17 h of the ^{1}H NMR spectra of the **1**−BCl_3 reacting system at 7 °C. Top to bottom: (a) aldehydic region, (b) methoxy region, and (c) aromatic region. The 32 spectra, from front to rear, are separated by 15 min (1−9), 30 min (10−26), and 60 min (27−32).

lifetime of the intermediate in our reaction mixtures is longer than the acquisition time, which is of the order of 1 s, which seems compatible with the above findings, since only traces of water are present in solution, if any.

To further support our hypothesis we ran the reaction using BBr_3 as Lewis acid. Assuming that the reaction proceeds by the same mechanism,[22] we should now observe formyl bromide as intermediate, whose proton resonance is predicted to be 10.72 ppm by DFT calculation. Indeed, the signal of the intermediate is observed at 10.70 ppm when BBr_3 is used. The "heavy-atom effect" (due to spin−orbit coupling, which is responsible for an additional contribution to the shielding constant, σ_{SO}) has been calculated to be −0.17 ppm at the BP86/TZ2P level using the software ADF;[29] therefore, it does not alter our conclusion. However, BBr_3 is known to behave as a dealkylating agent;[30] therefore, secondary products are observed at the end of the reaction, together with the expected product (4-methoxysalicylaldehyde). We did not further investigate this aspect and we proceeded only with BCl_3 as Lewis acid.

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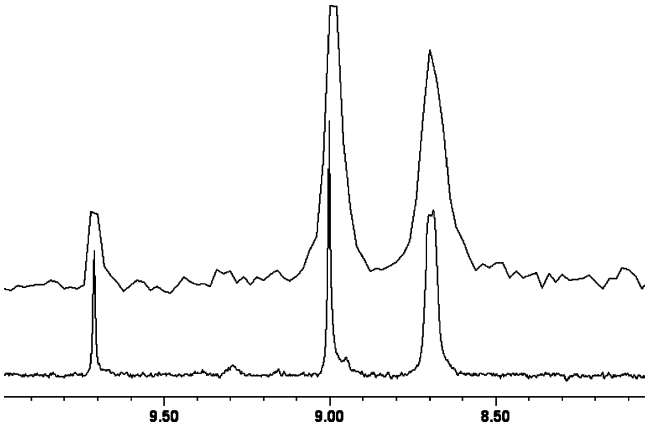

FIGURE 2. (top) ^{2}H NMR spectrum of **1**-*d* reaction mixture and (bottom) ^{1}H NMR spectrum of **1** reaction mixture after 4 h at 7 °C. The ^{2}H spectrum has been shifted so that the formyl signal is exactly superimposed on that of the ^{1}H spectrum.

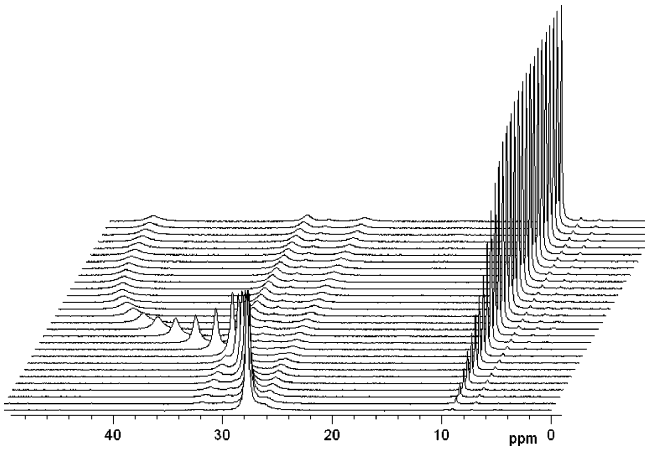

FIGURE 3. Time evolution over 17.5 h of the ^{11}B NMR spectra of the **1**−BCl_3 reacting system at 13 °C. The 29 spectra, from front to rear, are separated by 15 min (1−9), 30 min (10−22), 60 min (23−29).

The dependence of the formyl resonance of the intermediate on the halide of the Lewis acid also allows us to discard the hypothesis of the intermediate being the formylium cation, HCO^+, for which the calculation predicts a significantly shielded value of the proton resonance (7.28 ppm). Moreover, HCO^+ has been the most elusive of the acylium cations: it has been observed in condensed phase only in the presence of superacids, like HF-SbF_5, under high CO pressure.[31] Its high instability, compared to other substituted acylium cations, $R-CO^+$, is related with the easy loss of a proton to give the neutral CO molecule.[32] The high instability also means a high reactivity, which is inconsistent with the observed regioselectivity of the Fries rearrangement.

As a final test we also studied the kinetics at 7 °C of a sample of **1** deuterated at the formyl position, **1**-*d*, using ^{2}H NMR. In the deuterium spectra we could only observe, at the beginning, the signal of the formyl deuterium of the reactant, and, as the reaction proceeded, the signals of the intermediate and of the final product as observed in the aldehydic region of the ^{1}H NMR spectra of the nondeuterated sample in Figure 1a. In Figure 2 we show the superposition of the ^{1}H and ^{2}H NMR spectra, of the **1** and **1**-*d* reaction mixtures, after 4 h, as an example (see Figure S6 for the full kinetics). This clearly demonstrates that the intermediate at about 9.7 ppm is indeed originating from the formyl group of the reactant (9 ppm) and is transformed into the aldehydic group of the product (8.7 ppm) as discussed further below.

