JOC The Journal of Organic Chemistry

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Component Mobility by a Minute Quantity of the Appropriate Solvent as a Principal Motif in the Acceleration of Solid-Supported Reactions

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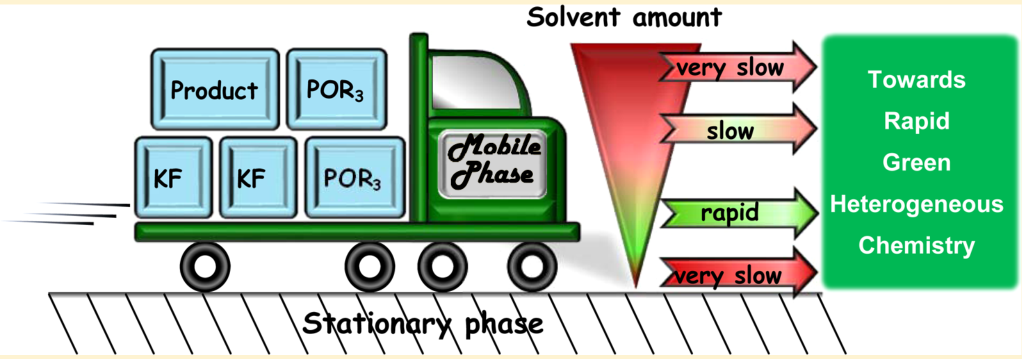
Supporting Information



ABSTRACT: The effects solvents have on fluoride-promoted heterogeneous hydrolysis and alcoholysis of various organophosphorus (OP) compounds on the surface of KF/Al_2O_3 are described. Solid-state magic angle spinning NMR analyses and SEM microscopy have shown that not only is the identity of the solvent important in these reactions but also its quantity. That is, minimal solvent amounts are favored and much more effective in such solid-supported reactions (and maybe generally) than those featuring solvent-free or excess solvent (>50 wt %) conditions. The addition of a minute quantity of the correct solvent (3−10 wt %, molar equivalent scale) avoids reagents leaching from the matrix, permits mobility (mass transport) of the reaction components and ensures their very high local concentration in close proximity to the solid-support large porous surface area. Accordingly, significant acceleration of reactions rates by orders of magnitude is obtained. Fascinatingly, even challenging phosphoesters with poor leaving groups, which were found to be very stable in the presence of solvent-free KF/Al_2O_3 or wetted with excess water, were efficiently hydrolyzed with a minute amount of this solvent.

INTRODUCTION

Inorganic oxides, such as alumina, silica, titania, clays, zeolite, and so forth, have gained wide use as catalysts or solid-supports in organic reactions due to their large porous surface area (typically >100 m^2/g^{-1}, 2−50 nm pore size) that holds acidic and/or basic active sites.[1−6] Reactions in the presence of these metal oxides often result in increased yields and easier procedures compared to those of conventional liquid-phase homogeneous setups. Furthermore, as the catalysts are typically effectively recycled, these reactions are considered to be environmentally benign. In addition, supporting reagents on such inorganic oxides, linked covalently or noncovalently (through electrostatic, ionic, or hydrogen bonds), is a well-known approach to increase their reactivity or selectivity. For example, immobilization of homogeneous asymmetric[7,8] or water-soluble[9−11] catalysts on the surface of porous inorganic solid supports furnishes heterogeneous catalysts, which are found to be effective in a variety of asymmetric transformations. Surprisingly, unlike the numerous synthetic laboratory applications of inorganic oxides developed over the last few decades, their use in industrial processes is very limited.[12] Perhaps one of the hardest tasks in the adaptation of inorganic oxide-supported procedures to large scales is the selection of the right solvent.[8] In general, solvents play a central role in heterogeneous reactions as they are responsible for the mass transport of multiple components present in the liquid phase to and within the solid support matrix. Selection of an inappropriate solvent may cause limited accessibility of the reaction components to the active catalyst and/or promote leaching of the catalyst from the surface/pores of the support, leading in either case to a decrease in the reaction rate and efficiency. Apart from reaction success, the environmental and economic aspects of solvent usage must also be considered once the type and amount of reaction solvent are determined. In this respect, many synthetic applications are not optimized as a large excess of volatile solvent compared to the solid support is typically used. Numerous studies have been

Received: March 15, 2015
Published: April 22, 2015

DOI: 10.1021/acs.joc.5b00492
J. Org. Chem. 2015, 80, 5176−5188

performed in an attempt to overcome this problem. For example, heterogeneous catalysis at supercritical conditions was developed as a means for the utilization of environmentally benign solvents.[13] Although effective, the benefits of these supercritical fluids must be considered carefully because their use is costly. An alternative approach aimed at this purpose utilizes supported reagents and microwave irradiation at solvent-free conditions.[14,15] However, as this attractive method depends on the capability of the inorganic solids to interact with microwave irradiation,[14−16] it is mainly suitable for thermal heterogeneous reactions. Therefore, the development of broad and effective procedures that feature optimized solvent consumption are still needed. To do so, the role of the solvents with respect to the various aspects of the heterogeneous processes must be explored. It appears that although large efforts have been invested in the development of synthetic applications of inorganic solid supports relatively less attention has been given to studying the mechanistic aspects of such heterogeneous reactions in terms of both their chemical and physical properties. Probing the solvent effects should provide valuable information to these respects and should therefore lead to the practical development of synthetic tools useful for implementation of so-called "green chemistry". Indeed, in recent years, continuing efforts have been invested in understanding the solvent effect on certain heterogeneous catalysis processes.[17−23] For example, Mantle and co-workers have examined the effect water has on diol catalytic oxidation in methanol in the presence of Au/TiO_2. Using a novel approach featuring a combination of pulsed-field gradient NMR diffusion and NMR relaxation time measurement techniques, they concluded that water addition caused both a decrease in the diffusion rate and adsorption strength of the diols to the catalyst, leading overall to limited accessibility to the active sites.[17,18] Most recently, Mitchell et al. studied the hydrogenation of 2-butanone using 1 wt % Pd/Al_2O_3 in the presence of 2-propanol, water, or 2-butanone as solvent.[24] Using the fast field cycling NMR technique to probe the slow dynamics of the liquid molecules imbibed in porous catalysts, they concluded that water forms much stronger interactions with the oxide surface compared to those of the organic solvents. In addition, water was found to exhibit biphasic behavior, which might explain its ability to promote or inhibit different heterogeneous catalytic reactions.[25−29] It is worth noting that, like others, the studies described above were performed in the presence of relatively large quantities of solvents, and they did not explore these effects with small amounts (<30 wt %).

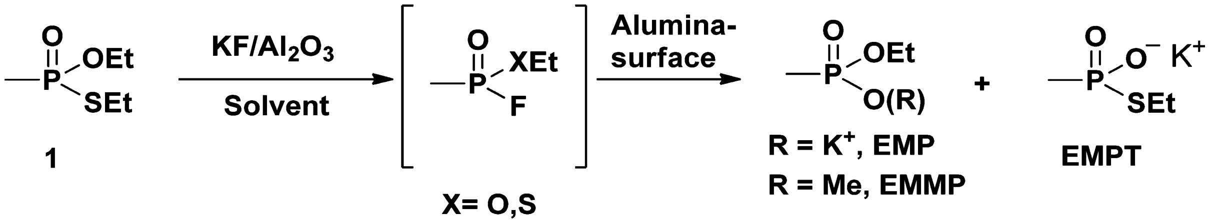
Solid-state magic angle spinning (SS MAS) NMR is a powerful tool for real-time monitoring of heterogeneous solid phase reactions because it can provide valuable information, such as the nature of the active site within the solid matrix, the identity of intermediates, the distribution of products, and the role diffusion plays in reaction kinetics.[30−43] Most reports to date describing the usage of this technique focus on reactions performed on various zeolites.[30−33] On the basis of their industrial significance, these types of reactions were thoroughly investigated. However, to the best of our knowledge, the solvent effect on heterogeneous reactions has never been studied systematically using MAS NMR. In recent years, we have been exploring organic transformations performed on inorganic solid supports using this NMR technique.[34−38] Among other reactions examined, hydrolysis reactions of organophosphorus (OP) warfare agents, which hold relatively good leaving groups, with alumina-supported fluoride reagents were specifically investigated.[35,37] Typically, impregnation of potassium fluoride on the surface of neutral alumina leads to the formation of a heterogeneous support, which is effective in a variety of substitution, elimination, addition, and condensation reactions.[44−52] However, from our studies, we concluded that standard KF/Al_2O_3 supports do not contain "available" (not connected to the surface) fluoride ions that are required for effective hydrolysis but rather hold hydroxide ions. Accordingly, a modified procedure for the preparation of "real" KF/Al_2O_3 and R_4NF/Al_2O_3 was established.[53] These supports were found to detoxify OP and sulfur mustard warfare agents extremely fast with reaction half-life scales of a few minutes.[37] It should be noted that only dry powders and powders wetted with a few percent of water were examined in these studies. The fact that the performance of the latter was by far more impressive provided an important clue on the potential effect that a small quantity of solvents may have on the outcome of a given reaction. Concurrently, we reported on fluoride-promoted homogeneous VX (*O*-ethyl *S*-2-(diisopropylamino)ethylmethylphosphonothioate) hydrolysis in dilute aqueous solutions.[54] In these reactions, the corresponding fluoridate (obtained from thiol group displacement by a fluoride ion) was initially formed as an intermediate and then quickly hydrolyzed to the appropriate phosphonic acid. Once the pH was maintained at its initial level (10.5) using a buffer, hydrolysis of the fluoridate intermediate to the phosphonate salt product was so fast that it could not be observed.

