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Mechanism of 1-Acetyl-2-methoxynaphthalene Isomerisation over a HBEA Zeolite

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Over HBEA, liquid phase acetylation of 2-methoxynaphthalene (2-MN) by acetic anhydride leads directly to 1-acetyl-2-methoxynaphthalene (I), to 2-acetyl-6-methoxynaphthalene (II), and to a small amount of 1-acetyl-7-methoxynaphthalene (III). At a long contact time, isomer I undergoes deacylation into 2-MN and isomerisation into II and III. Isomerisation of I is much faster in the presence of 2-MN than in its absence, which suggests that this reaction occurs through an intermolecular transacylation mechanism. The transformation of isomer I with a deuterated methoxy group (OCD_3) in the presence of 2-MN shows that isomer II results only from this mechanism whereas an intramolecular mechanism participates also in the formation of isomer III.

Key Words: **1-acetyl-2-methoxynaphthalene isomerisation; mechanisms, intramolecular and intermolecular; acetylation; HBEA zeolite.**

INTRODUCTION

Arylketones, which are intermediates in the synthesis of various fragrances and pharmaceuticals, are generally prepared by acylation catalysed by Lewis acids such as $AlCl_3$ (1–3). As the arylketone forms a stable 1 : 1 molar adduct with the catalyst, more than stoichiometric amounts of Lewis acids are required. The adduct is usually hydrolysed with water and consequently a large amount of inorganic by-product, more than 4 mol of Cl^-/mol of ketone, are generated when acylchlorides are used as acylating reagents. This is why the development of alternative acylation processes using other acylating agents such as carboxylic acids or acid anhydrides, and noncorrosive solid and reusable catalysts, is particularly active. The possibility of using zeolites as catalysts for acylation of various aromatics is well demonstrated (2–20). Furthermore, a commercial process of acetylation of anisole and of veratrole with acetic anhydride (selectively in the para position) was recently developed by Rhône Poulenc (7, 8).

This paper deals with the liquid phase preparation of 2-acetyl-6-methoxynaphthalene (II) which is a precursor of (*S*)-Naproxen, an important anti-inflammatory drug. Acetylation of 2-methoxynaphthalene (2-MN) was investigated over solid catalysts by various authors (17–20). Harvey and Mäder (17) studied the acetylation of 2-MN with acetic anhydride over large pore zeolites. They showed that 1-acetyl-2-methoxynaphthalene (I) and 2-acetyl-6-methoxynaphthalene (II) were initially formed, isomer I undergoing deacylation afterward. Thanks to this deacylation, isomer II was selectively synthesised at 100°C by use of a large amount of HBEA catalysts. However, at this temperature, the production of isomer I, which is too bulky to enter the pores of a HBEA zeolite, could only occur on the external surface (18), which is generally very large with this zeolite.

In this paper we confirm that acetylation of 2-MN over HBEA leads directly to I and II. Moreover, small amounts of 1-acetyl-7-methoxynaphthalene (III) are also formed. This direct acetylation is followed not only by deacylation of I but also by its isomerisation into II and III. This latter reaction is demonstrated to occur mainly through an intermolecular transacylation mechanism, part of III resulting however from an intramolecular process.

METHODS

The reactions were carried out in the liquid phase in a batch reactor over a HBEA zeolite (total and framework Si/Al ratios of 11 and 15, respectively) provided by PQ Zeolites and previously calcinated overnight under air flow at 500°C. The total pore volume of the zeolite was 0.694 $cm^3\ g^{-1}$, the total micropore volume of 0.269 $cm^3\ g^{-1}$ including 0.167 $cm^3\ g^{-1}$ for the structural micropores and the mesopore volume of 0.525 $cm^3\ g^{-1}$. These mesopores are due to intercrystalline voids resulting from the agglomeration of the very small crystallites of HBEA: a TEM micrograph shows that the sample presents crystals smaller than 20 nm. The concentrations of Brönsted and Lewis acid sites able to retain pyridine adsorbed at 150°C

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were found to be equal to 3.1×10^{20} and 2.3×10^{20} sites g^{-1} (21, 22).

Time zero of the reaction was taken as the time of introduction of the zeolite in the reactant mixture heated at the reaction temperature. Small samples of the reaction mixture (0.1 cm^3) were taken at various times and analysed by GC on a 25-m capillary CP Sil 8 CB column. Identification of the products was carried out by using reference samples or by mass spectrometry.

