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Solvent Effects on the Reactions of the Nerve Agent VX with KF/Al_2O_3: Heterogeneous or Homogeneous Decontamination?

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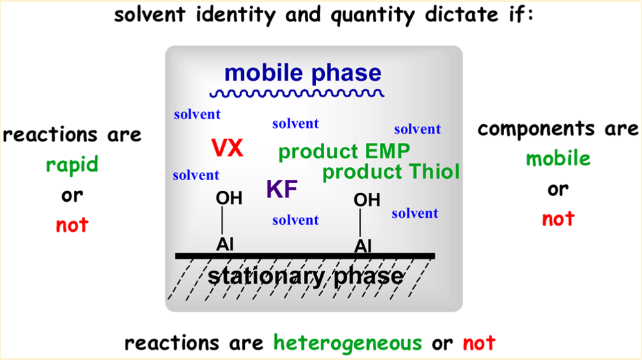
S Supporting Information

ABSTRACT: Solvent effects on the reactions of the extremely toxic nerve agent VX with KF/Al_2O_3 powder were explored. Small quantities of water or methanol (5−10 wt %), which effectively mobilized all components while maintaining the heterogeneous nature of the reaction, promoted much faster rates than those obtained with larger quantities. Any amount of acetonitrile resulted in extremely slow transformations. Surprisingly, 5−50 wt % of heptane led to fast reactions due to the combination of its ability to mediate fast diffusion of VX and a MAS centrifugation effect.



V-type nerve agents, such as VX (*O*-ethyl *S*-2-(diisopropylamino)ethyl methylphosphonothioate), are among the most toxic compounds known. They act as highly specific acetylcholinesterase inhibitors leading to cholinergic overstimulation.[1] In addition, they also exhibit almost indefinite persistence on common environmental surfaces.[2] Accordingly, the development of effective decontamination methods for such agents is required to address both military scenarios and continuously expanding terror threats.[3] Using reactive sorbents that adsorb and transform nerve agents to nontoxic products is an attractive approach. Ideally, these sorbents should be able to be safely handled and stable. Various powders, such as nanosized particles of MgO,[4] CaO,[5] NaY and AgY zeolite,[6] Al_2O_3,[7] $Zr(OH)_4$,[8] and TiO_2,[9−11] as well as various types of solid-supported fluoride reagents,[12−15] were proven to be destructive sorbents of chemical warfare agents (CWAs). Recently, metal organic frameworks (MOFs) were also shown to have potential for such applications.[16] Most studies with these solids involved neat agents and dry powders or powders wetted with a small amount of water. The dependence on water content was previously exhibited with titania materials.[9b] Under dry conditions, typically long reaction half-life times were obtained, and transformations were found to be strongly dependent on the vapor transport of the agent examined.[4,5] In decontamination scenarios in the field, such dry powders may possess serious drawbacks, not only from a reaction kinetics point of view but also from practical aspects of effective sorbent spraying. To achieve both efficient dispersal and rapid detoxification, one should use an appropriate volatile solvent. Solvent selection is a critical issue in heterogeneous reactions. Using an unsuitable solvent may lead to insufficient accessibility of the reaction components to the active sites. In addition, the impregnated catalyst can be leached out from the solid support. Either of these situations might eventually result in an undesired decrease in reaction rates. To the best of our knowledge, only few studies have to date dealt with solvent effects on such reactions.[9b,17]

Recently, we addressed the issue of how solvents affect organo-phosphorus (OP) compound transformations on a KF/Al_2O_3 solid support.[18] For this purpose, solid-state MAS NMR experiments were conducted using different solvents at various amounts: water and methanol as polar protic solvents, heptane as a nonpolar solvent, and acetonitrile as a polar aprotic solvent. Specific attention was given to *O*,*S*-diethyl methylphosphonothioate (DEMPT, a VX simulant). The central role of the fluoride ion as a catalyst in the hydrolysis or alcoholysis of DEMPT as well as other OPs was demonstrated. We concluded that mobility (not full solubility) of all components, i.e., fluoride ions and OP reagents/products, is the most important parameter influencing the reaction's outcome. The addition of small amounts (up to 10 wt %) of the right solvent (water or alcohol), which enabled mobility of the reaction components, led to rapid heterogeneous reactions. However, large amounts of these solvents (>50 wt %) promoted leaching of fluoride from the solid support, and accordingly, sluggish and wasteful "homogeneous-like" reactions were obtained.