With regard to the time evolution of the spectra of the methoxy region, the signals of the substrate completely disappear after 20 h; thus, e.g., the methoxy group at 3.86 ppm in Figure 1b is replaced by the signal of the main product at 4.02 ppm, together with a secondary product whose methoxy protons resonate at 3.81 ppm. The same considerations apply to the aromatic region (Figure 1c). The integrated intensity of the secondary product amounts to about 15% of the main product at 7 °C, but it is lower at lower temperatures. We will come back to this point later.

In the ^{11}B spectra of Figure 3 we clearly see the growth of a signal at 8.3 ppm, while the initial resonance at 27.3 ppm has a more complicated time evolution: the decrease of intensity is accompanied by a shift to higher values until, at the end of the reaction, we observe again the signal of free BCl_3 at 46.5 ppm. This behavior may depend on the fact that the initial signal does not correspond to a single species but is the weighted average of free and complexed BCl_3. In contrast, the final product does not seem to be involved in an exchange equilibrium. Other resonances, at 31.8 and 26.4 ppm, also appear in the final spectrum.

We have run the reaction also in the presence of an equimolar quantity of toluene to test whether tolualdehyde is formed and we have found no evidence, at least in the ^{1}H NMR, of tolualdehydes. We note, however, that this result is not conclusive regarding the intra/intermolecularity of the mechanism: in fact, the para position of the substrate **1** is certainly more reactive than any position of toluene. Nevertheless, the Fries rearrangement only produces the ortho isomer. As we will see in the computational section, such regioselectivity is nicely accounted for by the intermolecular mechanism. Likewise, the fact the toluene is not acylated can be explained. This observation supports the hypothesis that the acylating agent is a rather weak electrophile, like formyl chloride, rather that a strong one, like the formylium cation.

Structure of the Final Product in the Reaction Mixture. We now analyze the nature of the final products that are formed in the reaction. In Figure 4 we show the ^{1}H spectrum after the reaction has reached its endpoint at room temperature overnight, without any workup.

We note the presence of an aldehyde signal at 8.70 ppm, rather broad and poorly resolved in a doublet; its peculiar shape will be discussed later. The aromatic pattern is typical of a 1,2,4-trisubstituted benzene ring, which is consistent with the expected 4-methoxysalicylaldehyde. As already noted, there is also a methoxy resonance at 4.02 ppm. A secondary product is observed in the ^{1}H spectrum, with the characteristic pattern of a 1,3-disubstituted benzene ring: the H4 triplet, overlapped with the solvent resonance at 7.26 ppm; two doublets (6.77 and 6.62 ppm); and an unresolved triplet at 6.58 ppm. These signals are marked with an asterisk in Figure 4. As already mentioned, the methoxy protons of this secondary product resonate at 3.81 ppm. To confirm that the main product observed at the end of the reaction is the expected 4-methoxysalicylaldehyde, possibly in

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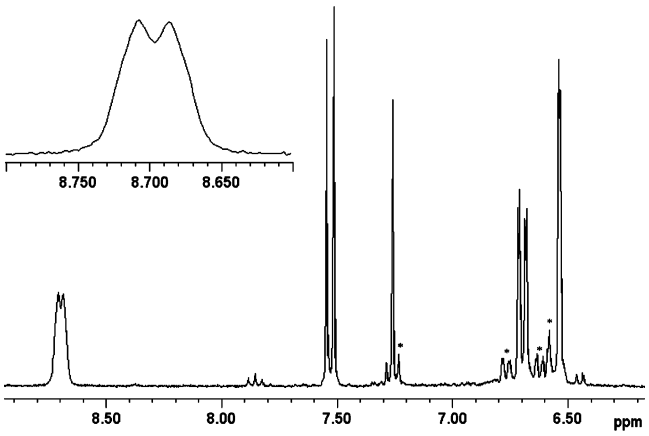


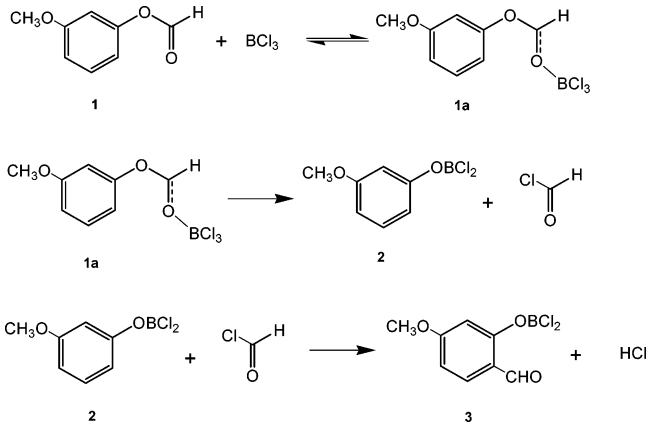
FIGURE 4. Final ^{1}H NMR spectrum of the reaction solution after 1 day at room temperature. The resonances of a secondary product are marked with an asterisk. The signal at 7.26 ppm is the residual solvent overlapped with a triplet of the secondary product. The aldehyde resonance is enlarged in the inset.