Aiming to further understand the mechanisms of solid-supported reactions, we were interested in answering the question as to what role solvents play in such heterogeneous reactions. We hypothesized that performing them in the presence of various quantities of common solvents would provide valuable chemical and physical information, which may be applied in the chemistry of more challenging OP compounds (i.e., phosphonic acid esters and phosphates). Herein, we disclose our findings regarding the effects solvents have on fluoride-promoted heterogeneous hydrolysis and alcoholysis of various OP compounds in the presence of KF/Al_2O_3. We will show that not only is the identity of the solvent important but also its quantity, that is, not solvent-free but minimal solvent amounts are favored and much more effective in such solid supported reactions (and maybe generally) than those featuring an excess of solvent. The addition of a minute quantity of the right solvent avoids reagents leaching from the matrix, permits mobility of all of the reaction components, and ensures their very high local concentration in close proximity to the solid support large porous surface area.

■ RESULTS AND DISCUSSION

Methodology. The SS MAS NMR technique was selected as the analysis method because it allows for effective real time monitoring of heterogeneous reactions over a broad range of solvent quantities, namely, from solvent-free reactions to 90 wt % of solvent. In addition, analyses of its data in terms of chemical shifts and line shape provide the ability to identify reagents, intermediates, and products within the solid matrix and to determine whether they are mobile or immobile, information that is crucial for understanding mechanisms of solid-supported reactions. In this respect, substantial information from SS MAS NMR experiments is achieved once the reaction components hold nuclei like ^{19}F and ^{31}P, which present high sensitivity. Reactions of OP compounds with fluoride ions are accordingly ideal for mechanistic studies using

Table 1. Reactions Kinetics and Products of 1 in the Presence of KF/Al_2O_3 and Solvents



entry	solvent	solvent (%)	k (10^4 h^{-1})	$t_{1/2}$ (h)	EMP[a] (%)	EMPT[a] (%)	EMMP[a] (%)
1	solvent free		16^c	433^c	95.0		
2	water	3	1551	4.5	88.5	2.7	
3	water	5	7176	1.0	81.4	17.2	
4	water	10	12441	0.6	76.6	19.1	
5	water	20	13580	0.5	75.0	23.3	
6	water	50	728	9.5	80.7	9.8	
7	water	90	199	34.8	92.0	4.7	
8	methanol	5	31856	0.22	57.4		42.1
9	methanol	10	47588	0.15	45.8		53.3
10	methanol	20	66811	0.10	13.3		83.0
11	methanol	50	63738	0.11	6.7		90.3
12	methanol	90	2364	2.9	2.1		80.9
13	ethanol	10	3702	1.9	22.5	2.3	61.3^d
14	ethanol	50	9691	0.7	4.5		91.6^d
15	acetonitrile	10	$6^{b,c}$	$1155^{b,c}$	72.4		
16	acetonitrile	50	$4^{b,c}$	$1733^{b,c}$	42.5		
17	heptane	10	44^c	158^c	97.0		
18	heptane	50	28^c	248^c	96.3		
19	water/acetonitrile	3/7	123^c	56^c	88.7	2.4	

[a] Product percent at the end of the measurement. [b] Estimation based on partial reaction. [c] On the basis of the second steady state slower reaction rate. [d] In these cases, the product is diethyl methylphosphonate (DEMP).

this NMR technique. It should be noted that although fluoride ions present on KF/Al_2O_3 promote the hydrolysis and alcoholysis of OP compounds they are consumed during the process and thus do not act as a reusable catalyst. On the basis of our previous results and as we will clearly show here, the fluoride ion initially reacts with the OP compound to furnish a fluoridate intermediate that immediately reacts with oxide groups present on the alumina surface or protic solvent to provide the product. This is the reason why a relatively large amount of solid support, as compared to the OP reagent, was applied in our experiments. We have chosen to use alumina impregnated with 20 wt % of KF because it gave the best results in a previous study.[35] As the reactions were performed in an NMR rotor without stirring the mixture and at ambient temperature, it was important to maintain the same experimental setup such that the experiments could be systematically and directly compared. Therefore, all of the experiments were conducted following the same protocol with the only variations being the identity and amount of the solvent. Moreover, as we were interested in relative kinetics and not absolute kinetic values, we performed all comparable reactions with the same batch of KF/Al_2O_3. Water, methanol, and ethanol were chosen as representatives of polar protic solvents. Acetonitrile was chosen as an example of a polar aprotic solvent, and heptane was selected as a nonpolar solvent. In all cases, the reaction profiles were of pseudo-first-order due to the large excess of fluoride ions and a rate-determining step, such as mass transport (or diffusion), of the reactants/products toward/from the active sites. The results of phosphonothioate **1**, phosphonates **2** and **3**, and phosphates **4**−**6** reacted with KF/Al_2O_3 in the presence of various solvents are described below.

Reactions of *O,S*-diethyl methylphosphonothioate 1 with KF/Al_2O_3. The first compound examined was *O,S*-diethyl methylphosphonothioate **1**, a good representative of the phosphonothioate family (Table 1). Thioates such as **1** are frequently used as a nontoxic simulant of V-type nerve agents and, accordingly, significant experimental and computational data on their reactions is published in the literature, allowing for direct comparisons.[55−57] In aqueous solutions, **1** was found to be much more stable[54] than VX, and its reaction with KF/Al_2O_3 is studied here for the first time. In general, as can be seen in Table 1, not only the solvents identity but also its amount significantly affected reactions kinetics and the types of products obtained. The hydrolysis of **1** to the corresponding product EMP in the presence of dry KF/Al_2O_3 (solvent-free) was extremely slow (entry 1).

The reaction profile consisted of two reaction rates. As with the other slow reactions, the second steady state slower reaction rate, which corresponds to the major part of the reaction, is presented in Table 1. EMP salt (appearing as a broad peak at 20 ppm, Figure S1, Supporting Information) was obtained and not EMPA, the acidic form, due to the local basicity of the solid surface. We have found that the addition of water, even at only 3 wt %, markedly influenced the reaction (entry 2). Interestingly, the best results with respect to reaction kinetics were obtained in the presence of 5−20 wt % of water (entries 3−5), whereas the reaction became sluggish at larger amounts of water (50−90 wt %, entries 6, 7). Once log *k* is plotted as a function of wt % of water added (Figure 1), a bell-

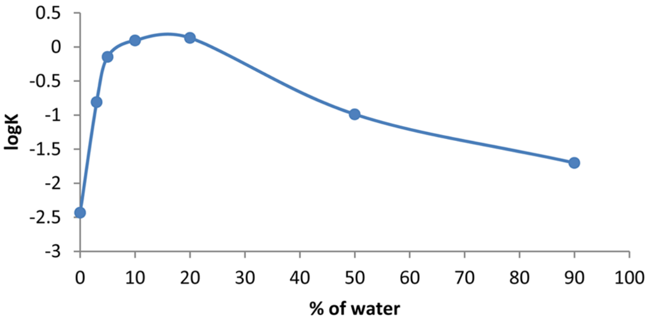


Figure 1. Hydrolysis of **1** with KF/Al_2O_3 in the presence of varying amounts of water.