In the present work, we examined whether we could implement the insights obtained with the solvents described above to our ongoing efforts toward the development of an effective VX decontamination method, which would exhibit optimal kinetics and result in nontoxic products. VX and DEMPT differ in the identity of their thiolic group. We envisaged that the different nature of these moieties, bulky

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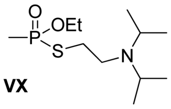
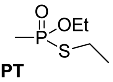
lipophilic ethyl diisopropylamine versus ethyl, would affect the reaction on KF/Al_2O_3, (one of our lead active powders for decontamination[12,13]) both chemically and physically. The fact that VX hydrolysis in an aqueous fluoride solution is much faster than that of DEMPT provided support for that reasoning.[19]

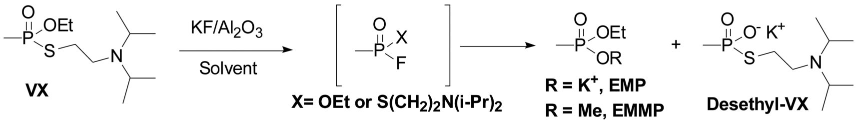

VX


DEMPT

As shown in Table 1, although dry KF/Al_2O_3 presents totally different conditions than an aqueous solution, a similar trend was observed. Namely, the VX reaction was found to be much faster than that of DEMPT (entry 1, $t_{1/2}$ of 6.2 vs 433 h[18]). In general, reactions of VX on KF/Al_2O_3 in the presence of water or methanol were much faster than those performed on the dry powder. Similar to DEMPT, in the case of VX the high reactivity obtained with water or methanol probably originates from their ability to mobilize all reaction components effectively. This observation is specifically emphasized with small amounts of these polar protic solvents (up to 10 wt %, entries 2–3, 7). Under these conditions, a very high local concentration of reaction components, which are well-dispersed on the large surface area of the solid support, is maintained, and fluoride leaching is prevented. Interestingly, the amount of water added to the powder did not have a significant effect on the ratio of products. According to NMR, in all cases the desired nontoxic EMP (ethyl methylphosphonate) product was obtained in >90% yield, whereas the toxic desethyl-VX was formed in only small amounts (4.2–7.5%). In the case of methanol, the distribution of products depended on the kinetics. Fast reactions (10–50 wt %) led rather selectively (94%) to the nontoxic product ethyl methyl methylphosphonate (EMMP), whereas in slower reactions, large amounts of EMP were formed as well due to the reaction of surface hydroxyl groups. Surprising results were obtained with heptane (entries 10–12). Despite the very low solubility of fluoride in this hydrophobic solvent, extremely fast transformations were achieved in the presence of 5–50 wt % amounts. A similar effect, but much less significant, was previously observed by us in the reactions of other OPs with KF/Al_2O_3 in the presence of heptane.[18] This behavior may be attributed to the combination of heptane's hydrophobic nature and the high reactivity fluoride ion exhibits toward VX. Being relatively polar, it appears that VX prefers to disperse onto the porous surface of the polar matrix KF/Al_2O_3 rather than to stay in the nonpolar medium.