the form of a borate ester, we have measured the ^{1}H spectra of a solution of 4-methoxysalicylaldehyde after the addition of a 20% excess of BCl_3. After allowing the system to react at room temperature, we obtained a spectrum identical to that of Figure 4, except for the absence of the secondary product. The secondary product has been identified as a borate ester of 3-methoxyphenol by comparing the proton resonances of the secondary product of Figure 4 with those of a solution of 3-methoxyphenol after the addition of a 20% excess of BCl_3, which showed the same proton resonances observed for the secondary product. A close inspection of the ^{1}H NMR spectrum also reveals the presence of a low intensity (less than 3% of the total) triplet at 7.86 ppm, a doublet at 6.45 ppm (both visible in Figure 4), a singlet at 4.09 ppm (not shown), and a broad signal at 9.30 ppm. These resonances, together with the weak signal in the ^{11}B spectrum at 26.4 ppm, have not been assigned. They are, however, compatible with the other ortho product, 2-hydroxy-6-methoxybenzaldehyde. We believe that the steric bulk of the methoxy group renders the rearrangement of the formyl group to position 2 of the substrate **1** largely disfavored compared to position 6.

We remark at this point that only the ortho isomer is obtained; no traces, at least detectable in the ^{1}H spectrum, of the para isomer are found. This is a sensitive point that of course has a bearing on all mechanistic issues and will be further dealt with below.

Proposed Main Steps of the Fries Rearrangement. On the basis of this evidence, we propose the following three steps for the Fries rearrangement of 3-methoxyphenyl formate, reported in Scheme 3: (a) first the substrate is predominantly converted to the complex at the acyl oxygen, **1a**; (b) **1a** then reacts to form HCOCl and a borate ester of 3-methoxyphenol (3-methoxyphenyl dichloroborate **2**), which is finally (c) formylated at the ortho position to give the borate ester of the rearranged product 4-methoxysalicylaldehyde as its dichloroborate ester **3**. We note that while the signal of the intermediate HCOCl actually decreases to zero at the end of the reaction, those of the other intermediate (**2**) persist in the mixture. This is probably due to the fact that during the course of the reaction a small amount (ca. 15% at +7 °C) of formyl chloride decomposes to

SCHEME 3. The Three Main Steps of the Fries Rearrangement as Indicated by NMR Spectroscopy



HCl and CO. Therefore, a corresponding amount of **2** cannot be acylated and remains in the reaction mixture.

The proposed steps are consistent with the above results and account for the observed products. However, this scheme leaves some major points unanswered. First of all, of course, the intermolecular mechanism proposed does not provide a cogent explanation for the high regioselectivity of the reaction. Second, the changes in the ^{11}B spectra need to be accounted for.

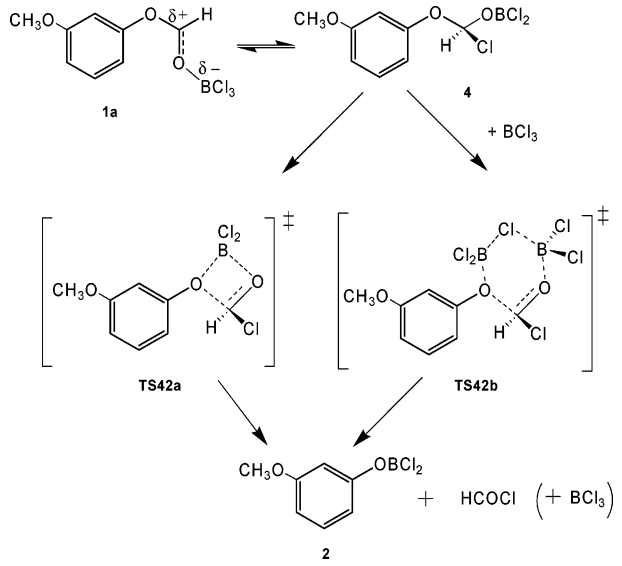
As far as the ^{11}B spectrum is concerned, calculated ^{11}B chemical shifts of chloroborate esters $B(OR)_{3-n}Cl_n$ (n = 0, 1, 2)[23] showed that dichloroborate monoesters ($B(OR)Cl_2$), chloroborate diesters ($B(OR)_2Cl$), and borate triesters ($B(OR)_3$) have ^{11}B chemical shifts of about 30, 20, and 10 ppm, respectively, almost regardless of the organic substituent R. Considering the systematic error of +2−3 ppm due to the neglect of spin−orbit coupling, the resonance at 31.8 ppm can then be assigned to the intermediate 3-methoxyphenyl dichloroborate **2**. However, it is difficult to assign the main product, at 8.3 ppm, to the similar boron monoester of the rearranged product, **3**. In fact, in ref 23 we suggested the possibility that the main product was the borate triester of the rearranged product. However, this hypothesis does not easily fit the mechanism proposed: in particular, there is no evidence in the ^{1}H and ^{11}B spectra of the presence of mono- and diesters of the rearranged product, which are expected to be precursors of the proposed triester.