shaped diagram is obtained with 10−20% being the optimal condition, leading to ∼800 times faster hydrolysis than that obtained on the dry solid support. On the basis of the fact that the fluoride ion is the first nucleophile acting in the OP compound hydrolysis, forming a fluoridate intermediate that is immediately hydrolyzed in basic aqueous environment,[54] it is reasonable to assume that the role of water as a solvent is more significant than its action in attacking this intermediate. This issue will be broadly discussed later. In addition to kinetics, the amount of water added also affected the product distribution. In this respect, it appears that the addition of 3 wt % of water is optimal, as relatively quick hydrolysis of **1** to the corresponding product EMP (P−S cleavage) with only minute amount of the side product (EMPT, P−O cleavage) was obtained compared to 19.1% of the side product formed in the presence of 10 wt % of water. Such reaction selectivity may be significant in cases like the decontamination of CWA VX, because its P−O cleavage product (desethyl-VX) has similar toxicity to VX itself.[57] With methanol, again, the addition of only 5 wt % significantly affected the reaction outcome (entry 8). The best results with respect to reaction kinetics were obtained with 20 and 50 wt % of methanol added (entries 10 and 11). Under these conditions, extremely fast reactions occurred that are ∼4000 times faster reactions than those obtained in the solvent-free reaction. However, methanolysis rather than hydrolysis (which occurs on the dry powder) is the main reaction in the presence of methanol (≥20 wt %). Similar to water, a bell-shaped diagram was also obtained for methanol once the reaction kinetics were plotted as a function of wt % of methanol added (Figure 2). However, the differences in reaction rates between examinations points were less significant for methanol than those of water. As might be expected, an increase in the amount of methanol added to the powder led to an increase in reaction selectivity and favored the production of the EMMP ester rather than the EMP analogue, generated as a side product due to reaction of the fluoridate intermediate with surface oxide groups. Performing the reaction in the presence of 20−50 wt % of methanol is accordingly optimal from both kinetics and product selectivity perspectives. A similar trend of reaction selectivity was observed with ethanol (entries 13 and 14). The reactivity order within the polar protic solvents in the presence of 10 wt % was found to be methanol > water > ethanol (entries 9, 4, and 13, respectively). We next proceeded to examine the polar aprotic solvent acetonitrile. Surprisingly, in the presence of 10 or 50 wt % of this solvent, very slow hydrolysis of **1**, even slower than that obtained in the solvent-free reaction, was observed (entries 15 and 16 vs 1).

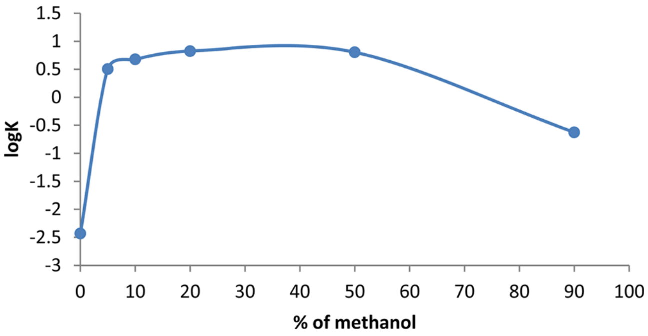


Figure 2. Methanolysis of **1** with KF/Al_2O_3 in the presence of varying amounts of methanol.

On the other hand, with 10 or 50 wt % of the hydrophobic solvent heptane, although very slow, somewhat quicker (factor of 2−3) hydrolysis than that obtained under solvent-free conditions was observed (entries 17 and 18 vs 1). Interestingly, in an experiment in which a mixture of water and acetonitrile (3/7 wt %) was used, the reaction was found to be slower than that obtained when only 3 wt % of water was added (entry 19 vs 2). Although the water amount in both experiments is equal, the reaction in the presence of the water/acetonitrile mixture is slower by more than an order of magnitude.

Mechanism. In general, most heterogeneous reactions are performed in the presence of a large quantity of solvent, and they involve five steps: (i) mass transfer of reactants from the bulk solution to the surface of the solid-support, (ii) adsorption of the reactants and diffusion to the active sites, (iii) chemical reaction, (iv) desorption of the products from the active sites, and (v) mass transfer of the products from the surface to the bulk solution.[58] Any one of these steps may be rate determining. To study a heterogeneous reaction with respect to these steps, it should first be determined what chemical species are involved in the reaction mechanism (step iii). We have previously proposed a mechanism for VX hydrolysis with KF/Al_2O_3 in the presence of water based on the literature. According to this suggestion, a fluoride ion reacts as a base to deprotonate water to afford a hydroxide ion that can attack the central phosphorus atom.[35] However, we did not exclude the possibility of an alternative mechanism by which the fluoride ion itself attacks the phosphorus atom to form a fluoridate intermediate, which immediately reacts with the basic surface of the alumina and water to furnish the final product EMP. According to both mechanisms, at the last stage of the hydrolysis, fluoride strongly binds to the alumina surface to form a strong Al−F bond.[59] This unreactive fluoride species, which is actually present in the form of K_3AlF_6, was clearly observed in the ^{19}F SS MAS NMR spectra of the final mixtures at −160 ppm even in the reactions performed without solvent. On the basis of our later results featuring the unique role the P−F bond has in the fluoride-promoted hydrolysis of phosphonotioate in dilute aqueous solutions[38,54] and the results obtained in this work, we now propose that the actual pathway occurring on the KF/Al_2O_3 support is one featuring a direct fluoride ion attack as illustrated in Figure 3. In neutral to mild basic solutions (up to pH 10), the fluoride ion reacts with **1** to give the appropriate fluoridate intermediate (observed by NMR), which hydrolyzes to EMP. However, in buffer solutions of higher basicity (pH 10.5), this fluoridate intermediate is immediately hydrolyzed to the product and is thus not observed.[54] Previously, we reported that our KF/Al_2O_3 support possesses a pH value of 10.6.[36] This basicity value most likely

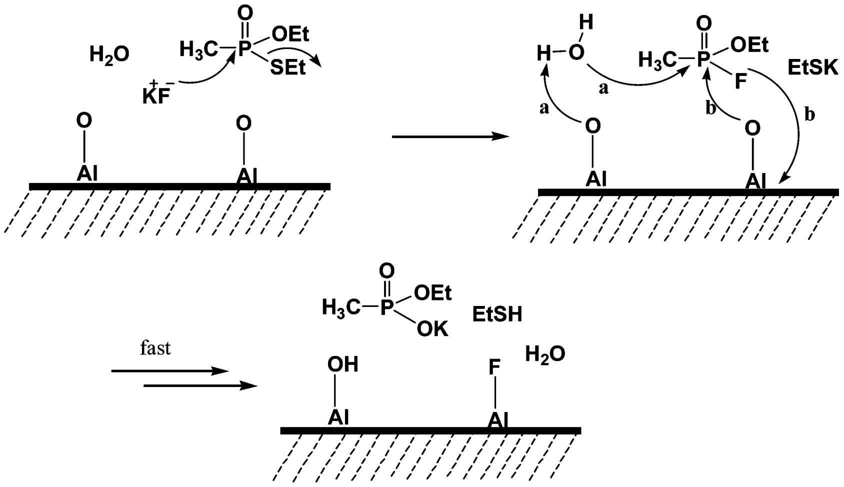


Figure 3. Proposed mechanism of reaction of **1** with KF/Al_2O_3 in the presence of water to form EMP. (a) Fluoride displacement through nucleophilic attack of a solvent molecule. (b) Fluoride displacement through nucleophilic attack of surface oxide groups. Similar reaction mechanisms are predicted in the cases of methanol and ethanol.

explains why the fluoridate intermediate was not observed in the reaction of **1** with KF/Al_2O_3 described in this work.

Therefore, the rate-determining step in the chemical reaction itself (stage iii of the overall mechanism) is the fluoride attack on the phosphorus atom to yield the fluoridate intermediate. Once it is generated, it immediately reacts with the solvent or surface oxide groups (paths *a* and *b* in Figure 3, respectively). Therefore, although water and alcohol may partially act as a reagent at this fast stage, their role as solvents to facilitate fluoride ion nucleophilic attack is more significant. The experiment in which 10 wt % of methanol was used (Table 1, entry 9), which ended with both methanolysis and hydrolysis products in similar quantities, strongly supports the two modes of immediate attack, *a* and *b*, as water was not present. Path *b* is the route that occurs when the solvent-free support is utilized. An experiment in which **1** was added to dry alumina, lacking KF, revealed that no reaction occurred after 2 weeks. The addition of 10 wt % of water or methanol to such alumina resulted in very slow reactions of **1** compared to its reaction with its wetted KF/Al_2O_3 counterpart ($t_{1/2}$ of 462 and 51 h, as compared to 0.6 and 0.15 h, respectively). These control experiments verify the importance of the fluoride ions.