The fast transfer of VX from the heptane mobile phase to the stationary phase is nicely demonstrated in the ^{31}P MAS NMR spectra (Figure 1). In the case of 5% heptane, only one broad peak (fwhm 580 Hz), attributed to adsorbed VX, is seen at the beginning of the reaction. Seemingly, this small volume of solvent easily disperses VX on the solid surface in a nonreversible manner. Indeed, when bigger amounts (10 and 50% heptane) are used, an additional narrow peak (fwhm 160/106 Hz) attributed to solvated VX appears, suggesting partition of VX between the two phases at the starting point of the reaction. Noteworthy is the fact that the sole product obtained in the presence of heptane is the surface-bound nontoxic EMP product (Figure S1 in the Supporting Information). The very fast VX dispersion led to the hypothesis that reactions in heptane's presence may be strongly affected by the MAS NMR conditions, i.e., by a centrifugation effect caused by the high spinning rate of the sample. Recently, we[12,13,20] and others[21] have shown that in some cases solid-supported reaction rates were affected by MAS NMR measurements. Specifically, this phenomenon was observed where diffusion of reactants toward the active site of the solid support had a significant role in the

Table 1. Reactions Kinetics and Products[a] of VX in the Presence of KF/Al_2O_3 and Solvents



run	solvent	solvent wt %	k (10^4 h^{-1})	$t_{1/2}$ (h)	EMP[b] (%)	desethyl-VX[b] (%)	EMMP[b] (%)
1	dry powder		1119	6.2	86.0		
2	water	5	43188	0.2	92.7	7.3	
3	water	10	12064	0.6	90.1	7.5	
4	water	50	1096	6.3	94.1	5.9	
5[c]	water	90	1055	6.6	91.6	4.2	
6	methanol	5	3560	2.0	60.0		40.0
7	methanol	10	41388	0.2	6.0		94.0
8	methanol	50	21672	0.3	3.0		94.0
9[c]	methanol	90	2355	2.9	38.2		61.8
10	heptane	5	9124	0.8	97.0		
11	heptane	10	6947	1.0	96.1		
12	heptane	50	22529	0.3	96.3		
13[c]	heptane	90	96	72.2[d]	94.3		
14	acetonitrile	5	11	630.1[d]	92.3		
15	acetonitrile	10	68	101.9	88.3		
16	acetonitrile	50	23	301.4	95.3		
17[c]	acetonitrile	90	12	577.6[d]	55.7		

[a] On the basis of our previous studies,[15,18,19] the reaction occurs via the fluoridate intermediate, which is not detected due to its fast hydrolysis on the surface of the alumina. [b] Product percent at the end of the measurement. [c] Examined using solution NMR. [d] On the basis of the second steady state slower reaction rate.

