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## ROLE OF SOLVENT AND BASE IN THE SILANIZATION REACTION OF SILICAS FOR REVERSED-PHASE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

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### SUMMARY

Reversed-phase packings were synthesized by reaction of *n*-alkyldimethylchloro- and trifluoroacetoxysilanes with silicas of 15 and 25 nm pore size, employing tetrahydrofuran, N,N-dimethylformamide, benzene, diethyl ether, dichloromethane and acetonitrile as solvents and triethylamine, pyridine, triazole, quinuclidine, 2,4- and 2,6-lutidine and imidazole as bases. With dichloromethane as solvent and 2,6-lutidine as base, *n*-alkyldimethyltrifluoroacetoxysilanes did not yield *n*-alkyl ligand densities higher than those obtained with *n*-alkyldimethylchlorosilanes under identical conditions.

With a given base and given *n*-alkyldimethylchlorosilane the solvent type was found to exert a noticeable influence on the kinetics of the silanization reaction, which can be interpreted in terms of three cooperative effects. The reactivity of solvents increased in the sequence tetrahydrofuran < benzene < diethyl ether < acetonitrile < dichloromethane < N,N-dimethylformamide.

Basic catalysts are known to accelerate the kinetics of the silanization reaction (owing to their acid-binding capacity) when *n*-alkylchlorosilanes are employed as reagents. Of the tertiary amines studied, imidazole was found to be much more reactive, which can be explained by the formation of reactive imidazolide intermediates via nucleophilic attack on the silane.

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### INTRODUCTION

In recent years, reversed-phase bonded silicas have become the most popular packings in high-performance liquid chromatography (HPLC). Although the role of the eluent composition in controlling retention and selectivity in reversed-phase HPLC is now well documented, limited information is available on the effects of stationary phase properties. This is undoubtedly due to the lack of precise and reliable methods for characterizing the bonded phases in terms of the density, homogeneity, topographical distribution of bonded *n*-alkyl ligands and residual hydroxy groups. Ultimately, these properties are directly controlled by the native silica, the silanizing reagent and the reaction conditions. Most preparations follows general recipes in

which the activated silica is treated with an excess of a reactive silane without a solvent<sup>1</sup> or dissolved in benzene or toluene, pyridine being added as an acid binder (acceptor)<sup>2-4</sup>. In some instances the experiences obtained in hydroxy group protection chemistry were adapted to the silanization of silica<sup>5,6</sup>.

Although much interest is currently focused on obtaining a dense ligand coverage, there are instances where packings with graduated ligand densities and those with mixed bonded ligands appear to provide chromatographic properties superior to those of fully covered surfaces, bonded with a single type of ligand. This reinforces the need for studies of the bonding reaction and the characterization of packings.

In this study, the reaction of silica HPLC packings with trialkylchloro- and trialkyltrifluoroacetoxysilanes was examined in a variety of solvents and with added bases, in an attempt to correlate the kinetic findings with the molecular structures of the reacting species.

## EXPERIMENTAL

### *Chemicals and materials*

Alkyldimethylchlorosilanes were prepared by hydrosilylation of the corresponding alkenes with dimethylchlorosilane, employing a solution of hexachloroplatinic acid ( $\text{H}_2\text{PtCl}_6 \cdot x\text{H}_2\text{O}$ ) in 2-propanol as catalyst<sup>4</sup>. All products were purified by fractional distillation.

According to a procedure described by Corey *et al.*<sup>6</sup>, alkyldimethyltrifluoroacetoxysilanes were prepared by adding an equivalent amount of trifluoroacetic acid to the alkyldimethylchlorosilane. After stirring the mixture for 30 min at room temperature, the product was separated by distillation. All silanes were identified by <sup>13</sup>C NMR spectroscopy and mass spectrometry.

Solvents, all of analytical-reagent grade, were carefully distilled and freed from water by use of molecular sieve 4A or by treatment with sodium wire.

The liquid bases were purified and dried by distillation from KOH or CaH-*n*-decane. Imidazole, triazole and quinuclidine were dried in a drying pistol.

### *Surface modification*

*Series 1.* A 20-g amount of silica (10  $\mu\text{m}$  particle size, nominal pore size 25 nm,  $S_{\text{BET}} = 296 \text{ m}^2/\text{g}$ ) was activated at 473°K and at a reduced pressure of  $< 10^{-3}$  mbar. After 12 h, the material was cooled to room temperature. A sample of 0.047 mole of the appropriate monochlorosilane or monotrifluoroacetoxysilane and 10.07 g (0.094 mole) of 2,6-lutidine were dissolved in 100 ml of dry dichloromethane. The mixture was added to the activated silica, which was still under vacuum, using a dropping funnel and a vacuum line flushed with dry argon. The reaction mixture was rotated and refluxed for 24 h. The silica was then filtered and thoroughly washed with dichloromethane, methanol, methanol-water (50:50), methanol and diethyl ether.