Role of the Mobile Phase. To properly understand the solvents effects, we believe that the solid support should be considered a "stationary phase", whereas the solvent and species dissolved in it should be seen as a "mobile phase" (analogous to the chromatography world). The term "mobile phase" was selected rather than solution-phase (or liquid-phase) because in most of our experiments only a minute amount of solvent was added to the KF/Al_2O_3 such that it kept its powdery nature. However, this small amount was sufficient to interact with the reaction components without promoting their leaching from the solid matrix. According to this view, a minute quantity of water, methanol, or ethanol leads to the fastest OP transformations as they form an optimal "mobile-phase". Namely, these polar solvents mobilize all reactants, including KF and OP, as well as the reaction products better than the other solvents examined, resulting in very high concentration reactions in the microenvironment of the porous solid support. Mobilization of the EMP product as well as the inorganic component KF plays a central role. The fact that water, methanol, and ethanol dissolve KF much better than acetonitrile and heptane is documented in the literature.[60−62] The increased mobility of KF in water and methanol or even ethanol compared to its mobility in acetonitrile and heptane was confirmed by our SS MAS NMR studies. Narrow peaks of fluoride (as indicated by the full width at half-maximum (fwhm); Figure 4) indicative of mobile species were obtained in the case of KF/Al_2O_3 wetted with 30 wt % of water and methanol (180 and 76 Hz, respectively), whereas broad signals indicative of immobile species were obtained when heptane and acetonitrile were applied (1100 and 1070 Hz, respectively). In the case of the polar protic solvents water, methanol, and ethanol, mobility increased upon increasing their amount (Figures S2−S4, Supporting Information). However, because high loading of KF is present in our porous alumina, even very small amounts of these solvents manage to partially mobilize KF. Interestingly, in the presence of ethanol, two types of signals were observed. The appearance of both broad and sharp ^{19}F peaks implies that two types of fluoride ions exist under these conditions. This phenomenon, also observed by SEM microscopy, will be discussed later. The fact that similar broad signals were obtained in the presence of acetonitrile and heptane and in the dry solid support further proves that the availability of KF in these solvents is limited (Figure 4). The

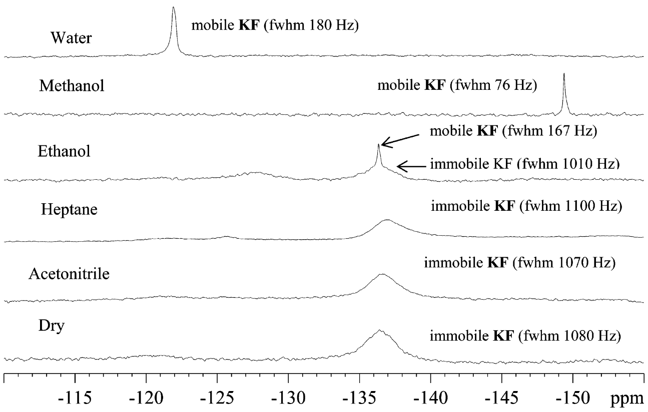


Figure 4. ^{19}F SS NMR spectra of KF/Al_2O_3 in the presence of 30 wt % of various solvents.

lack of ability to effectively mobilize KF partially explains the slow reaction rates obtained in the presence of these solvents.

Similar line width analysis of ^{31}P SS MAS NMR spectra featuring phosphonothiote **1** reactions in the presence of solvents provided information on the mobility of OP components under these conditions. This analysis show that in the presence of 10 wt % of the various solvents the signals of **1** appear sharp in all solvents, indicating that it is mobile (Figure S5, Supporting Information). In water and heptane, two types of adsorbed **1** were observed. Apart from "successful meeting" of the reaction components (step iii), the products of a solid-support-mediated transformation must be cleared effectively from the matrix "active sites", such that the reaction may be repeated in those venues and an overall synthetic useful reaction rate is obtained (step iv). This feature mostly depends on the chemical nature of the relevant products generated and the solvent used.

In this respect, the products obtained from the transformation of **1** (Table 1) are mobile thiol or alcohol leaving groups together with the more polar OP salts EMP and EMPT (except of EMMP and DEMP). Accordingly, water, methanol, and ethanol, which are polar, possess an improved ability to clear the polar OP products from the matrix pores compared to solvents like acetonitrile and heptane. This increased clearance contributes to the overall faster reactions. The improved ability of water and methanol to mobilize the products is demonstrated nicely in Figure 5, which shows that the EMP and EMMP products appear in the NMR spectra as sharp peaks indicative of their mobile nature, whereas in the case of acetonitrile and heptane, EMP appears as a broad peak indicating that it is relatively immobile. Altogether, the analyses described above suggest that, in the case of water and methanol, the mobile phase within the solid support holds fluoride ions (either fully or partially depending on the solvent amount), OP reactant, and products (even OP salts at any amount of solvent used), whereas in the case of acetonitrile and heptane, it only holds the OP reactant. The fact that only a few percent of the polar protic solvents (3−10 wt %), which are in molar proportions to both fluoride and EMP, affect the reactions rates by supposedly mobilizing these salts is especially impressive and somewhat surprising. These observations provide significant evidence on the role solvents play in the mechanism of these reactions.

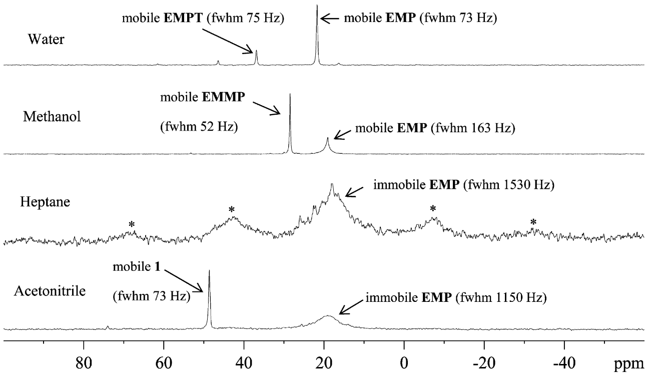


Figure 5. Selected SS MAS NMR ^{31}P spectra from the reactions of **1** with KF/Al_2O_3 in the presence of 10 wt % of various solvents at the end point of the reactions. *Denotes side bands.

SEM Studies. We were next interested in direct visualization of the solvent effects. Accordingly, we turned to inspect the dry and wetted KF/Al_2O_3 particles using SEM microscopy. Dried commercial alumina particles were examined first. As seen in Figure 6a, they are constructed from flat crystalline layers that form particles in the 30−100 μm range. Some smaller "grains" can also be detected on the surface. Energy dispersive X-ray analysis (EDAX) of the alumina particles shows that only Al and O atoms are present. Alumina impregnated with KF looks almost the same as untreated alumina, and aggregates of KF on the alumina particles are not observed (Figure 6b).

The impregnated KF is thus assumed to be mostly inside the pores in the form of nano-sized aggregates or molecularly dispersed on the surface. EDAX of such KF/Al_2O_3 particles shows that KF is indeed present at the expected level of ~20% (Figure 6c, lower circle). In addition to these KF/Al_2O_3 particles, a relatively minor amount of smaller round microparticles in the form of entangled wires were observed. EDAX of these structures shows that they are constructed mainly from KF (Figure 6c, upper circle). Control experiments indicate that the process of impregnation (i.e., rotary evaporation of the solvent from a mixture of Alumina/KF/ethanol) is the source of these entangled wires. Namely, two types of KF particles are generated during the impregnation procedure: one dispersed inside the pores having a nanometric size (internal KF) and the other outside the pores with a micrometric size (external KF).

Adding a small amount of water (i.e., 5−10 wt %) did not seem to affect the KF/Al_2O_3 except that an even smoother surface of the alumina particles was observed (Figure 7a). On the other hand, KF "stringlike" particles were harder to visualize, indicating that the external KF had dispersed. Our results showed that the addition of a higher amount of water (≥20 wt %), leads to higher mobility of the impregnated KF. As SEM images are taken under vacuum, this mobility translates under the microscope to sedimentation of microKF particles (~1−3 μm) on the external surface of the alumina (Figure 7b and c). Adding more water leads to larger dissolution of the KF and loss of KF from the alumina. At 90% water, much of the KF has been washed away.