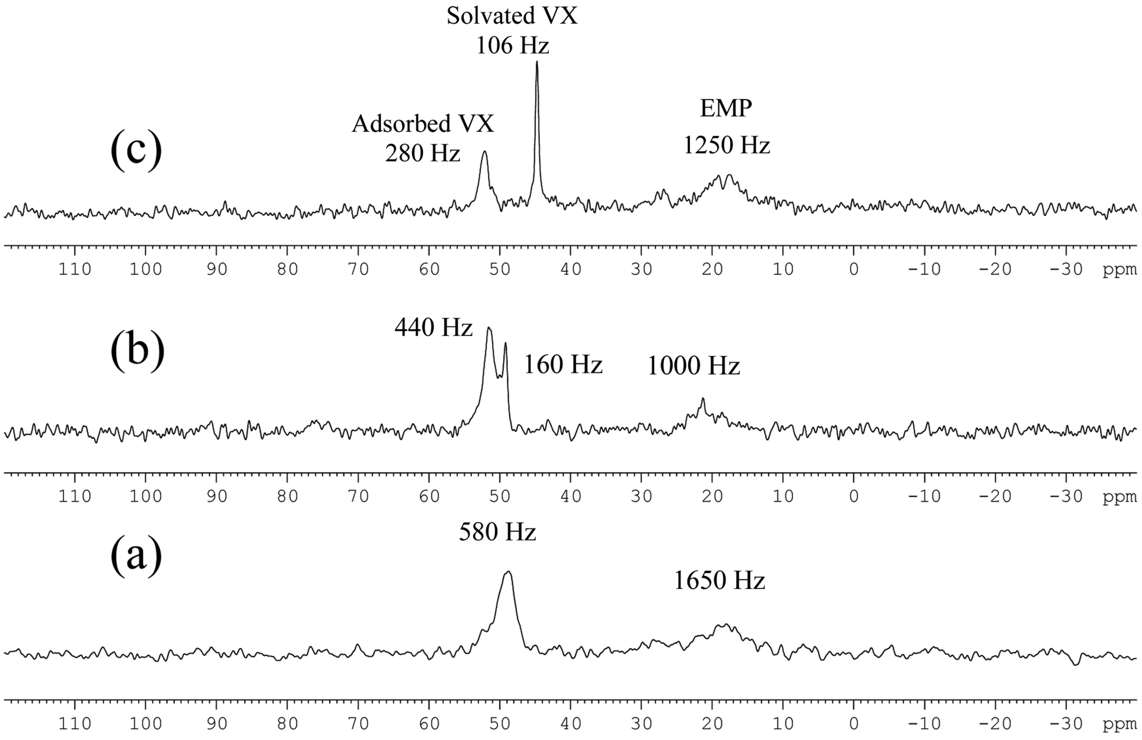


Figure 1. Selected ${}^{31}P$ MAS NMR spectra from the reactions of VX with KF/Al_2O_3 in the presence of (a) 5, (b) 10, and (c) 50 wt % of heptane at the beginning of the reaction (20−30 min).

reaction kinetics. This centrifugation effect was not observed in the VX reaction with water-wetted KF/Al_2O_3.[12] Being relatively soluble in water, VX can migrate freely to the powder and does not remain as insoluble drops/deposits. For examining whether the reaction of VX in the presence of heptane is affected by MAS NMR, two parallel experiments of rotors holding KF/Al_2O_3, 50% heptane, and VX were run simultanously. The first was periodically monitored by MAS NMR, and the second was set aside. Once the end point of the first reaction was detected, monitoring of the second rotor commenced. Indeed, the $t_{1/2}$ value of the former was found to be five times faster than that of the latter (0.3 vs 1.6 h, Figure 2). Seemingly, the high centrifugation exerted by the spinning indeed promoted rapid transfer of the VX molecules, present as drops/deposits, to their preferred polar environment by squeezing them into the small pores of the KF/Al_2O_3.

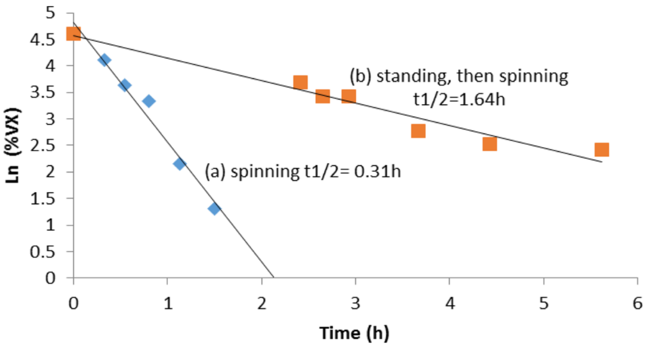


Figure 2. Kinetic profiles of the VX reaction with KF/Al_2O_3 in the presence of 50 wt % heptane using (a) MAS NMR (5 kHz spinning) monitoring from the beginning, and (b) periodic monitoring started once the end point of experiment (a) was detected.

In contrast to water, methanol, and heptane, the addition of any amount of acetonitrile to the KF/Al_2O_3 powder resulted in extremely slow transformations (Table 1, entries 14−17, and Figure S2). We assume that these results were obtained due to a combination of the low solubility of fluoride in acetonitrile[22] and the relatively high solubility of VX in this polar solvent. As this solvent "holds" VX effectively, reactions in its presence were even slower than those obtained on the dry powder (entry 1). Comparison of the width of the solid state MAS NMR peaks of VX in all four solvents (Figure 3, 50 wt %) shows that its value in acetonitrile is comparable to those obtained in water and methanol (fwhm 65−89 Hz). This suggests that under these conditions VX is mobile in acetonitrile to the same extent as in water and methanol. On the other hand, the very broad peak of the product in that solvent (EMP, fwhm 1450 Hz) implies that it is strongly adsorbed or bound to the solid matrix, whereas the products in water and methanol are mobile. Although not observed previously,[18] it cannot be ruled out that acetonitrile negatively affects the reaction by blocking active sites or reacting with the porous solid matrix.