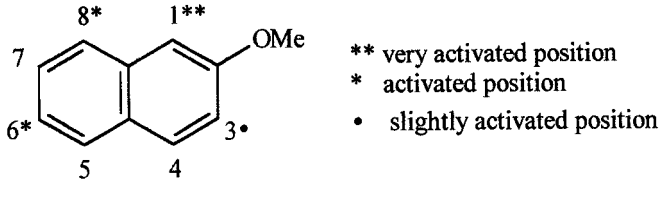
The synthesis of nondeuterated 1-acetyl-2-methoxynaphthalene (isomer I) was performed according to Ref. (23) by reacting 1-acetyl-2-hydroxynaphthalene (1 equiv) with Me_2SO_4 (1 equiv) in the presence of K_2CO_3 (1 equiv) using acetone as a solvent (54 equiv) under stirring at room temperature for 24 h. The product is recovered and recrystallised in petroleum ether (yield of 83%). Isomer I deuterated on the methoxy group was prepared through the same reaction by using deuterated Me_2SO_4 instead of nondeuterated Me_2SO_4. Due to a primary isotopic effect, 5 days (instead of 1) are necessary for the reaction (yield of 80%; 99% of [D_3] species).

RESULTS AND DISCUSSION

1. *Preliminary Results*

Acetylation of 2-methoxynaphthalene (2-MN) with acetic anhydride was first carried out in a batch reactor under the following conditions: 500 mg of HBEA, 35 mmol of 2-MN, 7 mmol of acetic anhydride, 39 mmol of nitrobenzene, which corresponds to a total volume of 10 cm^3, and temperatures of 90, 120, and 155°C.

Whatever the temperature, the reaction products are mainly three isomers indicated as I (1-acetyl-2-methoxynaphthalene), II (2-acetyl-6-methoxynaphthalene), and III (1-acetyl-7-methoxynaphthalene) resulting from acetylation of 2-methoxynaphthalene, acetic acid resulting from this reaction but also from hydrolysis of acetic anhydride and cracking of the acylation products. The other isomers, and particularly the one which corresponds to the slightly activated 3-position of 2-MN (Scheme 1), are observed only in trace amounts: the sum of their concentrations is always less than one-third of the concentration of isomer III. Figure 1 shows that while initially 2-MN is rapidly transformed, the conversion is nearly constant



SCHEME 1

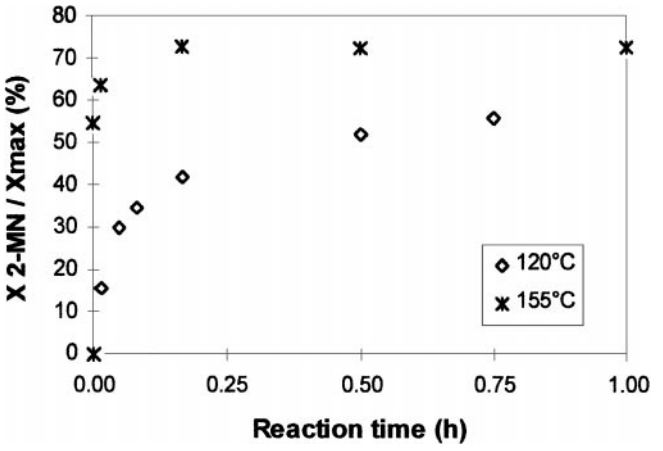


FIG. 1. Influence of reaction time (from 1 min to 1 h) on the conversion of 2-methoxynaphthalene (2-MN) at 120 and 155°C. $X_{2\text{-MN}}/X_{max}$ is the ratio between the actual conversion and the maximum possible conversion (0.2) with the initial acetic anhydride/2-MN ratio.

after 10–30 min. This quasi-plateau is due to the fact that acetic anhydride is completely converted both by acetylation of 2-MN and by hydrolysis during the first 10–30 min of reaction time. It may be noted that acetic acid was found to be inactive as an acylating reagent (4).