We next examined KF/Al_2O_3 wetted with 30 wt % of the organic solvents methanol, ethanol, acetonitrile, and heptane. This solvent percent was selected because under these conditions KF/Al_2O_3 still maintains its solid nature and two phases still do not form. Visually, methanol did not seem to affect the KF/Al_2O_3 particles themselves. However, almost all external KF (entangled wires) disappeared (Figure 8a). Instead, amorphous "puddles" of KF appeared, suggesting that the KF dissolved and sunk in, resulting in a different form under the SEM conditions. Contrastingly, in the case of heptane (Figure 8b) and acetonitrile (Figure 8c), both external KF as well as the KF/Al_2O_3 particles appeared identical to those observed in the case of the dry powder (Figure 6b). Interestingly, 30 wt % of ethanol (Figure 8d) also had no effect, and both types of particles appeared similar to those present in the dry powder.

The SEM observations complemented the data obtained by SS MAS NMR (Figure 4). Namely, it provided additional evidence that external KF is completely mobilized by water and methanol and lacks mobility in heptane and acetonitrile. The fact that in both groups of solvents there is only one peak present in the NMR, sharp versus broad, suggests that the internal KF species are mobile and immobile, respectively. The most interesting case is ethanol. NMR showed the presence of both mobile and immobile species. As SEM indicated that the external particles remained the same, the combined results

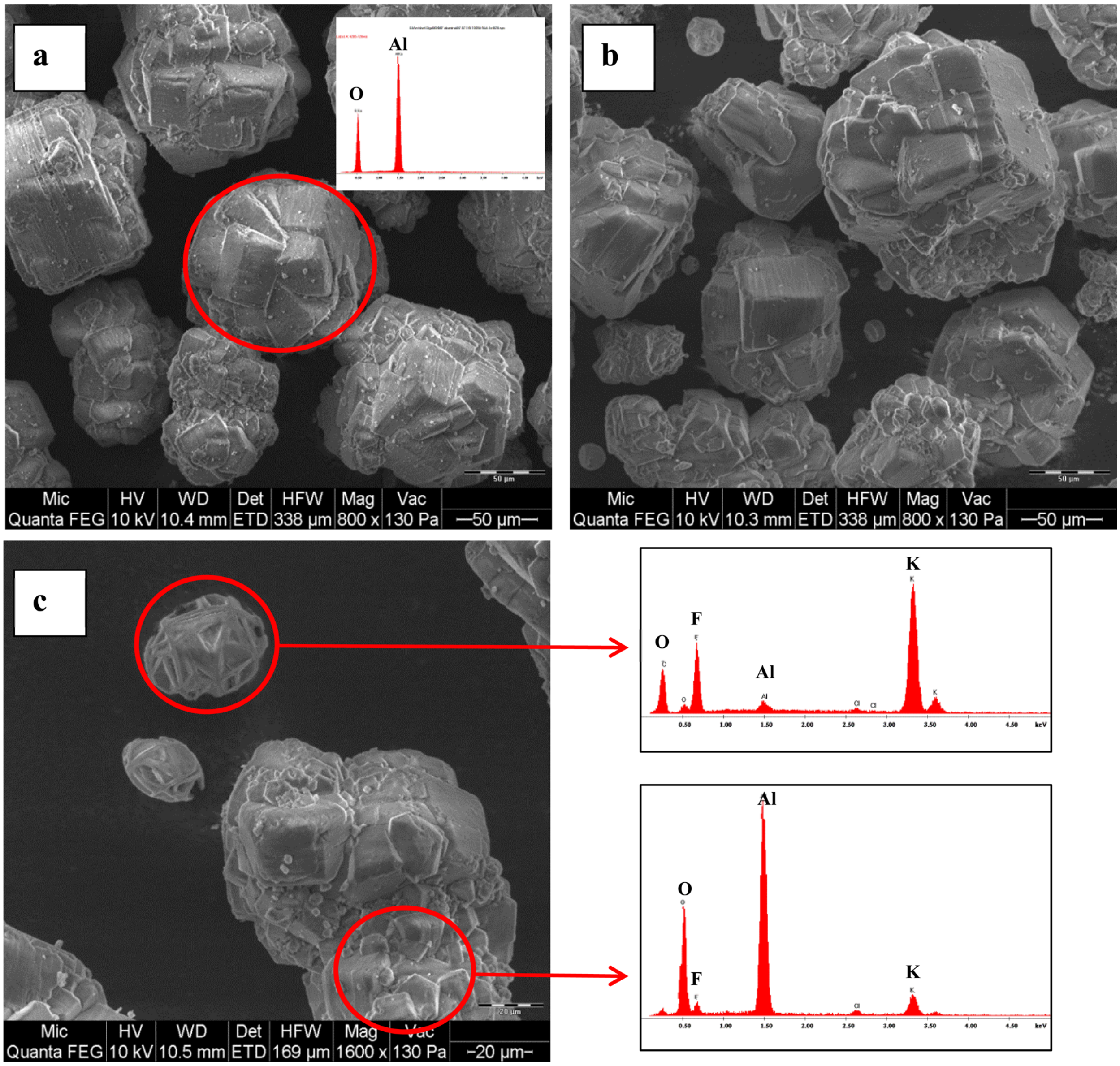


Figure 6. SEM microscopy images of (a) Dried commercial Al_2O_3. (b) KF/Al_2O_3 particles. (c) Higher magnification and EDAX analysis of the two types of particles observed in KF/Al_2O_3.

suggest that the internal KF species are partially mobile in the presence of ethanol.

Our combined findings from SS MAS NMR and SEM provide insight into what role solvents may play in such heterogeneous reactions. As discussed below, these discoveries apply to other OP families as well. For example, it was observed that in the presence of small amounts of solvents that mobilize all reaction components (i.e., water, methanol, and ethanol), the reactions are faster than those obtained in the presence of large volumes of these solvents. Under the latter conditions, the reaction components are leached from the solid support, which accordingly becomes irrelevant, and the reaction becomes homogeneous and wasteful. Once small amounts of the appropriate solvent are used, the reactions are heterogeneous, rapid, "green", and feature maximum utilization of the solid support large porous surface area and a very high local concentration of the reactants. Under these conditions, steps i and v in the mechanism of a heterogeneous reaction, which involve mass transfer of reactants and products from or to the solution bulk, practically do not exist, and accordingly, the reaction kinetics are faster.

A similar effect of using a minute quantity of solvents (e.g., 10 wt %) was observed in the field of enzymatic synthesis.[63−65] These types of reactions, termed "solid-to-solid", are performed in the presence of a small volume of liquid-phase with mainly undissolved substrates at very high concentrations. The solid products obtained continuously precipitate out from the liquid-phase along the reaction course. This interesting approach may be promising in terms of its industrial applications as it is environmentally benign and economical.

Utilizing solvents that do not mobilize the reaction participants effectively result in a different picture. That is, the use of any amount of such solvents (i.e., acetonitrile and heptane) leads to extremely slow transformations similar in nature to those performed on the dry support. Reactions in the presence of these types of solvents may thus be considered as wasteful heterogeneous reactions. Therefore, we may conclude that first, the solvent of choice must effectively mobilize the