The three main steps reported in Scheme 3 will be analyzed in more detail in the next section with the aid of DFT calculations; we will then show that the ^{11}B spectrum can be easily assigned to the species reported in Scheme 3 and that the proposed mechanism can also explain the high regioselectivity.

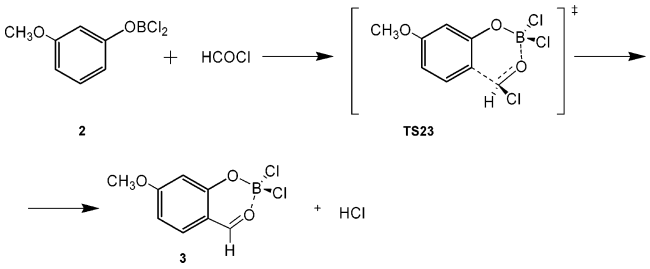
DFT Calculations of the Reaction Mechanism. In ref 23 we investigated several pathways for the Fries rearrangement of a model aryl formate (phenyl formate). Here we will discuss in more detail some of them for the system investigated experimentally, 3-methoxyphenyl formate **1**. They are presented in Schemes 4 and 5. We can safely assume that *O*-acyl complexation yielding **1a** is not the rate-determining step; therefore, we turn our attention to the second and third steps in Scheme 3.

The second step of Scheme 3 is detailed in Scheme 4: we assume a pre-equilibrium where the activated carbonyl carbon is attacked by a chloride anion lost by the Lewis acid coordinated to the oxygen, yielding the chloroalkyl dichloroborate **4**. We have not attempted a computational investigation of

SCHEME 4. Details of the Second Step of the Fries Rearrangement Shown in Scheme 3



SCHEME 5. Details of the Third Step of the Fries Rearrangement Shown in Scheme 3



this step (**1a** → **4**), since it may be intermolecular, through the participation of HCl present in the system. We remark that reacting species **4** in Scheme 4 is not detected in the NMR spectrum. We can even exclude that **4** is the one observed at the beginning of the reaction in the ^{1}H spectrum, since the calculated ^{1}H chemical shift of the ArOC*H*OCl proton is 7.32 ppm, significantly more shielded than the resonance observed at about 9 ppm. Even so, its intermediacy is a conceivable and logical step in the reaction sequence. Moreover, a very similar nucleophilic attack of chloride anion to a carbonyl of a benzaldehyde has been found to be promoted by BCl_3 in hexane, leading to the formation of an intermediate strictly related to **4**.[33]

Subsequently the boron atom migrates from the acyl oxygen to the aryl oxygen together with cleavage of the ArO−C bond (**4**) and formation of HCOCl and 3-methoxyphenyl dichloroborate **2** as intermediates; the involved transition states are labeled **TS42a,b** in Scheme 4. The calculations (see Table 1 and Table S3 of Supporting Information) suggest that this pathway is viable for the first step of the rearrangement. The activation enthalpy for **TS42a**, at the DFT level, is 25.7 kcal/mol and decreases to 12.7 kcal/mol if we include an additional BCl_3 molecule assisting the migration of boron (**TS42b**). The calculated activation Gibbs free energies are, instead, 27.7 and 28.0 kcal/mol, for **TS42a** and **TS42b**, respectively. The geometry of the two transition states is reported in Figure 5. However, it is important to note that if we calculate the electronic energy at the MP2 level of theory (using the DFT-optimized geometries with ZPE and thermal corrections) the calculated enthalpies and free energies are noticeably lowered, as reported in Tables 1 and S3. This approach may be questionable, since a different theoretical level may alter not only the energetics but also the nature of a sensitive point on the potential energy surface, like a transition state, and therefore it is not free from pitfalls (for example, it overestimates the stabilization of transition state **TS42b**). Nonetheless, it gives an indication that a proper account of electron correlation, also in optimizing the geometries and in calculating vibrational frequencies, would be needed for an accurate quantitative result. This is, however, outside the scope of the present work.

Then we have investigated the third step of Scheme 3 in more detail, considering the acylation both in the ortho and para positions (Scheme 5). We have found that the transition state for the ortho substitution (**TS23**) is relatively low in energy because of a strong stabilizing interaction of the oxygen of formyl chloride with the boron atom: the activation enthalpy is 13.4 kcal/mol and the Gibbs free energy 29.0 kcal/mol; the latter is again reduced to 25.8 kcal/mol using MP2 electronic energies and further reduced to 22.7 kcal/mol including the corrections for changing the reference state from the ideal gas at 1 atm to concentration units and including the correction for a condensed phase.[34] Such corrections do not alter the energy of the other stationary points, which are unimolecular. In the transition state (**TS23**, Figure 6), the distance between the boron

TABLE 1. Calculated Enthalpies and Free Energies in kcal/mol for the Reaction Path Shown in Figure 7[a]

species	ΔH_{corr}, DFT	ΔG_{corr}, DFT	MP2
1a	0.0	0.0	0.0
4	2.8	3.5	4.1
TS42a	25.7	27.7	22.2
2 + HCOCl	4.4	−8.4	−9.6[b]
TS23	17.8	20.6	16.2
3 + HCl	−17.8	−25.6	−22.0[b]