Whatever the temperature, I, II, and III isomers appear as primary products. Initially, isomer I is largely predominant, particularly at low temperatures (Table 1). This favourable substitution of 2-MN at the 1-position could be expected, this position being the most activated one (Scheme 1). However, isomer I disappears afterward at the benefit of II and III, (Fig. 2). The higher the reaction temperature, the faster this disappearance; thus, after 8 h at 155°C, isomer I has completely disappeared, whereas at 90°C it remains largely predominant after 25 h (Table 1). Figure 2 shows that this isomerisation is slower than the direct acetylation of 2-MN into I and even into II. Therefore, the initial formation of II cannot be due to a rapid isomerisation of the predominant

TABLE 1

Distribution (%) of Acetylmethoxynaphthalene Isomers as a Function of Reaction Temperature

Temperature	Reaction time (h)	I	II	III
90°C	0[a]	88.3	8.6	3.1
	1	80.8	16.2	3.0
	25	73.7	23.7	2.6
120°C	0[a]	77	20.6	2.4
	1	63.9	33.3	2.8
	25	35.9	58.4	5.7
155°C	0[a]	74.5	23.5	2.0
	1	34.0	59	7.0
	8	0	85.7	14.3

[a] Estimated by extrapolation at zero conversion.

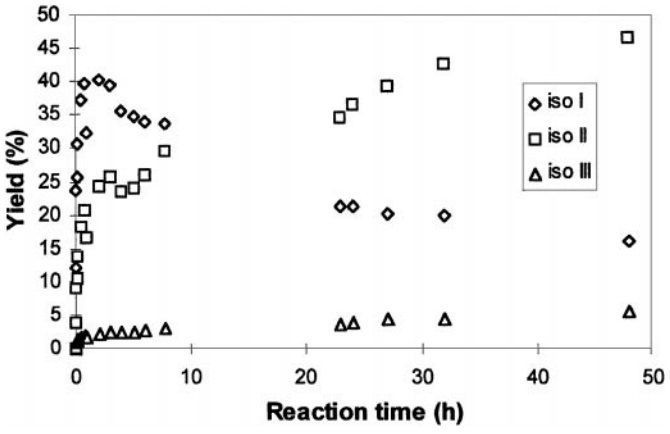


FIG. 2. Acetylation of 2-methoxynaphthalene at 120°C. Yields into acetylmethoxynaphthalene isomers I, II, and III versus reaction time.

product of 2-MN acetylation (I), hence results truly from acetylation of 2-MN with acetic anhydride.

Whereas isomer I can be completely transformed at 155°C (after 8 h of reaction), this transformation is not only due to isomerisation into II and III but also to deacylation. This deacylation is well-known to occur easily with ketones hindered in the ortho position in the presence of acidic solutions (24). It is practically negligible at lower temperatures: at 155°C, there is a decrease in the apparent conversion of 2-MN whereas it is not the case at lower temperatures (Fig. 3). This is why afterward all the reactions were carried out at 120°C.

The transformation of I was investigated under the following conditions: 500 mg of HBEA, 20 mmol of I, and 9.7 mmol of nitrobenzene, which corresponds to a total volume of 5 cm^3, i.e., with a concentration of isomer I 14 times higher than the maximum concentration obtained during

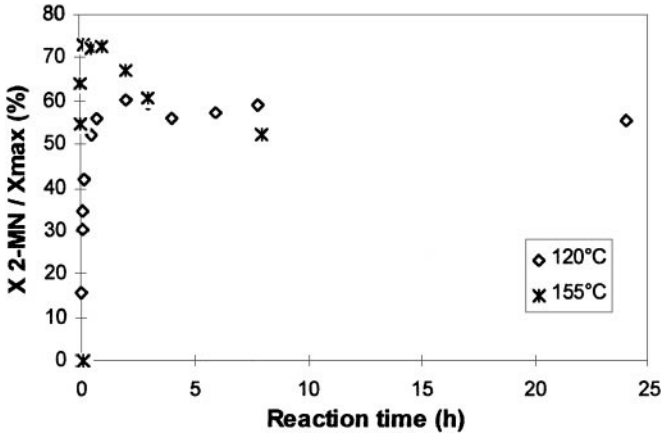
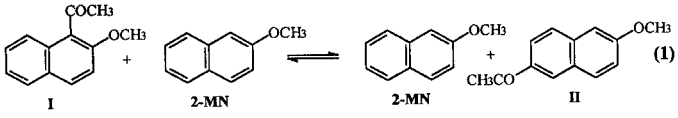


FIG. 3. Influence of reaction time (from 1 min to 25 or 8 h) on the conversion of 2-methoxynaphthalene (2-MN) at 120 and 155°C. $X_{2\text{-MN}}/X_{\max}$ is the ratio between the actual conversion and the maximum possible conversion (0.2) with the initial acetic anhydride/2-MN ratio.

