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ALUMINA-ACCELERATED METHANOLYSIS AND HYDROLYSIS OF ACYL AND PHOSPHORYL FLUORIDES

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SUMMARY

We have discovered that Woelm chromatographic γ-alumina substantially accelerates hydrolysis (and methanolysis) of acyl and phosphoryl fluorides. Compared to the corresponding homogeneous reactions, these heterogeneous alumina-promoted reactions occur about 250-350 times faster for acyl fluorides and about 1800-3000 times faster for phosphoryl fluorides.

INTRODUCTION

Our interest in reactions of alkyl fluorides [2] at alumina surfaces [3] has led us to explore the behavior of acid fluorides on untreated alumina and on alumina doped with methanol. We anticipated that the very high affinity (i.e. Lewis acidity) of aluminum ions for fluoride ions [4] combined with the basic properties of alumina would promote rapid and complete hydrolysis and methanolysis of various acid fluorides. We report here very large rate enhancements in the heterogeneous alumina-accelerated hydrolysis and methanolysis of acyl fluorides and of phosphoryl fluorides. Our intention in this initial study was to establish qualitative differences between homogeneous and heterogeneous (alumina) reactions, and therefore the rates cited in this paper are very rough numbers, probably accurate to about ±25%.

RESULTS AND DISCUSSION

Carboxylic acid fluorides are known to undergo homogeneous solvolysis less rapidly than the corresponding acyl chlorides; for example, acetyl fluoride is hydrolyzed 1/100 times as fast as acetyl chloride in 25:75 water: acetone [5]. Likewise, we have found that homogeneous methanolysis of pentanoyl fluoride [6] proceeds at a rate of about 1/25-1/35 times that of the homogeneous methanolysis of heptanoyl chloride, as judged in an experiment in which one equivalent each of pentanoyl fluoride and heptanoyl chloride competed for one equivalent of methanol (plus triethylamine) in CCl_4 solution; the relative methanolysis rates were determined by the relative amounts of the methyl esters formed. In sharp contrast, in an experiment in which one equivalent each of pentanoyl fluoride and heptanoyl chloride competed for one equivalent of methanol stirring in CCl_4 solvent over Woelm-200-dehydrated neutral γ-alumina [7], the acid fluoride was methanolyzed at about the same rate as the acid chloride, as determined by the roughly equal amounts of the methyl esters formed. This ability of alumina to accelerate the methanolysis of acid fluorides more than the methanolysis of acid chlorides represents a relative rate enhancement of between 25-35 (1/25-1/35 → 1/1).

But we have also found that methanol-doped dehydrated alumina accelerates methanolysis of heptanoyl chloride by at least a factor of 10 over the rate of the corresponding homogeneous reaction. Therefore, the overall rate of alumina-accelerated methanolysis of acid fluorides is at least 250-350 (10x25-35) times that of the corresponding homogeneous reaction.

In contrast to carboxylic acid fluorides, sulfonic acid fluorides (e.g. benzenesulfonyl and p-toluenesulfonyl fluorides) did not undergo more rapid methanolysis over alumina than under homogeneous conditions. We have noted previously that sulfonate esters behave differently than carboxylate and phosphonate esters on alumina [2].

Because of the importance of various phosphonyl fluorides as anticholinesterase agents [8], it was critical to determine the extent to which alumina would accelerate methanolysis and/or hydrolysis of phosphonyl and phosphoryl fluoride linkages. Because of its well-studied chemical and physical properties, its moderate toxicity, and its commercial availability (Aldrich) diisopropyl fluorophosphate (DFP) was selected as a simulant for fluorophosphonate nerve agents [9].

The experimental design involved injecting 18 mg (0.1 mmol) of DFP (in ether solution) into magnetically stirred serum-stoppered flasks each containing different amounts of Woelm alumina at 25° with several ml of diethyl ether as solvent. Samples were taken for glpc analysis by stopping the stirring at various intervals and withdrawing a sample from the supernatant solution using a 10 μl syringe. The results are summarized in Table I.