[a] DFT, MPW1K/6-311+G**//MPW1K/6-311+G**; MP2, MP2/6-311+G**//MPW1K/6-311+G**. ZPE and thermal corrections refer to the gas phase at 298 K and 1 atm and are calculated at the DFT level. [b] For the bimolecular states **2** + HCOCl and **3** + HCl, corrections to free energies in order to change the standard state from gas at 1 atm to concentrations units and accounting for the condensed phase amount to 3.1 kcal/mol, thus reducing the reaction barrier of **TS23**.[34]

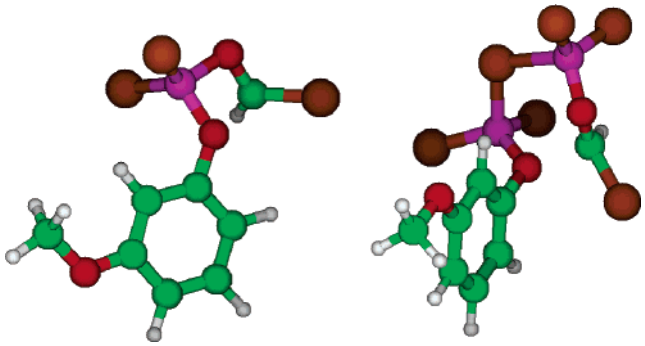


FIGURE 5. The transition states for the boron migration (second step of Schemes 3 and 4) and ArO−COHCl bond cleavage: left, **TS42a**; right, an additional BCl_3 molecule is involved (**TS42b**).

(33) (a) Kabalka, G. W.; Wu, Z. *Tetrahedron Lett.* **2000**, *41*, 579. (b) Kabalka, G. W.; Wu, Z.; Ju, Y. *J. Organomet. Chem.* **2003**, *680*, 12.

(34) (a) Benson, S. W. *Thermochemical Kinetics*; J. Wiley & Sons: New York, 1976; p 9. (b) Benson, S. W. *The Foundation of Chemical Kinetics*; McGraw Hill: New York, 1960; p 507.

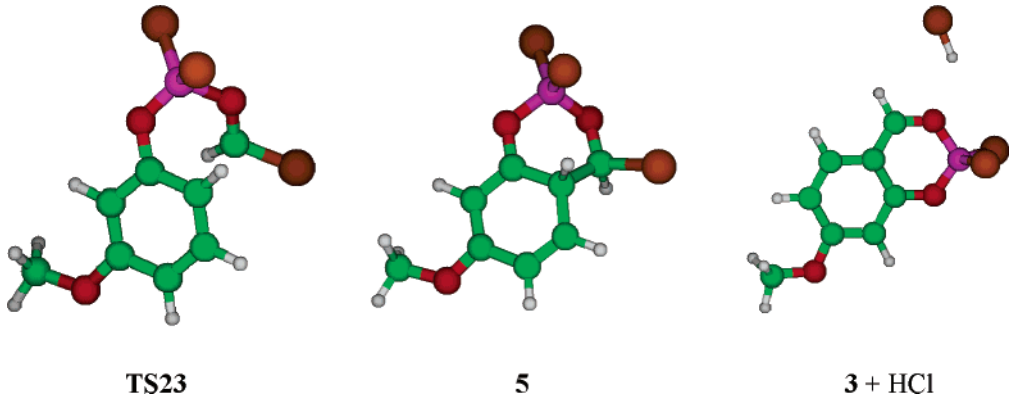


FIGURE 6. Transition state **TS23** (left), Wheland intermediate **5** (middle), and rearranged product **3** + HCl (right) for the ortho acylation.

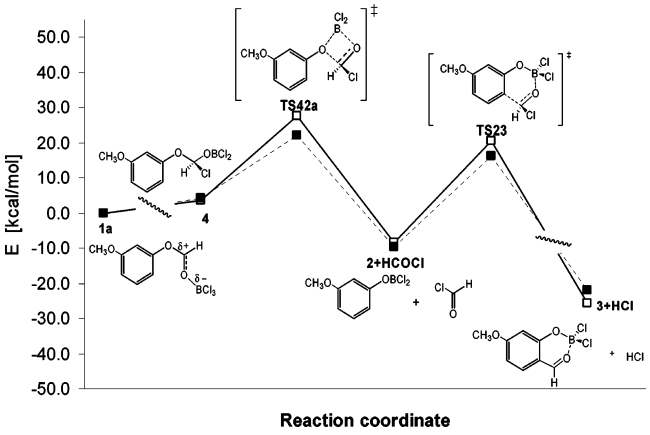


FIGURE 7. Energy profile of the Fries rearrangement. Calculated Gibbs free energies at the DFT level (open squares) and MP2 level (solid squares) include ZPE and thermal corrections at 298 K, gas phase, 1 atm. See Table S3 of Supporting Information for more details. For bimolecular states contributions are calculated by adding those of the two isolated molecules.

atom and the oxygen of formyl chloride is only 1.553 Å, slightly longer than the bond length between boron and the aryl oxygen (1.440 Å). In contrast, the C−C bond between the acyl group and the benzene ring is not yet formed, the distance being 2.192 Å. Such a strong boron−oxygen interaction also stabilizes the ortho Wheland intermediate **5** and the final borate ester of the rearranged product **3**, as shown in Figure 6.