2-MN acetylation with acetic anhydride. Under these conditions, the isomerisation of I is very slow: only 4% of II and III can be obtained after 40 h whereas during acetylation with acetic anhydride, 50% of these isomers were formed during the same time, half of this production occurring after the total disappearance of acetic anhydride. A possible origin of this very low rate of isomerisation could be the absence of 2-MN in the reactant. Indeed, this compound which is present in large amounts during acetylation could participate through transacylation in an intermolecular mechanism of isomerisation (reaction **1**).



It should however be noted that a small amount of 2-MN is rapidly formed by deacylation of I (14% after 40 h).

2. *Influence of 2-MN on the Rate of Isomerisation of I*

To confirm the participation of 2-MN in isomerisation, the transformations of I in the presence and in the absence of 2-MN were compared under identical conditions of concentrations of I and of nitrobenzene. Indeed, polar solvents, such as nitrobenzene, can compete with reactants for adsorption on the acidic sites (25–27). The following conditions were chosen: 4 mmol of isomer I, 9.7 mmol of nitrobenzene, and either 20 mmol of 2-MN (A) or of 1-methylnaphthalene (B) (we have checked that 1-methylnaphthalene underwent no reaction), which corresponds in both cases to a total volume of 5 cm^3. Figure 4 shows that isomerisation is much faster in the presence of 2-MN than in its absence. The positive effect of 2-MN is more pronounced for the formation of isomer II (Fig. 4a) than for that of III (Fig. 4b): the rate of formation of II is 10 times higher, that of III is 5 times higher.

From these experiments it can be concluded that the formation of isomer II occurs essentially through an intermolecular mechanism (reaction **1**). This mechanism is probably the only one which is involved in this formation. Indeed, the slow formation of II which is observed in conditions B could be due to the small amount of 2-MN rapidly formed through deacylation of isomer I. On the other hand, the less pronounced effect of 2-MN on the formation of isomer III suggests a small participation of an intramolecular mechanism in its formation. Figure 4a shows that the nonsterically-hindered ketone II undergoes deacylation but, however, more slowly than isomer I.

3. *Confirmation of the Isomerisation Mechanisms by Use of Deuterated Isomer I*

To confirm the isomerisation mechanisms, the transformation of isomer I with a deuterated methoxy group

(OCD_3) in the presence of 2-MN was investigated under conditions A, the products being analysed by mass spectrometry after various reaction times. Only species with OCD_3 or OCH_3 groups were found in 2-MN and isomers I, II, and III, i.e., no single exchange of deuterium atoms occurs during isomerisation. Both formations of II and III were slightly slower from deuterated isomer I than from the nondeuterated one (very small secondary isotopic effect).

Figure 5 shows the change with reaction time in the percentage of deuterated species in isomers I (a), in isomers II and III (b), and in 2-MN (c). A considerable change in the isotopic composition of the reactants is observed in the first minute of reaction: the percentage of deuterated species of isomer I passes from practically 99% to approximately 70% whereas the percentage of deuterated species of 2-MN increases from 0 to 30%. Afterward, the change is much less pronounced, in particular, for 2-MN. The isotopic composition of isomers II and III depends only slightly on the reaction time: approximately 15% of the deuterated species in isomer II and 25% in isomer III.

The small amount of deuterated species in isomers II and III indicates that at least a large part of isomerisation does not occur through an intramolecular process