TABLE I.
Hydrolysis of DFP (0.1 mmol, 18 mg) of Woelm alumina at 25° with Et_2O solvent

Alumina Activity	Alumina Amount	Per Cent DFP Hydrolysis in 0.5 min	10 min	30 min	60 min
super-I	1g	99%	100%		
I	2g	86%	100%		
	1g	75%	97%	100%	
	0.5g	56%	83%	96%	99%
II	2g	80%	100%		
	1g	52%	91%	100%	
	0.5g	19%	51%	69%	82%
IV	2g	44%	57%	74%	92%

Several important conclusions emerge from the data in Table I, as follows:

(1) The rate of DFP hydrolysis is highest for the highest activity alumina. With commercially available super-I [7a] activity alumina, virtually complete hydrolysis occurred within 30 seconds. Even with activity II alumina, 100% hydrolysis was achieved within 10 minutes.

(2) Activity IV alumina is prepared by adding 10% by weight of water to activity super-I alumina. Even with this well-hydrated and relatively air-stable activity-IV alumina, 44% of DFP was hydrolyzed within 30 seconds.

(3) The loading capacity of alumina for DFP is comparable to the solubility of DFP in water (1.5% w/w) [10]. About 15 mg of DFP will dissolve in 1 gm of water, and about 18 mg of DFP were hydrolyzed rapidly by 1 gm of activity I-II alumina. If more than 18 mg (0.1 mmol) of DFP were put on 1 gm of alumina, hydrolysis was slowed somewhat but still occurred relatively rapidly; for example, 36 mg of DFP on 1 gm of activity-I alumina was 83% hydrolyzed in 10 minutes.

(4) DFP is hydrolyzed 15-30 times more slowly than Sarin, which has a h life of about 30 minutes at pH 7.9 at 25° in water [11]; therefore, 75% hydrolysis (2 half-lives) of DFP in water at pH 7.9 should take 900-1800 minutes (2x30 minutes x 15-30). In comparison 75% hydrolysis of DFP on activity I neutral Woelm alumina occurred within 30 seconds. The approximate rate enhancement of DFP hydrolysis by alumina under these conditions is therefore at least 1800-3600.

Although our glpc assay indicates the disappearance of DFP from the supernatant solution, this loss of DFP from solution is not due simply to adsorption to the alumina surface; such adsorption is expected to be immediate and should not increase with time (e.g., 10→60 minutes). To prove unambiguously that hydrolysis and not simply adsorption of DFP was occurring, methanol-doped alumina was used and the methanolysis product $(i\text{-PrO})_2P(O)OMe$ was isolated and identified [12].

It is worth noting that some other porous solids (e.g., Baker chromatographic alumina, chromatographic silica gel, Montmorillonite KSF clay) are much less effective than Woelm chromatographic alumina in promoting DFP hydrolysis.

EXPERIMENTAL

Analytical gas chromatography was performed on a Varian Aerograph Model 120 equipped with a flame ionization detector using a 1/8"x10' column of 5% SE-30 on 100-140 mesh Chromosorb G. The He carrier gas flow rate was maintained at 20 ml per minute. Quantitative GC analyses were performed using peak areas recorded by electronic integration on a Cole-Palmer Model 8384 Recorder. Detector response ratios were determined from carefully prepared standards. Spectral data were obtained with a Perkin-Elmer 457-A infrared or a Varian T-60 nmr spectrometer. All substances and standards were the best commercially available reagent grades or were prepared from such. Anhydrous diethyl ether was used as received. Carbon tetrachloride was stored over Linde 4A Molecular Sieves. The diisopropyl fluorophosphate (DFP) was used as received from Aldrich Chemical Company.