In contrast, at the level of theory used, the para Wheland intermediate is not even a minimum on the potential energy surface. Therefore, the interaction of formyl chloride with the Lewis acid coordinated to 3-methoxyphenol lowers the activation barrier, thereby driving the reaction through the ortho substitution pathway.

The calculated activation enthalpies, although affected by the approximations due to the level of theory used, are in the typical range for organic reactions occurring at or below room temperature, as our experimental case. Therefore, the paths investigated are viable routes connecting the intermediates that we have identified by comparing experimental and computed chemical shifts. In Figure 7 we summarize the energy profile of the mechanism proposed; full data are reported in Table S3.

We can now comment on the ^{11}B and ^{1}H chemical shifts of the final rearranged product shown in Figure 6 (right panel). The calculated value of the ^{11}B chemical shift of the dichloroborate monoester of 4-methoxysalicylaldehyde is 11.1 ppm, in quite good agreement with the experimental result of 8.3 ppm, considering the neglect of spin−orbit effects. We note that the ^{11}B chemical shift of this compound is in the same range of borate triesters that we investigated in our previous work.[23] Nevertheless, the tetracoordination of boron, with salicylaldehyde acting as a chelating agent, causes a relatively strong shielding of the boron nucleus.

Inspection of the aldehyde resonance in Figure 4 reveals that the proton signal appears as a broad doublet with a separation of about 6 Hz and clearly exhibiting side shoulders, for a total line width of about 15 Hz. Since no ^{1}H−^{1}H correlation involving the resonance at 8.70 ppm has been observed in the COSY spectrum, this splitting can only arise from coupling to boron, whose ^{11}B signal is fairly narrow. A DFT calculation on **3** predicts a ^{1}H−^{11}B coupling constant (Fermi contact term only)[35] of about 5 Hz, in reasonable agreement with the observed splitting. However, since ^{11}B has $I = 3/2$, one would expect a 1:1:1:1 quartet broadened by the quadrupolar ^{11}B. The discrepancy can be reconciled by recalling that ^{11}B has a natural abundance of 80%, the remainder being ^{10}B ($I = 3$) with a magnetogyric ratio 1/3 of that of ^{11}B. Therefore, a proton coupled to ^{10}B is split into a 1:1:1:1:1:1:1 septet with a separation of ca. 1.6−2 Hz, possibly with a small isotope shift. A simulation (see Figure S9) reveals that the peculiar shape of the resonance at 8.70 ppm indeed derives from the superposition of a poorly resolved quartet and septet with the given coupling constants, further confirming the structure of the raw product as **3**. We recall that such large broadening is only observed in the proton resonance of the final product and not, for example, in the proton resonance of the intermediate. This is an indication that in the intermediate the boron atom is not bound to the formyl oxygen, confirming the hypothesis that such an intermediate is formyl chloride. In contrast, we do not expect any broadening in **1a** because of the fast exchange regime.

Relative Reactivity of Phenyl and 3-Methoxyphenyl Formates. Useful information can be obtained also by comparing the reactivity of phenyl and 3-methoxyphenyl formates. It is known that the reaction of phenyl formate with BCl_3 does not proceed to the rearranged product.[22,23] Generally speaking, this result is consistent with the activating effect of the 3-methoxy group with respect to the acylation in ortho position. However, the first and second step of the Fries rearrangement reported in Scheme 3 should not be influenced by the presence of a substituent on the phenyl ring. Therefore, this comparison offers

(35) Onak, T.; Jaballas, J.; Barfield, M. *J. Am. Chem. Soc.* **1999**, *121*, 2850.

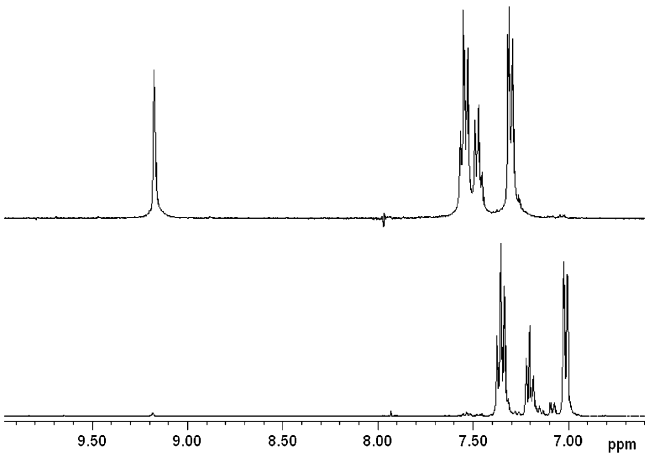


FIGURE 8. (Top) ^{1}H NMR spectrum of phenyl formate at 273 K just after the addition of BCl_3 in 1:1.2 ratio. (Bottom) the same sample after 1 day at room temperature.