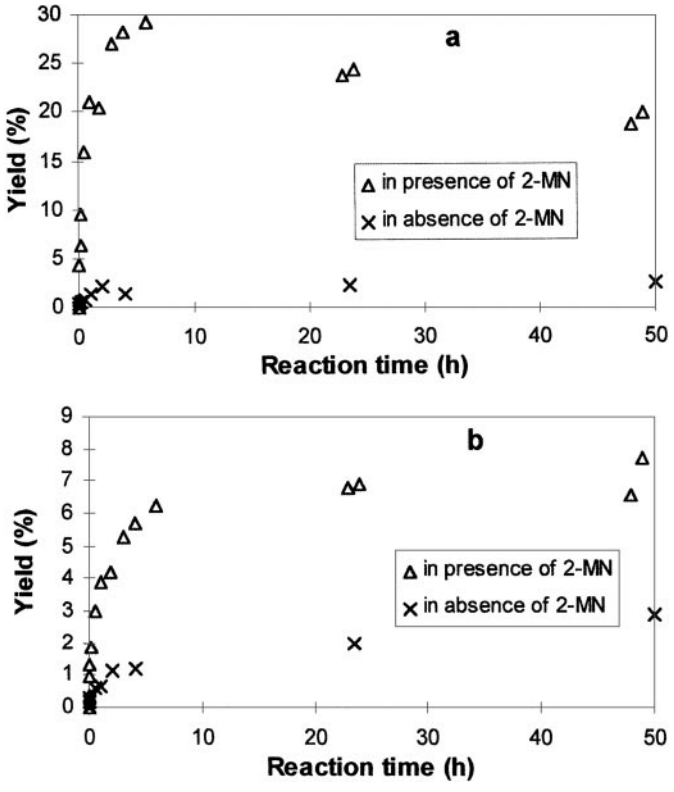


FIG. 4. Isomerisation of 1-acetyl-2-methoxynaphthalene (I) at 120°C. Yields in isomers II (a) and (III) (b) versus reaction time in the presence or in the absence of 2-methoxynaphthalene.

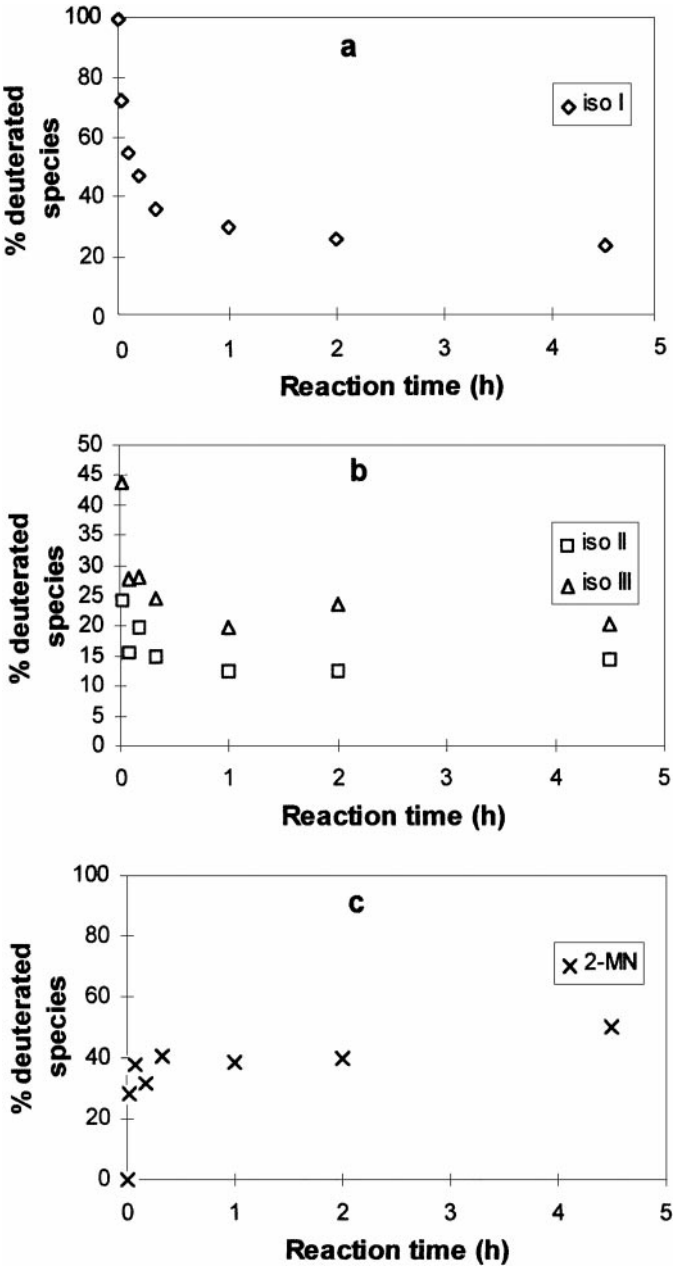
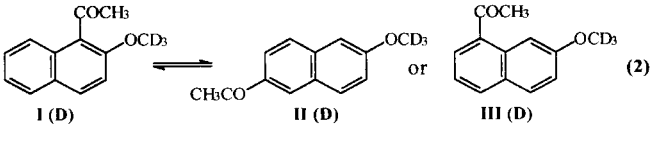
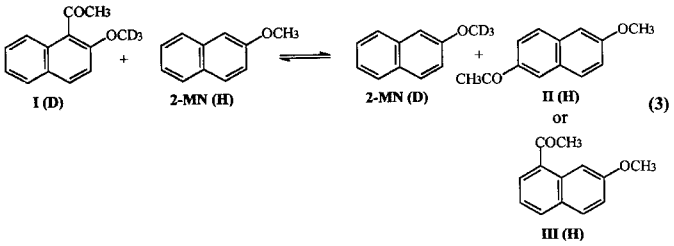