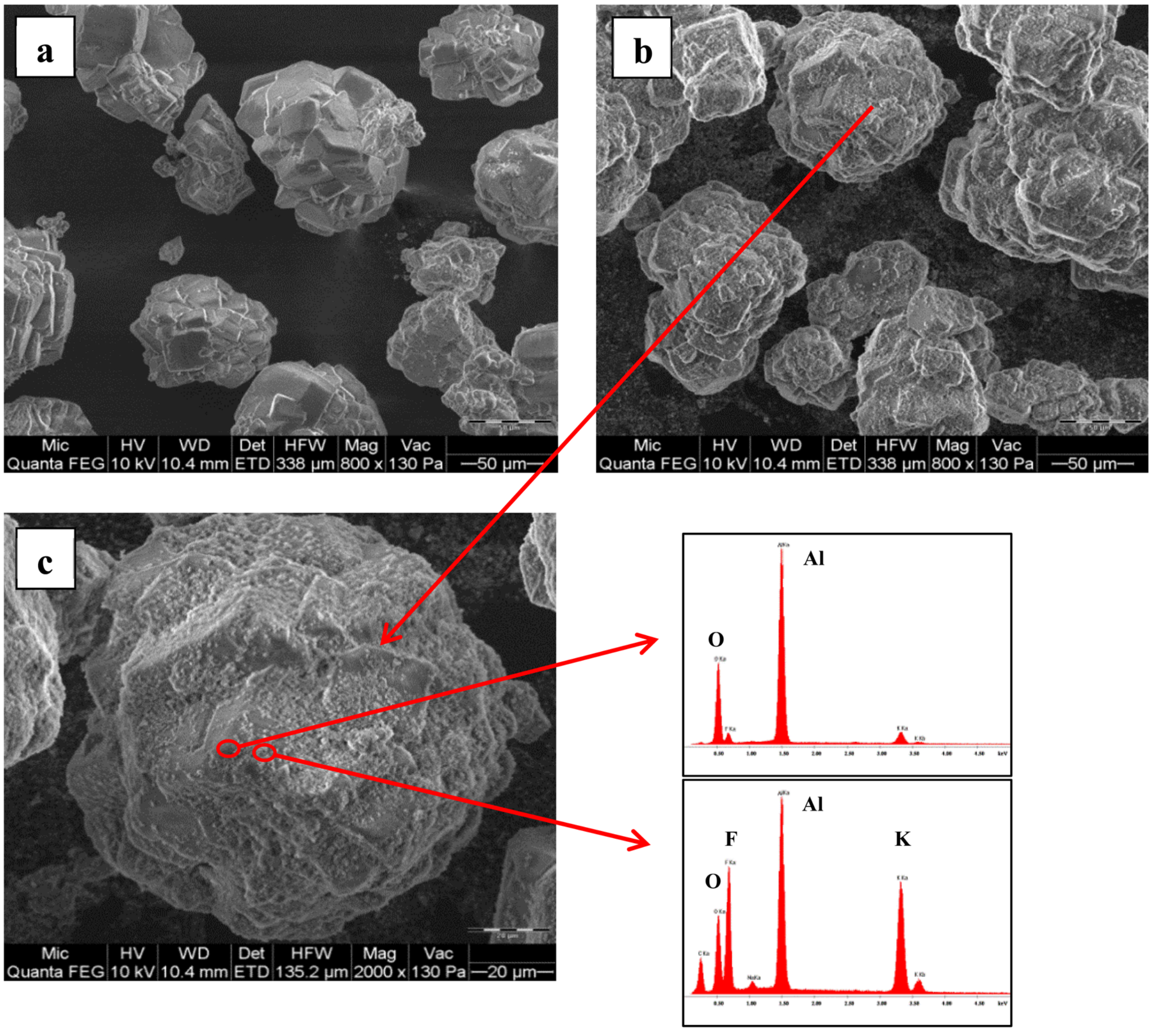


Figure 7. SEM microscopy images of KF/Al_2O_3 with (a) 5% and (b) 20% water. (c) Enhanced image of one particle and EDAX on a smooth part and a part with KF sedimentation.

reaction participants. Second, a minimum amount of that solvent that still permits mobility of the reaction participants should be used to maintain the character of the heterogeneous reaction and the benefits of the solid support. In reactions in which the solid porous matrix is present in large excess it actually acts as a stationary reaction medium and substitute for the solvent. As discussed in the introduction, selection of an appropriate solvent for both homogeneous and heterogeneous organic reactions is still a significant challenge from synthetic and environmental perspectives.[66] Our approach, using a large amount of solid support and a small amount of the appropriate solvent, has advantages regarding these issues. The benefits of using small amounts of solvents in chemical reactions with respect to the environment are clear. The synthetic advantages stem mainly from the high local concentration of reactants dispersed on the large surface area of the alumina. In the cases in which molar proportions of protic solvents are used, the low level of solvation present under these conditions may also somewhat enhance the reaction rate.[67] On the basis of these potential advantages, we propose that optimization of heterogeneous processes should include not only the selection of the right solvent but also its amount. Next, we validate our findings using other more challenging OP compounds, such as phosphonic acid diesters and phosphates.

Reactions of *O*,*O*-diethyl methyl- and phenyl-phosphonates 2 and 3 with KF/Al_2O_3. Phosphonate diesters and their corresponding phosphonic acids have marked importance in medicinal chemistry.[68−70] As methods to effectively achieve this hydrolysis are still required, we selected diethyl methylphosphonate (DEMP) **2** as our next target. Typically, phosphonate diesters are hydrolyzed under acidic or alkaline conditions. Lewis or mineral acids may be used to promote acidic hydrolysis. Most common in both laboratory and industry applications is the use of trimethylsilyl bromide, chloride, or iodide.[71,72] Although effective, these reagents exhibit disadvantages such as toxicity, moisture sensitivity, corrosive properties and a high price. Acids like hydrobromic acid and hydrochloric acid are also commonly utilized.[73] The latter is less reactive than its hydrobromic counterpart and thus higher reaction temperatures and prolonged reaction times are needed. In general, alkaline hydrolysis of phosphonate diesters is limited to unhindered derivatives like methyl esters.[74,75] Furthermore, such hydrolyses typically stop at the stage of the monoester.

Unlike the hydrolysis of phosphates using fluoride ions, which is known, the hydrolysis of phosphonate diesters using this species has never been explored to the best of our knowledge. In preliminary studies, we have found that

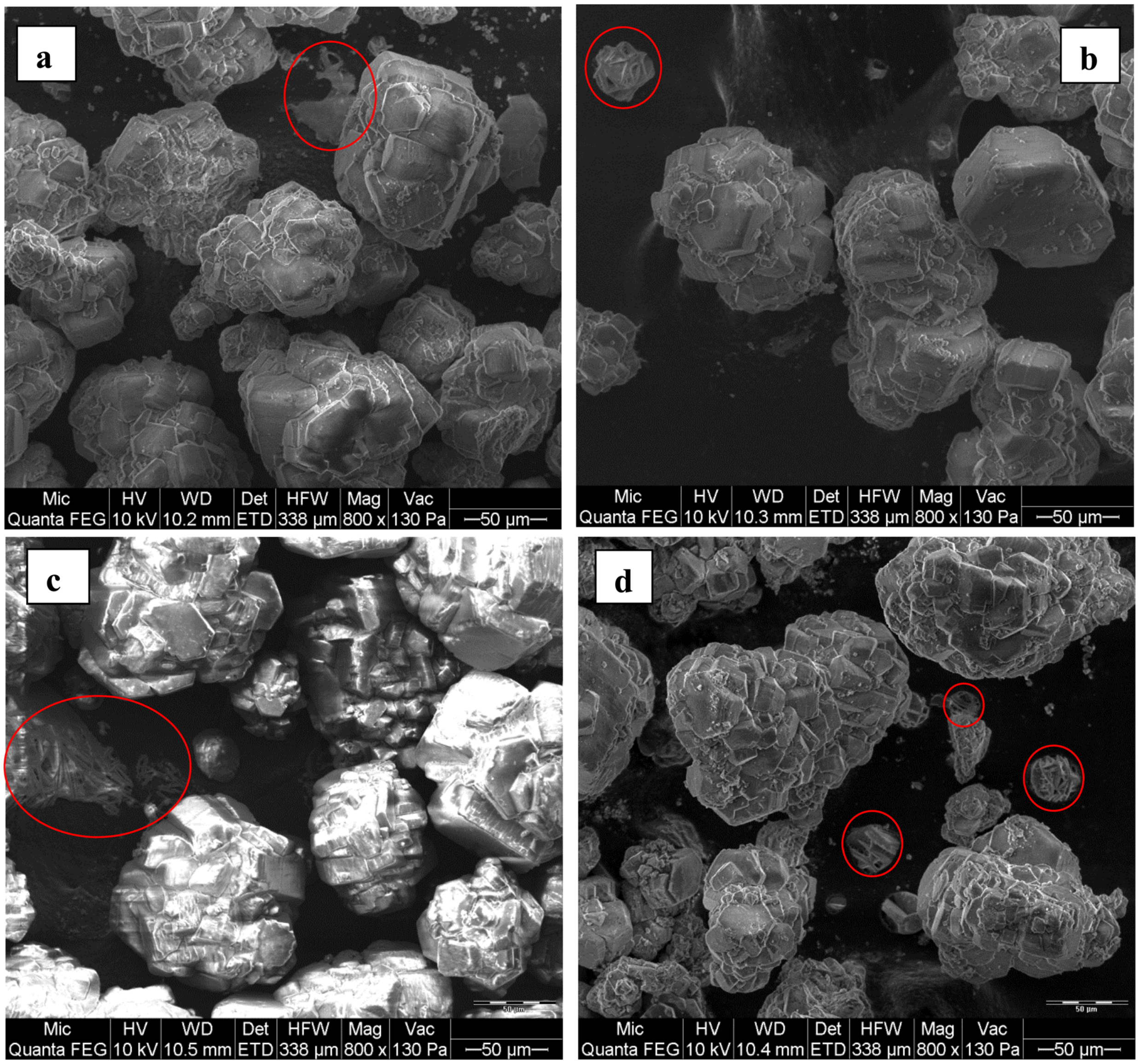


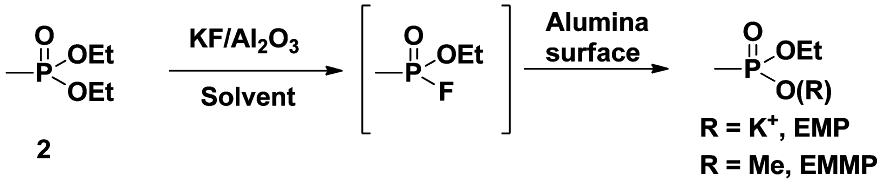
Figure 8. SEM microscopy images of KF/Al_2O_3 wetted with 30% of (a) methanol, (b) heptane, (c) acetonitrile, and (d) ethanol. Red circles designate external (a) amorphous or (b–d) entangled wire KF.