The Woelm alumina, W-200 neutral (activity grade Super I) was obtained from ICN Pharmaceuticals, Inc., Cleveland, Ohio. The alumina was further activated according to the published procedure [7b] and designated W-200-N-D, the D meaning dehydrated. The activated alumina was dispensed into vials containing the approximate amount for 1 run, 1 or 10 grams, and sealed in glass. All samples of alumina of activity grade I or higher were handled in a nitrogen filled glove bag. All reaction vessels, stoppers, stirring bars, syringes and needles were oven-dried at 120°C and cooled in a desiccator. All acid halide solutions were prepared by taking the approximate volume necessary, determining the solute weight and calculating the volume from the reported density. Enough CCl_4 solvent was then added via syringe to give a solution such that 2.0 ml would contain 1.0 mmole of solute. For solids, the approximate amount was weighed and the solution prepared in a volumetric flask. The methanol solution was prepared in the same manner as those of the acid halides except that the CCl_4 was measured with a graduated cylinder and the concentration was such that 10.0 ml contained 1.0 mmole of methanol.

The ether solution of DFP was prepared in a sealed, septum capped vial by injecting 10.1 ml of anhydrous ether and 82 µl of DFP into the vial. An internal standard of n-undecane was added by injecting 200 µl of a solution of 0.158 grams of n-undecane in 1.0 ml of ether. With this solution, 2.0 ml contained 0.09 mmole of DFP.

General procedure for the alumina accelerated methanolysis of carboxylic acid halides

The strategy was to allow 1.0 mmole of each of the acid halides to compete for 1.0 mmole of methanol. The alumina was first exposed to the methanol to allow the alcohol to be adsorbed onto the alumina surface. The reactions were all conducted at room temperature. In a nitrogen filled glove bag one sealed ampule containing approximately 10 grams of W-200-N-D alumina was emptied into a preweighed flask with stirring bar. The stoppered flask was reweighed and in the glove bag a quantity of the methanol solution was added such that the ratio of methanol to alumina was 1.0 mmole per 10.0 grams (i.e., 10.0 ml of solution per 10.0 grams of alumina). The stoppered flask was removed to the hood and quantities of acid halide solutions were simultaneously added, with stirring, such that equimolar amounts were provided (i.e., 2.0 ml of acid halide solution per 10.0 grams of alumina). The mixture was stirred for 1.0 hr and then filtered through Celite on a medium porosity sintered glass filter. The contents of the flask were transferred into the filter with a few ml of CCl_4. The CCl_4, which contained only traces of material, was set aside and the alumina washed with five 10 ml portions of anhydrous ether. The five ether washings were sufficient to remove nearly all the non-acidic material adsorbed on the surface of the alumina, as judged by glpc analysis.

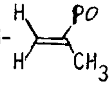
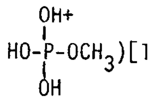
General procedure for homogeneous control reactions

The strategy was the same as for the alumina reactions. One mmole of each of the acid halides was allowed to compete for 1.0 mmole of methanol in the same total volume of solvent. In addition, 1.0 mmole of triethylamine was added in the case of carboxylic acid halides. To a flask containing a stirring bar was added, via syringe, 10.1 ml of the methanol solution and 140 μl of triethylamine, to provide 1.0 mmole of base. Then with stirring, 2.0 ml of each of the acid halide solutions were simultaneously added. Samples were withdrawn periodically for glpc analyses.

General procedure for alumina-accelerated hydrolysis of DFP

The precautions for handling DFP were essentially those described in the Technical Information provided by Aldrich Chemical Company. The appropriate quantity of the desired adsorbent was transferred into a preweighed flask equipped with a stirring bar and stopper. The weight of adsorbent, usually about one gram, was determined and the flask was clamped into position over a magnetic stirrer in a hood. Then, a quantity of the DFP in ether solution corresponding to 2.0 ml per 1.0 gram of a adsorbent or multiple thereof, was added with stirring. Samples were taken for glpc analyses by stopping the stirrer and withdrawing the sample directly into the 10 μl syringe.

Alumina-accelerated methanolysis of DFP.