FIG. 5. Isomerisation of deuterated 1-acetyl-2-methoxynaphthalene (I) at 120°C. Percentage of deuterated species in I (a), II and III (b), and 2-MN (c) versus reaction time.

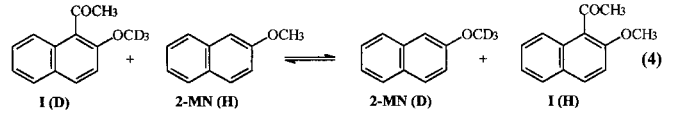
(reaction **2**)



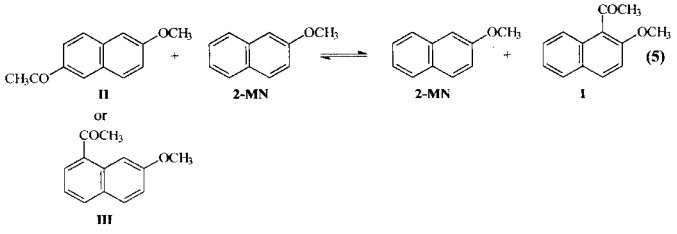
but involves most likely transacylation reactions (reaction **3**).



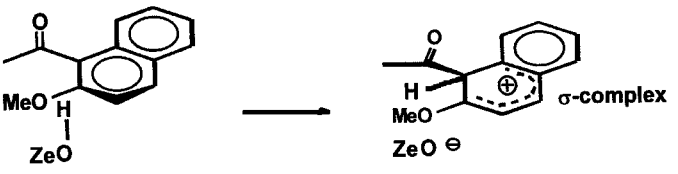
On the other hand, the deuterated species of isomers II and III do not result necessarily from reaction **2**. Indeed, this reaction cannot explain the simultaneous formation of nondeuterated species in isomer I and of deuterated species in 2-MN. This formation, which occurs very quickly, can be explained by an intermolecular process involving both compounds I and 2-MN (reaction **4**), i.e., by a transacylation process similar to the one proposed for the formation of the nondeuterated isomers II and III.



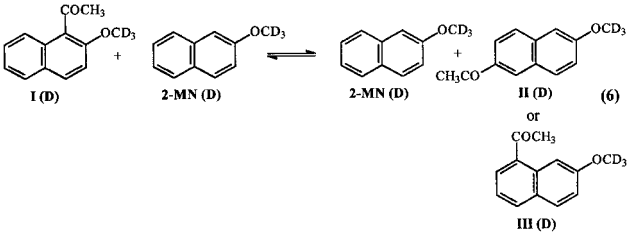
The non deuterated isomer I can only result from reaction **4**. Indeed, in agreement with the literature (19), we have found that reaction **5**, which could lead to this compound,



was impossible for thermodynamic reasons (28). On the other hand, deuterated 2-MN can be formed through reaction **4** and also through deacylation of deuterated isomers I, II, and III. Therefore, if reaction **4** is faster than reaction **3**, a large part of the deuterated species found in isomers II and III should result from transacylation between deuterated isomer I and deuterated 2-MN molecules (reaction **6**).



SCHEME 2. Formation of the σ-complex from 1-acetyl-2-methoxynaphthalene on zeolite.