phosphonate **2** is extremely stable in aqueous fluoride solutions, contrary to phosphonothioate **1**, which reacted under these conditions. We were accordingly surprised to observe that we could promote rather effective hydrolysis of **2** at room temperature in the presence of KF/Al_2O_3 and as low as 3–5 wt % of water (Table 2, entries 2 and 3). We further noticed that the same trends recognized with **1** were repeated for **2**. Namely, the amount of water added to the KF/Al_2O_3 support had a large effect on the hydrolysis kinetics and, similar to the results obtained before, the hydrolysis rate was much faster once a small rather than large amount of water was used (entries 2–6). Once again, a bell shapelike diagram was obtained with 5 wt % of water being the optimal condition (Figure S12, Supporting Information). Adding any amount of water to KF/Al_2O_3 obviously greatly improved the hydrolysis rate compared to the reaction in solvent-free conditions, which almost did not occur (entry 1). However, this effect was diminished significantly once more than 50 wt % of water was applied. The reaction of **2** in the presence of 10 wt % of methanol primarily provided a mixture of hydrolytic products. The rate was comparable to the hydrolysis in the presence of 10 wt % of water. The hydrolysis in the presence of heptane and acetonitrile was, as expected, extremely slow and hence was only partially followed.

The heterogeneous hydrolysis of **2** using a minute amount of water and KF/Al_2O_3 at room temperature is impressive because this reaction virtually does not occur in homogeneous aqueous fluoride solution, not even in buffered (pH 10.5) solution, which simulates the conditions present once the KF/Al_2O_3 support is applied. Here again, choosing the right reaction conditions (i.e., appropriate solvent and small amount) can lead to results that otherwise would not be achieved. The synthetic utility of this approach on a larger scale was proven by the quantitative hydrolysis of an analogous phosphonate **3** (Scheme 1, details in the Supporting Information).

Reactions of Phosphates 4–6 with KF/Al_2O_3. Hydrolysis of phosphate groups is of great importance in light of their crucial role in key biological processes. Contrary to mono- and diesters, which are involved in countless biological pathways, triesters do not occur naturally. However, due to their

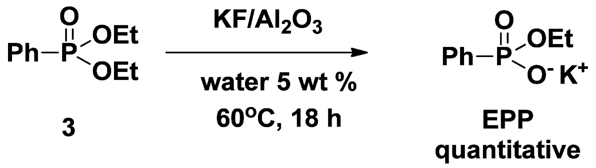
Table 2. Reactions Kinetics and Products of 2 in the Presence of KF/Al_2O_3 and Solvents



entry	solvent	solvent (%)	k (10^4 h^{-1})	$t_{1/2}$ (h)	EMP[a] (%)	EMMP[a] (%)
1	solvent free		1	6931[b]	5	
2	water	3	501	13.8	96.1	
3	water	5	982	7.1	94.0	
4	water	10	306	22.7	97.1	
5	water	50	119	58.3	85.5	
6	water	90	4	1733[b]	66	
7	methanol	10	380	18.2	80.2[c]	13.9[d]
8	acetonitrile	10	15	462[b]	34.5	
9	heptane	10	5	1386[b]	12.9	

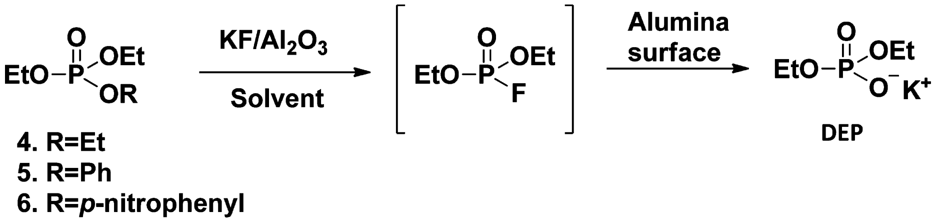
[a] Product percent at the end of the measurement. [b] Estimation based on partial reaction. [c] Mixture of hydrolytic products. [d] Mixture of transesterification products.

Scheme 1. Reaction of 3 with KF/Al_2O_3 Wetted with 5 wt % of Water Provided EPP in a Quantitative Yield



anticholinesterase activity, triesters have found widespread use as herbicides and insecticides; accordingly, there is a strong interest in the development of efficient antidotes to such OP poisons.[76−78] Phosphate esters are also widely used in prodrug strategies.[79−81] The hydrolysis reactions of phosphate triesters, as well as their reactions with various nucleophiles, including the fluoride ion, were therefore thoroughly investigated.[82−84] However, to the best of our knowledge, their fluoride ion-based hydrolysis in heterogeneous medium was never explored. Accordingly, we were interested in examining whether effective hydrolysis of phosphate triesters, even highly stable ones such as triethyl phosphate **4**, may be obtained on KF/Al_2O_3 in the presence of small amounts of our selected solvents. On the basis of our results described above, water was the solvent of choice and 10% was the volume selected for this focused study. Phosphate **4** reacted under these conditions and low heating at 60 °C to furnish the corresponding diethyl phosphate (DEP; Table 3, entry 2). Heating phosphate **4** in a fluoride aqueous solution at 60 °C did not lead to the corresponding hydrolysis

Table 3. Reactions Kinetics and Products of 4−6 in the Presence of KF/Al_2O_3 and Solvents



entry	phosphate	solvent	solvent (%)	k (10^4 h^{-1})	$t_{1/2}$ (h)	DEP[c] (%)
1	4[a]	none		nr	nr	
2		water	10	82	84.5	95.4
3		heptane	10	nr	nr	
4		acetonitrile	10	nr	nr	
5	5[a]	none		68	101.9	86.0[d]
6		water	10	804	8.6	97.0[d]
7		heptane	10	179	38.7	100.0[d]
8		acetonitrile	10	70	99.0	94.0[d]
9	5[b]	water	10	37	187.3	64.8
10	6[b]	none			157.5	93.6
11		water	10	1601	4.3	100.0
12		heptane	10	88	78.8	100.0
13		acetonitrile	10	31	223.6	83.6

[a] Reaction was performed at 60 °C. [b] Reaction was performed at room temperature. [c] Product percent at the end of the measurement. [d] Also contains *O*-ethyl-*O*-phenyl phosphate as a minor product.

product, implying that enlarging the solid-support water quantity may considerably slow the reaction. Under solvent-free, or with the organic solvents heptane and acetonitrile, the reaction did not occur (entries 1, 3, 4). Replacing the poor leaving group ethoxide (**4**) with a phenolate (**5**) or *p*-nitro phenolate (**6**, paraoxone) provided substrates that were more prone to fluoride-based hydrolysis. For example, the reaction of phosphate **5** with KF/Al_2O_3 at the same conditions applied to **4** was faster by an order of magnitude. Performing the same reaction at room temperature resulted in a relatively slow transformation (entry 9). On the other hand, the reactions of *p*-nitro derivate **6** do occur at room temperature (entries 10−13).

Interestingly, similar to the pattern observed with OP **1**, the organic solvents order of reactivity was found to be heptane > dry > acetonitrile. The reactivity difference between heptane and acetonitrile may be explained by the mobility of the various reaction components in these solvents. Because of its polar nature, acetonitrile strongly "holds" (solvates) **5** and **6**, preventing them from penetrating and reacting with the solid matrix. Heptane, on the contrary, does not interact strongly with **5** or **6** and accordingly resulted in increased diffusion, and quicker total reactions are achieved.