Next, solvent effects with relatively large quantities of solvents (i.e., 90 wt %) were examined. Because of technical issues, these experiments were performed using standard solution NMR. Namely, only soluble species could be monitored. In the case of water and methanol, where significant leaching of fluoride from the solid matrix occurred, the reactions were practically homogeneous. As the products of VX decomposition (EMP and EMMP) are also soluble in these solvents, reaction rates were obtained directly (Figures S3−S4). On the other hand, in heptane and acetonitrile, fluoride did not leach out from the solid at all (as indicated by control experiments), such that the reactions maintained their heterogeneous nature.

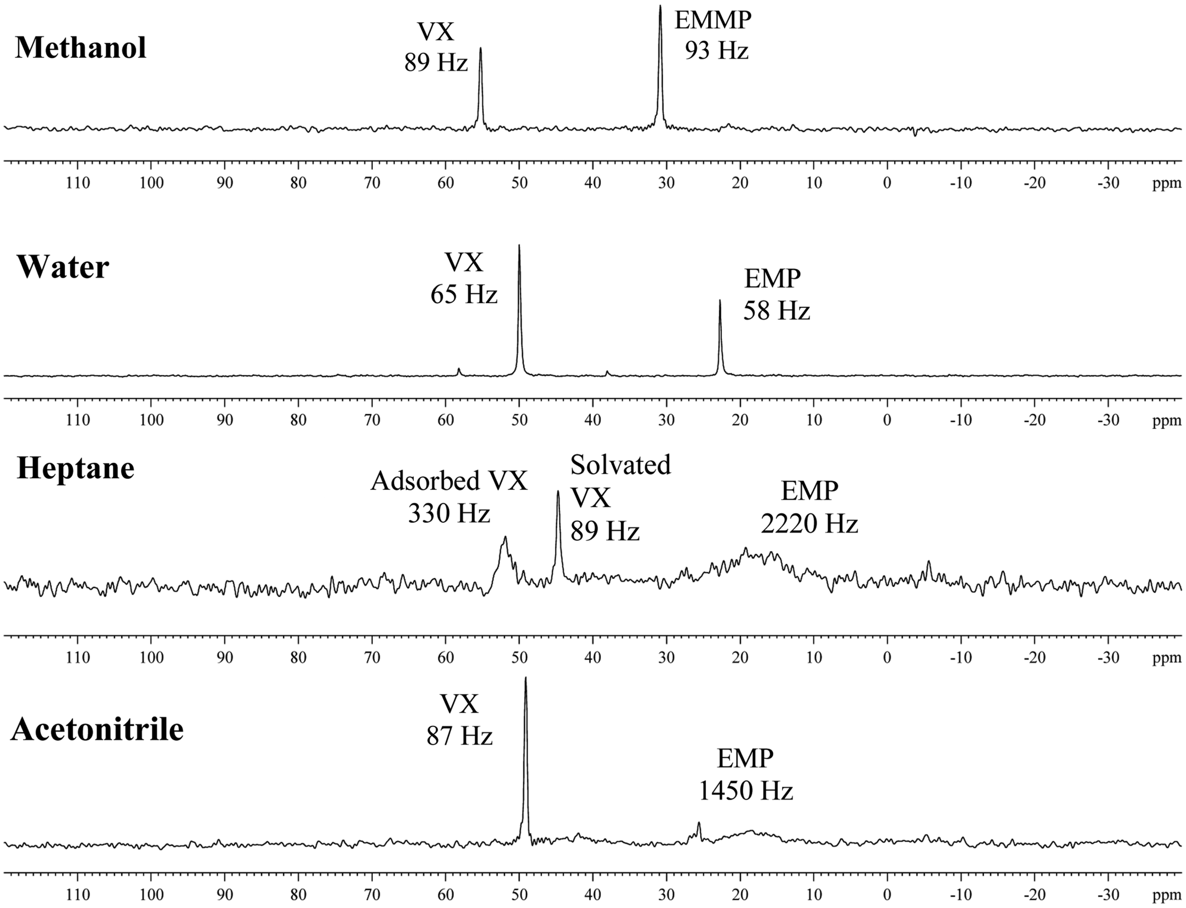


Figure 3. Selected ^{31}P MAS NMR spectra from the reactions of VX with KF/Al_2O_3 in the presence of 50 wt % of the solvents after ∼50% conversion.

Because the EMP salt product is not soluble in these solvents, reaction rates were deduced from VX disappearance from the solvents (i.e., VX adsorption, Figures S5−S6). However, as in acetonitrile (50 wt %), the peak of adsorbed VX was not observed, and in heptane (50 wt %), it did not accumulate (Figures S1 and S7); we assume that the adsorption of VX on the solid matrix at 90 wt % solvent is also the rate-determining step. Similar to other OPs,[18] reactions of VX in the presence of 90 wt % of solvents resulted in slower rates than those obtained with smaller volumes (5−50 wt %) (Table 1, entries 5, 9, 13, and 17). In the case of methanol, it appears that "homogeneous-like" conditions (slow rate) are reached at 90 wt %, whereas at 50 wt %, the reaction is still heterogeneous (fast rate) due to the relatively low solubility of fluoride in this solvent. In the case of water, however, "homogeneous-like" conditions are already obtained at 50 wt %, and accordingly similar reaction rates are obtained with 90 and 50 wt %. The most significant decrease in rate was observed with 90 wt % heptane. The relative large volume of this solvent sufficiently solubilizes small amounts of VX, such that its diffusion toward the solid support is reduced. In acetonitrile, efficient solubility of VX already occurs in minute amounts and a large volume does not promote further effect.