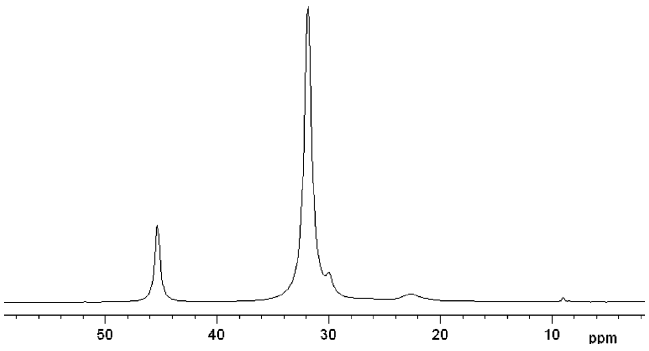


FIGURE 9. ^{11}B spectrum of the equilibrium (after 2 days at room temperature) reaction mixture of phenyl formate and BCl_3.

the opportunity to investigate the early events of the reaction, without intervention of the rearrangement step.

We thus consider the effect of adding BCl_3 (again in the ratio 1:1.2) to phenyl formate. In Figure 8 we report the ^{1}H spectrum of the overnight equilibrated reaction mixture of phenyl formate and BCl_3 (see Figure S10 for a time evolution of the NMR spectra). We note that, compared to the spectrum acquired just after the addition of BCl_3, the aldehydic resonance has disappeared. According to the second step of Scheme 3, the Lewis acid should remove the formyl group producing phenyl dichloroborate and formyl chloride. The latter, at room temperature, is completely decomposed into HCl and CO and therefore it is not detected in the spectrum. If this is correct, the low-intensity resonance at 31.8 ppm observed in the final ^{11}B spectrum in Figure 3, which corresponds to the monoester intermediate, should now be the only one observed, together with the excess free BCl_3 at 46.5 ppm. This is indeed the case as we can see in Figure 9.

Therefore, only the first and second steps of Scheme 3 take place if the activating 3-methoxy group is not present, strongly supporting the proposed mechanism. Analogous lack of reactivity is found for 4-methoxyphenyl formate, where the methoxy group cannot act as activating group toward ortho electrophilic substitution. In contrast, the Fries rearrangement does proceed with 3,5-dimethoxyphenyl formate.

Conclusion

We have investigated the mechanism of the Fries rearrangement of aryl formates promoted by the Lewis acid boron trichloride. ^{1}H, ^{2}H, and ^{11}B NMR spectroscopy have given essential insights on the key steps of the reaction. The reaction proceeds in two main steps, after the formation of an initial 1:1 substrate−Lewis acid adduct: in the first major step, formyl chloride is produced in the reaction mixture; the aldehyde functionality is then introduced in the aromatic ring through an electrophilic acylation. The mechanism in this case is intermolecular. The ortho position is strongly favored because the corresponding transition state benefits from a chelating effect of the two ortho oxygen atoms on the boron atom. Such an interaction significantly lowers the energy barrier, in contrast to the case of the para isomer, where it is not effective. DFT calculations of the energetics of several reaction paths have confirmed that the proposed mechanism is indeed a viable route to the ortho rearranged product. DFT calculations of ^{1}H and ^{11}B chemical shifts agree with the observed resonances in the NMR spectra.

The general validity of this mechanistic proposal for the Fries rearrangement at large remains, however, still an open question. Clearly, in all cases where the para isomer is the major or the only product, a different scheme has to be invoked. Indeed, even in the reaction investigated herein, if the rearrangement of aryl formates is carried out with a protic superacid such as CF_3SO_3H in place of the Lewis acid, the para isomer is also obtained.[22] In this case, several features can be expected to be different, like the strength of the aryl formate−acid interaction and the structure of all intermediates; thus, for example, one would not expect any favorable interaction of the ortho oxygen atoms with the catalyst. Hence, whereas this reaction probably possesses a multifaceted course depending on the precise nature of reactant and catalyst, we hope to have at least clarified most factors that underlie the final outcome in this instance.

Experimental Section

Preparation of Samples. The nondeuterated formates have been prepared according to ref 36. The reaction mixtures were prepared directly in the NMR tube with a 0.082 M solution of 3-methoxyphenyl formate in $CDCl_3$ (0.6 mL, 0.05 mol) and adding ca. 0.06 mL of a 1 M solution of BCl_3 in heptane. The reaction mixture was kept in dry ice/acetone during the first few minutes before inserting the tube into the probehead. Usually the tube was allowed to equilibrate for a few minutes before starting the acquisition. The solution turns to a pale orange/yellow color as soon as BCl_3 is added and eventually it becomes dark red as the substrate has completely reacted.

Preparation of 3-Methoxyphenyl Formate-1-*d* (1-*d*). 1-*d* was prepared according to a new synthetic procedure that employs triformamide as formylating reagent, prepared in situ from methanesulfonyl chloride and sodium diformamide.[36] This method allows us to use formic acid (99% D, 95% in D_2O) as deuterated starting material according to the following procedure.