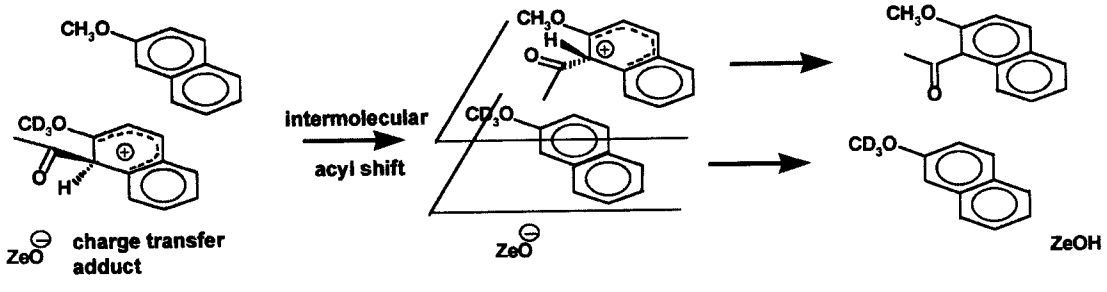


The initial rate of formation of nondeuterated isomer I (measured after 1 min) was found to be 20 times greater than the rate of production of isomers II and III, indicating that reaction **4** is really much faster than reactions **3** and **6**. Therefore, it can be considered that most of the deuterated species found in isomers II and III result from reaction **6**, i.e., that isomerisation of I into II and III occurs mainly through an intermolecular mechanism.

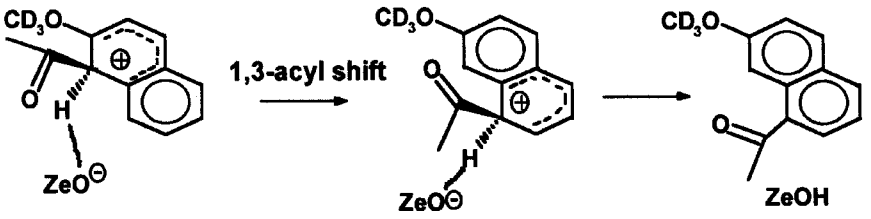
However the greater percentage of deuterated species in isomer III than in isomer II suggests that an intramolecular process (reaction **2**) is involved with reaction **3** in the formation of III. This participation of reaction **2** was proposed above to explain the lower effect of 2-MN on the rate of formation of isomer III compared to isomer II (Fig. 4).

The mechanism of isomerisation of deuterated I into nondeuterated I can be explained as follows. The attack of a proton from the zeolite at the position bearing the acyl group (IPSO position (29)) leads to a positively charged σ-complex that is partially stabilised by the methoxy group and the adjacent aromatic ring (Scheme 2).

This complex can also be stabilised by a 2-methoxynaphthalene molecule: indeed, the electron-rich aromatic ring of 2-methoxynaphthalene can form some kind of charge transfer adduct with the σ-complex with both



SCHEME 3. Formation of 1-acetyl-2-methoxynaphthalene from [D_3]-1-acetyl-2-methoxynaphthalene.



SCHEME 4. Intramolecular formation of [D_3]-1-acetyl-7-methoxynaphthalene from [D_3]-1-acyl-2-methoxynaphthalene.

molecules having their aromatic ring plans roughly parallel to each other (Scheme 3). In this conformation, acyl transfer from the deuterated σ-complex to the nondeuterated 2-MN may occur easily because of entropic factors: (favorable conformation) and of energetic (both reactants and products have nearly the same formation energies). The intermolecular acyl transfer occurs preferably on the most reactive C_1 carbon of 2-methoxynaphthalene to form deuterated 2-MN and the C_1 σ-complex of nondeuterated 1-acetyl-2-methoxynaphthalene (I). This last σ-complex may then lose a proton to afford nondeuterated I (Scheme 3). This intermolecular acyl transfer may also occur in the other activated positions, leading to isomers II and III.

On the other hand, the formation of the minor isomer III was shown to occur partly through an intramolecular process. This intramolecular process may be proposed as resulting from an acyl shift between carbons 1 and 8 of the σ-complex resulting from *IPSO* protonation on the C_1 carbon. The σ-complex obtained leads by proton elimination to the deuterated III isomer (Scheme 4). A cyclic transition state can be postulated.

The same mechanism could explain a transformation of III into II. However, as only a small amount of III is obtained, this secondary transformation plays, most likely, a limited role in the production of II, as furthermore confirmed by the primary formation of II. On the other hand, a direct acyl shift between the carbons 1 and 6 of the σ-complex is most unlikely because of the large distance between these carbons, which explains that intramolecular isomerisation of I into II, if it exists, is very limited.

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