Similar to prior observations with other OPs, significant solvent effects were found for the reactions of VX with the KF/Al_2O_3 sorbent. In the case of water and methanol, the addition of a minute quantity permitted mobility of all reaction components, and accordingly, rapid heterogeneous reactions occurred. Excess of these solvents promoted leaching of fluoride from the matrix and led to relatively slow and wasteful "homogeneous-like" transformations. Interestingly, small volumes of heptane (5−50 wt %), albeit, did not mobilize KF at all, promoted relatively fast reactions as they mediated rapid diffusion of VX to the matrix. Under MAS NMR conditions, heptane led to reaction outcomes similar to those obtained with water or methanol. However, reduction of the centrifugation effect resulted in a slower (∼5 fold) yet still effective rate. The addition of large quantities of heptane or any volume of acetonitrile prevented effective transfer of VX to the matrix, resulting in a very slow and wasteful heterogeneous hydrolysis. Therefore, for rapid and effective VX decontamination, it seems better to use a KF/Al_2O_3 powder that contains a minute quantity of the optimal additive water or methanol (up to 10 wt %). However, moderate volumes of a nonpolar inert solvent, such as heptane (up to 50 wt %), should also be added at a second stage to promote both effective spraying of the active powder on the contaminated surfaces and diffusion of the low vapor pressure toxic compound toward the solid active sites.

■ EXPERIMENTAL SECTION

Caution! *These experiments should only be performed by trained personnel using applicable safety procedures.*

Materials and Chemicals. VX was obtained locally at IIBR (>99% purity). KF (≥99%), Al_2O_3 (activated, neutral, 150 mesh 58 Å), methanol (HPLC grade), heptane (HPLC grade), and acetonitrile (HPLC grade) were purchased from commercial suppliers. Deionized water was obtained from a laboratory water purification system. KF/Al_2O_3 powder was prepared as previously described.[18]

Preparation of Powders Wetted with Solvents. For 5−50 wt % solvent: prepared as previously described.[18] For 90 wt % solvent: dry powders, 0.03 g, were placed in Teflon NMR tubes, and 0.27 g of solvent (which contained 1.5 μL of VX) was added.