Methyl Formate-1-*d* ($DCOOCH_3$). A mixture of DCOOD (5.10 g, 95% D, 0.1 mol), calcium chloride (1.20 g), and dry methanol (30 mL) is heated at 60−65 °C, under distillative removal of the product methyl formate-1-*d* through a 25-cm Vigreux column (∼3 h) to yield 3.51 g (57%); bp 31 °C/720 Torr.

Formamide-1-*d* ($DCONH_2$). Ammonium chloride (10 g, 0.18 mol) is suspended in dry methanol (30 mL). A 30% solution of sodium methoxide (32.40 g, 0.18 mol) in methanol is added

(36) Ziegler, G.; Kantlehner, W. *Z. Naturforsch. B.* **2001**, *56*, 1172.

dropwise with stirring at 0 °C. After the addition is terminated, the mixture is stirred for 30 min and then filtered. The methanolic ammonia solution thus obtained is mixed with methyl formate-1-*d* (3.51 g, 57 mmol). After 30 min of stirring at room temperature, the mixture is heated for 1 h under reflux and then left standing for 12 h. Methanol is distilled off and the residue is distilled in vacuum to give 1.90 g (74%) of formamide-1-*d*; bp 58−60 °C/0.1 Torr.

Sodium Diformamide-1,1′-d_2 [$(DCO)_2N^-$ Na^+]. A solution of sodium ethoxide in ethanol is prepared from sodium (0.60 g, 26 mmol) and dry ethanol (15 mL). After the addition of formamide-1-*d* (1.90 g, 41 mmol) in 10 mL of absolute ethanol, the mixture is left standing for 18 h at room temperature. The product is filtered off, washed with absolute ethanol, and dried in vacuum to yield 1.6 g (84%); mp 234−236 °C (dec).

3-Methoxyphenyl Formate-1-*d* (1-*d*). Methanesulfonyl chloride (0.57 g, 5 mmol) is added at −10 °C dropwise with stirring to a suspension of sodium diformamide-1,1′-d_2 in 30 mL of absolute acetonitrile (see Scheme S1). The temperature is left to increase to 0 °C within 20−22 h under stirring. At this temperature, 3-methoxyphenol (0.62 g, 5 mmol) is added. The mixture is heated under reflux for 90 min. After removal of the acetonitrile by distillation the residue is cooled to 0−2 °C and 30 mL of absolute ether is added with stirring. After 12 h the ethereal solution is separated. The ether is removed by distillation and the residue is distilled through a 15-cm Vigreux column in vacuum to yield 0.46 g (61%) of 3-methoxyphenyl formate-1-*d*; bp 41 °C/10^{-3} Torr. The product contains small amounts of formamide. To obtain a sample free from formamide, the product is extracted three times with cyclohexane. The combined cyclohexane extracts are evaporated. The residue (156 mg, 20%) consists of 3-methoxyphenyl formate-1-*d* with an 88% deuterium content (NMR, see Figure S7).

NMR Spectroscopy. All ^1H and ^2H NMR measurements have been run at 400 and 61 MHz, respectively, with a 5-mm multinuclear inverse probehead. ^2H measurements were run unlocked, with lock cables unplugged to prevent RF interference. The magnet stability was preliminarily checked to be sufficient within the time frame of the experiments. ^{11}B and ^{13}C NMR measurements have been run at 96 and 75 MHz, respectively, with a 5-mm multinuclear probehead. Kinetics measurements have been run in the range of temperatures between 263 and 298 K over a time period of 20 h following the time evolution of ^1H and ^{11}B spectra. For ^2H kinetics experiments only a single temperature was selected.

QM Calculations. Density functional theory calculations have been run using the software Gaussian 03.[37] Following the work of Truhlar and coworkers[38] and Gilbert,[39] we have used the MPW1K functional[40] with the 6-311+G** basis set for energy calculations and for geometry optimization of reactants, products, and transitions states, the latter ones using the QST3 algorithm. The MPW1K functional has been found to have a better performance than other functionals, particularly B3LYP, for the calculation of transition barriers;[38] it was also found to give very accurate geometries in cases where dative bonds with boron are involved.[39] Therefore, it appears to be the method of choice for our system. In addition to this, we have also calculated single point energies at the MP2/6-311+G** level for the structures optimized at the DFT level. ZPE and thermal corrections to free energy are calculated at the DFT level and referred to the gas phase at 1 atm and 298 K. Transition states have been checked by frequency calculations and intrinsic reaction coordinate calculations to confirm that the observed transition state is characterized by a single negative vibrational frequency and that the corresponding normal mode connects reactants and products. NMR properties calculations were carried out at the B3LYP/cc-pVTZ//B3LYP/6-31G** level as previously described.[23,25] The chemical shift is calculated as $\delta = \sigma_{ref} - \sigma$, where σ is the shielding constant of the nucleus investigated and σ_{ref} is the shielding constant in TMS.

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Supporting Information Available: NMR spectra of compounds, Cartesian coordinates, and computed energies of optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(40) The route section of Gaussian03 input files was # mpwpw91 IOp(3/76=1000004280) IOp(3/77=0572005720) IOp(3/78=1000010000).