To a round bottom flask containing 3.15 g of W-200-N (not dehydrated) alumina doped with 4% by weight of absolute methanol was added 6 ml of a 0.05 M solution of DFP in anhydrous ether. The mixture was allowed to stir for 3h at which time glpc analysis indicated complete disappearance of DFP and the appearance of a new component (column 190°, retention 3.8 min). Work was accomplished by filtering the reaction mixture through a pad of celite and washing the solids with ether. Concentration gave 21.9 mg of a crude liquid which when purified by tube to tube distillation gave 9.5 mg (16%) of a clear colorless liquid (b.p. 40-50° at 0.2 mmHg) : nmr ($CDCl_3$) δ4.70 (m,2H) 3.75(d, J=11Hz, 3H) 1.39(d, J=6Hz, 12H); ir($CHCl_3$) 2900, 1120, 1030 cm^{-1}; MS(m/e) 181($M-CH_3$) 139(M- ) 113(base,  $HO-\overset{OH^+}{\underset{OH}{P}}-OCH_3$)[13].

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REFERENCES

1 Visiting Professor, 1979-1980, from Eastern Illinois University.

2 G.H. Posner, G.M. Gurria, and K.A. Babiak, J. Org. Chem. 42 (1977), 3173.

3 G.H. Posner, Angew. Chem. Int. Ed. Engl, 17 (1978), 487, and references therein.

4 Al^{+3} complexation with fluoride is stronger than that observed for Cu^{+2}, Fe^{+3}, and Zr^{+4}: "Stability Constants of Metal-ion Complexes," Special Publication No. 7, The Chemical Society, London, 1964 (Section 1, Inorganic Ligands).

5 (a)C.G. Swain and L.B. Scott, J. Amer. Chem. Soc., 75 (1973) 246; (b)A. Kivinien in "The Chemistry of Acyl Halides," S. Patai, Ed., Interscience, New York, 1972, p. 204.

6 Prepared according to J. Cuomo and R.A. Olofson, J. Org. Chem. 44 (1979) 1016.

7 (a)Activity Super-I on the Brockmann scale: H. Brockmann and H. Schodder, Ber. Dtsch. Chem. Ges., 74B (1941), 73, surface area about 200 m^2/g;
(b) dehydrated according to G.H. Posner, A.W. Runquist, and M.J. Chapdelaine, J. Org. Chem. 42, (1972), 1202.

8 H. Behlback and W.A. Williams, Arch. Environ. Health, 30 (1975), 49, and references therein.

9 For a study of adsorption and decomposition of nerve agent sarin (isopropy methylphonofluoridate) and γ-alumina, see A.E.T. Kuiper, Ph.D. Thesis, 1974, Chemical Laboratory, National Defense Research Organization TNO, Rijswijk, the Netherlands.

10 Aldrich Technical Information Sheet.

11 J. Epstein, Science, 170 (1970), 1396; at lower pH, however, the hydrolysis rate decreases dramatically; for example, at pH 7.6 the half-life of Sarin is about 60 minutes and at pH 6.5 about 150 hours!

12 (a)It was not possible to extract the hydrolysis product $(\text{i-PrO})_2\text{P(O)OH}$ from the alumina, and therefore methanolysis was examined assuming reasonably that alumina-accelerated hydrolysis and methanolysis are very similar processes.

(b)Confirmation of structure was made by comparison of the nmr and mass spectra of triethyl phosphate [13], DFP [14], trimethyl phosphate [14], and triisopropyl phosphate [15] to that of the spectra for the diisopropyl methyl phosphate prepared here (see experimental section).

13 H. Budzikiewicz, C. Djerassi and D.H. Williams 'Mass Spectrometry of Organic Compounds,' Holden-Day, San Francisco, 1967, p. 645, and references therein.

14 C.J. Pouchet and J.R. Campbell 'The Aldrich Library of NMR Spectra' Aldrich Chem. Co. vol X, 1974.

15 Thermochemical Records Center nmr spectra #89, Thermochemical Records Center, College Station, Texas.