Sample Preparation. For 5−10 wt % solvent: samples of the appropriate powders (0.04 g) were added to the 0.4 cm ZrO_2 rotor and 2 μL of VX, 5 wt %, were applied via syringe to the center of the sample. The rotor was then sealed with a fitted Kel-F cap. For the 50 wt % solvent: 2 μL of VX was added directly using a syringe to the center of the NMR rotor holding the powder/solvent mixture, and then the rotor was sealed with a fitted Kel-F cap. For the 90 wt % solvent: 1.5 μL of VX was added to the solvent as described above.

Kinetic Studies Using NMR. MAS NMR: ^{31}P spectra were obtained at 202 MHz 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 were referenced to external trimethyl phosphate (TMP) as 0 ppm. The ^{31}P signal was collected with a 5.5 μs pulse width. The pulse delay was 2 s, which is considered sufficient for relaxation in OP esters on solid matrices. The number of transients per spectrum varied between 100 and 2000. For comparison purposes, spectra were recorded under identical conditions. Spectra were measured periodically to determine the remaining starting material and identify degradation products. Solution NMR (for the 90 wt % solvent experiments): ^{31}P spectra were obtained at 202 MHz on an 11.7 T (500 MHz) spectrometer equipped with a QNP probe. The Teflon tubes were vigorously shaken before and after each examination. For a direct comparison, the probe was tuned before each spectra, and the scan number was maintained. Although the temperature was not adjusted in the NMR measurements, RF-induced sample heating in all conditions examined is negligible.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02733.

> NMR spectra of VX reactions in the presence of KF/Al_2O_3 and solvents and kinetic reaction profiles (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Benschop, H. P.; DeJong, L. P. A. *Acc. Chem. Res.* **1988**, *21*, 368−374.

(2) Mizrahi, D. M.; Columbus, I. *Environ. Sci. Technol.* **2005**, *39*, 8931−8935.

(3) Recent reviews: (a) Smith, B. M. *Chem. Soc. Rev.* **2008**, *37*, 470−478. (b) Singh, B.; Prasad, G. K.; Pandey, K. S.; Danikhel, R. K.; Vijayaraghavan, R. *Def. Sci. J.* **2010**, *60*, 428−441. (c) Kim, K.; Tsay, O. G.; Atwood, D. A.; Churchill, D. G. *Chem. Rev.* **2011**, *111*, 5345−5403. (d) Jang, Y. J.; Kim, K.; Tsay, O. G.; Atwood, D. A.; Churchill, D. G. *Chem. Rev.* **2015**, *115*, PR1−PR76. (e) See also: Louise-Leriche, L.; Păunescu, E.; Saint-André, G.; Baati, R.; Romieu, A.; Wagner, A.; Renard, P.-Y. *Chem. - Eur. J.* **2010**, *16*, 3510−3523.

(4) Wagner, G. W.; Bartram, P. W.; Koper, O.; Klabunde, K. J. *J. Phys. Chem. B* **1999**, *103*, 3225−3228.

(5) Wagner, G. W.; Koper, O.; Lucas, E.; Decker, S.; Klabunde, K. J. *J. Phys. Chem. B* **2000**, *104*, 5118−5123.

(6) Wagner, G. W.; Bartram, P. W. *Langmuir* **1999**, *15*, 8113−8118.

(7) (a) Wagner, G. W.; Procell, L. R.; O'Connor, R. J.; Munavalli, S.; Carnes, C. L.; Kapoor, P. N.; Klabunde, K. J. *J. Am. Chem. Soc.* **2001**, *123*, 1636−1644. (b) Wagner, G. W.; Procell, L. R.; Munavalli, S. *J. Phys. Chem. C* **2007**, *111*, 17564−17569. (c) Saxena, A.; Sharma, A.; Srivastava, A. K.; Singh, B.; Gutch, P. K.; Semwal, R. P. *J. Chem. Technol. Biotechnol.* **2009**, *84*, 1860−1872.