■ CONCLUSIONS

To answer the question of how solvents (as solvents or as additives) affect OP compound transformations on KF/Al_2O_3, we have conducted a large series of experiments using different solvents in various amounts. These solid supported reactions, which were investigated using SS MAS NMR and SEM microscopy, provided very interesting and even surprising results. The essential action of the fluoride ion as the nucleophilic trigger in the hydrolysis or alcoholysis of phosphonothioate **1**, phosphonates **2** and **3**, and phosphates **4**−**6** was demonstrated. On the basis of our studies, we conclude that the mobility of the fluoride ions, OP reagents, and products is the most important factor affecting the outcome of the reactions. The addition of a minute quantity of the proper solvents (e.g., water or methanol/ethanol), which still permits mobility of the various reaction components, leads to rapid and environmentally benign heterogeneous hydrolysis or alcoholysis of OP via a fluoridate intermediate. Excess of these solvents promotes leaching of all of the reaction components from the matrix and leads to slow wasteful homogeneous hydrolysis or alcoholysis. Apolar aprotic solvents, such as heptane, do not mobilize KF at all, and although they somewhat enhance the mobility of OP reagents, they lead to slow wasteful heterogeneous hydrolysis. Finally, polar aprotic solvents, such as acetonitrile, only promote leaching of the OP reagent, resulting in the worst case, which is very slow and wasteful heterogeneous hydrolysis. Thus, the use of a minute quantity of the appropriate solvent as described above seems to result in a very high local concentration of components dispersed on the high surface area of the alumina support, which in turn leads to rapid and efficient heterogeneous reactions. The efficiency of this synthetic approach was unambiguously demonstrated by the hydrolysis of challenging phosphoesters, such as **2** and **4**, at room temperature or low heating, respectively, in the presence of KF/Al_2O_3 and a minute quantity of water. Interestingly, two types of fluoride species were observed in the SEM microscopy of KF/Al_2O_3: external entangled KF wires (micrometric size) and internal fluorides dispersed inside the alumina surface area (apparent nanometric size). Combining our SS MAS NMR and SEM analyses of KF/Al_2O_3 powders wetted with solvents allowed us to conclude the following: 30 wt % (and less) of water or methanol fully mobilizes and disperses the fluorides on the alumina surface, the same quantity of ethanol mobilizes only internal fluorides, and any amount of acetonitrile or heptane does not affect either type of fluorides. To the best of our knowledge, such correlation between SS MAS NMR data and SEM microscopy observations has not previously been reported in the literature.

The results presented here, together with previous studies reported by others,[17−29] prove that solvents have a crucial role in heterogeneous reactions. Our interpretation of the effects of minute relative to excess quantities of various solvents opens a new paradigm for the design of these types of reactions. Therefore, we believe that examination of the effect of a small quantity of the right solvent that efficiently mobilizes all reaction components should be taken into account in the tedious optimization process of heterogeneous solid-supported reactions. Although our cases represent a heterogeneous system in which the impregnated reagent (KF) is consumed during the reaction course, our conclusions may be relevant to a broad range of heterogeneous solid-supported reactions, including heterogeneous catalysis. For example, one may enlarge the reaction "medium" by using a more solid porous support (concomitantly lowering the catalyst loading to remain at the same overall catalytic percent) instead of enlarging the reaction's volatile solvent volume. Considering the solvent quantities in this way may lead to not only more efficient heterogeneous reactions but also more economical and environmentally benign processes.

■ EXPERIMENTAL SECTION

Materials and Chemicals. Methanol (HPLC grade), ethanol (analytical grade), acetonitrile (HPLC grade), heptane (HPLC grade), Al_2O_3 (activated, neutral, 150 mesh 58 Å), KF (≥99.0%), diethyl methylphosphonate **2**, diethyl phenylphosphonate **3**, triethyl phosphate **4**, and diethyl *p*-nitrophenyl phosphate **6** were purchased from commercial suppliers. OP **1**[54] and **5**[85] were prepared according to reported procedures in high purity (>99%) and did not contain any hydrolysis products. Anhydrous ethanol was used for preparations of KF/Al_2O_3. Deionized water was obtained from a laboratory water purification system.

Preparation of KF/Al_2O_3 Powder. KF (20 g) followed by dry ethanol (150 mL) were placed in a 500 mL round-bottom flask, and the KF was ground using a glass rod to provide a rather homogeneous emulsion. Dry Al_2O_3 powder (80.2 g, dried overnight at 160 °C) was then added to the flask to form a slightly orange-colored mixture, which was put on an evaporator for stirring and heating (49 °C) without vacuum. After a period of 40 min, vacuum and heating to 55 °C were applied for about 30 min. After no solvent could be observed, the temperature was raised to 70 °C and evaporation was continued for an additional 60 min. At this point, the dry powder was ground again and put back on the evaporator for an additional 30 min with heating to 73−74 °C. The powder was transferred to a beaker, ground, and placed in an oven (160 °C). Following heating for 24 h, the powder was taken out of the oven and examined by NMR to ensure that it was dry and that it holds free fluoride ions. It should be mentioned that some reproducibility difficulties may appear once moving from one batch of KF/Al_2O_3 to another. This irreproducibility, typically differences of 2−3 factors and rarely 4−5 factors, may occur in reactions that exhibit very slow kinetics. To avoid these issues, we performed all comparable reactions in the same batch.

Preparation of Powders Wetted with 3−20% of Solvents. Dry powders (0.45 g in the case of 10% solvent) were placed in glass vials, and solvents (0.05 g in the case of 10%) were added on top. The mixtures were vortexed and ground thoroughly using a glass rod until homogeneous powders were obtained (typically two or three cycles).

DOI: 10.1021/acs.joc.5b00492
J. Org. Chem. 2015, 80, 5176−5188

Preparation of Powders Wetted with 50% of Solvents. Dry powder (typically 0.04g) was added directly to the NMR rotor and 0.04 g of solvent, calculated by density, was then added using a dispenser.

Preparation of Powders Wetted with 90% of Solvents. Dry powders (0.2 g) were placed in glass tubes, and 1.8 g of solvents, calculated by density, were added. The mixtures were stirred gently with a small magnet.

Sample Preparation. In the case of powders wetted with 3−20% of solvents, samples of the appropriate powders (40 mg) were added to the 0.4 cm ZrO_2 rotor, and 2 μL of OP (5% w/w) were added via a syringe to the center of the sample. The rotor was than sealed with a fitted Kel-F cap. In the case of powders wetted with 50% of solvents, 2 μL of OP was added directly using a syringe to the center of the NMR rotor holding the powder and solvent, and then the rotor was sealed with a fitted Kel-F cap. In the case of powders wetted with 90% of solvents, 10 μL of OP was added to the mixture of powder, and solvent and the stirring was maintained for 30 min. Following that time, a sample of the mixture was taken with a pipet and put in the NMR rotor, which was than sealed with a fitted Kel-F cap.

Kinetic Studies Using SS-MAS NMR. ^{31}P and ^{19}F NMR spectra were obtained at 202 and 471 MHz, respectively, on an 11.7 T (500 MHz) spectrometer equipped with a 0.4 cm standard CP-MAS probe using direct polarization (i.e., no cross-polarization (CP) was used). Typical spinning rates were 5 kHz. Chemical shifts for ^{31}P and ^{19}F were referenced to external trimethyl phosphate (TMP) and $CFCl_3$, respectively, as 0 ppm. For ^{31}P and ^{19}F spectra, the pulse delay was 2 s, which is considered sufficient for relaxation in organo phosphorus esters on solid matrices. The number of transients per spectrum varied between 100 and 1000. For comparison purposes, spectra were recorded under identical conditions. Spectra were measured periodically to determine the remaining starting material and identify products.

SEM. The scanning electron microscopy (SEM) images were obtained with an SEM-Quanta 200 FEG from FEI, Netherlands. The composition was determined by energy dispersive X-ray spectroscopy (EDX). All samples were attached on aluminum specimen mount stubs by double-sided tape made of electricity-conductive carbon.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Selected NMR spectra, kinetic data of the reactions, and detailed discussion of the quantitative hydrolysis of phosphonate 3. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00492.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was internally funded by the Israeli Prime Minister's office.

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DOI: 10.1021/acs.joc.5b00492
J. Org. Chem. 2015, 80, 5176−5188