*Series 2.* Seven 5-g samples of silica (10  $\mu\text{m}$  particle size, nominal pore size 14.8 nm,  $S_{\text{BET}} = 320 \text{ m}^2/\text{g}$ ) were placed in 100-ml two-necked flasks, fitted with a G4 porous glass frit and a stopcock, and activated in a vacuum furnace at 473°K and a reduced pressure of  $< 10^{-2}$  mbar for 12 h. After it had cooled to room temperature, the furnace was flushed with dry nitrogen. Solutions of 0.024 mole of bases (listed in Table I) and 4.17 g (0.012 mole) of *n*-octadecyldimethylchlorosilane in 50

ml of dry dichloromethane were added to each flask. All reaction vessels were heated together in the same heating bath (bath temperature 323°K). After 0.25, 4.0, 13.0 and 41, samples were taken, washed as above, dried and analysed for their carbon contents.

*Series 3.* Six 5-g samples of silica were treated as described for series 2. After activation, a solution of 4.17 g (0.012 mole) of *n*-octadecyldimethylchlorosilane and 2.57 g (0.024 mole) of 2,6-lutidine in 50 ml of the solvent (listed in Table II) was added and stirred at room temperature. After 0.25, 4 and 28 h, samples (washed as described above and dried) were taken for elemental analysis.

*Series 4.* (a) A 10-g amount of silica of series 2 was activated at 473°K and reduced pressure ( $< 10^{-3}$  mbar) for 12 h. After it had cooled to room temperature, a sample of 8.5 g (0.026 mole) of *n*-octadecyldimethylchlorosilane and 5.6 g (0.052 mole) 2,6-lutidine was dissolved in 100 ml of dichloromethane and added to the activated silica. The reaction mixture was stirred and heated under reflux for 24 h. After 5, 10, 20, 40, 60, 90, 120, 240 and 360 min, samples were taken for elemental analysis.

(b) A 10-g amount of silica of Series 2 was activated at 473°K and reduced pressure ( $< 10^{-3}$  mbar) for 12 h. After it had cooled to room temperature, 50 ml of *n*-octadecyldimethylchlorosilane were added to the silica, which was still under vacuum. After reaction for 24 h at 433°K, the sample was treated as described above.

## RESULTS AND DISCUSSION

### *Trialkyltrifluoroacetoxy- vs. trialkylchlorosilanes in the silanization of silica*

Trialkyltrifluoroacetoxy-silanes are known to be highly reactive in the silylation of tertiary and unreactive secondary alcohols, when dichloromethane and 2,6-lutidine as base are used. Corey *et al.*<sup>6</sup> adapted the reaction to the preparation of *n*-octadecyl-bonded phases, achieving a ligand density ( $\alpha_{\text{exp}}$ ) of  $3.00 \mu\text{mole m}^{-2}$ .



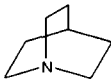
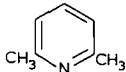


In series 1, four different pairs of trialkylsilanes, each having a reactive trifluoroacetate or chloro group, were allowed to react with the same silica under identical conditions. The ligand densities obtained in  $\mu\text{mole m}^{-2}$  were as follows:  $4.40 \pm 0.1$  for trimethylchlorosilane and  $4.48 \pm 0.1$  for trimethyltrifluoroacetoxy silane;  $4.01 \pm 0.1$  for ethyldimethylchlorosilane and  $3.93 \pm 0.1$  for ethyldimethyltrifluoroacetoxy silane;  $3.48 \pm 0.1$  for *n*-octyldimethylchlorosilane and  $3.45 \pm 0.1$  for *n*-octyldimethyltrifluoroacetoxy silane; and  $3.34 \pm 0.1$  for *n*-octadecyldimethylchlorosilane and  $3.32 \pm 0.1$  for *n*-octadecyltrifluoroacetoxy silane.

The data show no significant differences in the ligand density between the chloro- and the trifluoroacetoxy-silane for a given *n*-alkyl group. This may serve as an indication that the type of reactive group is less important in the bonding reaction than the type of base or solvent. The ligand density obtained for the trimethylsilyl-modified silica was about  $0.3 \mu\text{mole m}^{-2}$  lower than the value reported by Gobet and Kováts<sup>7</sup> ( $4.75 \mu\text{mole m}^{-2}$ ) on Cab-O-Sil treated with trimethyl (dimethylamino)silane. The decrease from 4.75 to 4.44 may account for steric effects taking place in the silanization reaction of the porous silica. For the silicas modified with *n*-octyl- and *n*-octadecyldimethylchlorosilane the  $\alpha_{\text{exp}}$  values are identical with those reported by Berendsen *et al.*<sup>4</sup>.