(8) Bandosz, T. J.; Laskoski, M.; Mahle, J.; Mogilevsky, G.; Peterson, G. W.; Rossin, J. A.; Wagner, G. W. *J. Phys. Chem. C* **2012**, *116*, 11606−11614.

(9) (a) Wagner, G. W.; Chen, Q.; Wu, Y. *J. Phys. Chem. C* **2008**, *112*, 11901−11906. (b) Wagner, G. W.; Peterson, G. W.; Mahle, J. *Ind. Eng. Chem. Res.* **2012**, *51*, 3598−3603.

(10) Prasad, G. K.; Singh, B.; Ganesan, K.; Batra, A.; Kumeria, T.; Gutch, P. K.; Vijayaraghavan, R. *J. Hazard. Mater.* **2009**, *167*, 1192−1197.

(11) Hirakawa, T.; Sato, K.; Komano, A.; Kishi, S.; Nishimoto, C. K.; Mera, N.; Kugishima, M.; Sano, T.; Ichinose, H.; Negishi, N.; Seto, Y.; Takeuchi, K. *J. Phys. Chem. C* **2010**, *114*, 2305−2314.

(12) Gershonov, E.; Columbus, I.; Zafrani, Y. *J. Org. Chem.* **2009**, *74*, 329−338.

(13) Zafrani, Y.; Goldvaser, M.; Dagan, S.; Feldberg, L.; Mizrahi, D.; Waysbort, D.; Gershonov, E.; Columbus, I. *J. Org. Chem.* **2009**, *74*, 8464−8467.

(14) Zafrani, Y.; Yehezkel, L.; Goldvaser, M.; Marciano, D.; Waysbort, D.; Gershonov, E.; Columbus, I. *Org. Biomol. Chem.* **2011**, *9*, 8445−8451.

(15) Marciano, D.; Goldvaser, M.; Columbus, I.; Zafrani, Y. *J. Org. Chem.* **2011**, *76*, 8549−8553.

(16) For example, see: (a) Mondloch, J. E.; Katz, M. J.; Isley, W. C., III; Ghosh, P.; Liao, P.; Bury, W.; Wagner, G. W.; Hall, M. G.; Decoste, J. B.; Peterson, G. W.; Snurr, R. Q.; Cramer, C. J.; Hupp, J. T.; Farha, O. K. *Nat. Mater.* **2015**, *14*, 512−516. (b) Moon, S.-Y.; Wagner, G. W.; Mondloch, J. E.; Peterson, G. W.; DeCoste, J. B.; Hupp, J. T.; Farha, O. K. *Inorg. Chem.* **2015**, *54*, 10829−10833.

(17) Narske, R. M.; Klabunde, K. J.; Fultz, S. *Langmuir* **2002**, *18*, 4819−4825.

(18) Fridkin, G.; Columbus, I.; Saphier, S.; Yehezkel, L.; Goldvaser, M.; Marciano, D.; Ashkenazi, N.; Zafrani, Y. *J. Org. Chem.* **2015**, *80*, 5176−5188.

(19) Marciano, D.; Columbus, I.; Elias, S.; Goldvaser, M.; Shoshanim, O.; Ashkenazi, N.; Zafrani, Y. *J. Org. Chem.* **2012**, *77*, 10042−10049.

(20) Zafrani, Y.; Gershonov, E.; Columbus, I. *J. Org. Chem.* **2007**, *72*, 7014−7017.

(21) Peterson, G. W.; Wagner, G. W. *J. Porous Mater.* **2014**, *21*, 121−126.

(22) Labban, A. K. S.; Marcus, Y. *J. Solution Chem.* **1991**, *20*, 221−232.