TABLE I

LIGAND DENSITY OF SILICA 2 (REACTED WITH *n*-OCTYLDIMETHYLCHLOROSILANE DISSOLVED IN DICHLOROMETHANE AND DIFFERENT BASES) AS A FUNCTION OF THE DURATION OF REACTION

Base	Formula	$pK_a$	Ligand density ( $\mu\text{mole m}^{-2}$ )			
			0.25 h	4.0 h	13.0 h	41.0 h
Triethylamine	$\text{N}(\text{C}_2\text{H}_5)_3$	10.8	1.95	2.70	2.79	3.04
Pyridine		5.35	1.92	2.68	2.85	3.03
Triazole		—	1.59	2.61	2.80	2.86
Quinuclidine		8.9	1.35	2.07	2.36	2.39
2,6-Lutidine		6.72	2.04	2.76	2.90	3.10
2,4-Lutidine		6.99	2.07	2.74	2.86	3.06
Imidazole		6.95	2.36	3.35	3.45	3.53

maximum ligand density. Thus, the cause of the discrepancies needs to be determined by additional experiments before any firm conclusions can be drawn. From the values of Table I it can be inferred that the type of base does not cause drastic differences in the kinetics of the silanization reaction.

A much more complicated situation is met when the effect of the solvent on the kinetics is examined. The solvent is capable of interacting specifically with the surface hydroxy groups, the silane and the base. First, the solvent molecule interacting with a silanol group is assumed to have a considerable effect on the strength of the ( $d\pi-p\pi$ ) bond between the silicon and the oxygen atom. With solvents having both a pronounced Lewis acid and a Lewis base character, the Si-O bond strength is weakened and either the silicon atom (by the Lewis base) or the oxygen atom (by the Lewis acid) increases in polar character. Based on the extent of the frequency shift  $\Delta\nu$  of the Si-H stretching vibration band of trialkylsilanes in IR spectroscopic measurements, Marciniak and Gulinska<sup>9</sup> postulated relative values for the Lewis-donating and Lewis-accepting properties of some solvents (see Table II). Similar

TABLE II

LEWIS-DONATING AND -ACCEPTING PROPERTIES OF SOLVENTS AND LIGAND DENSITY OF SILICA 2 (REACTED WITH *n*-OCTADECYLDIMETHYLCHLOROSILANE AND 2,6-LUTIDINE IN DIFFERENT SOLVENTS) AS A FUNCTION OF THE DURATION OF REACTION

Solvent	Lewis-donating property (relative value)*	Lewis-accepting property (relative value)*	Ligand density ( $\mu\text{mole m}^{-2}$ )		
			0.25 h	4.0 h	28.0 h
Tetrahydrofuran	20.0	8.0	0.85	1.66	2.00
N,N-Dimethylformamide	26.6	16.0	2.08	3.06	3.09
Benzene	0.1	8.2	1.05	1.78	2.07
Diethyl ether	19.2	3.9	1.27	2.15	2.40
Dichloromethane	—	20.4	2.06	2.73	3.07
Acetonitrile	14.1	18.9	1.94	2.72	3.03

\* Taken from ref. 9, with permission.

gradations were found in the spectra of trimethylchlorosilane<sup>10</sup> and *n*-octadecyldimethylchlorosilanes<sup>11</sup> in various solvents. Hence, solvents with both pronounced Lewis acid and Lewis base character should facilitate the reaction. Such solvents are dichloromethane, acetonitrile and N,N-dimethylformamide, while benzene, tetrahydrofuran and diethyl ether are less efficient.

Second, the solvent can also activate the silicon atom of the organohalosilane by forming a pentacoordinated intermediate through nucleophilic attack. As a consequence of bond lengthening, a nucleophilic activation occurs, favouring attack by a second nucleophile.

Third, the course of the reaction may be affected by the influence of the solvent on the added base. It is known that in aprotic polar solvents the nucleophilic character of reactants is more pronounced. In other words, effects other than the  $pK_a$  of the base may be dominant in the kinetics.

The synergistic action of the three effects described above is not yet known. Hence, predictions on an optimum solvent-base combination cannot be made.

Ligand densities ( $\alpha_{\text{exp}}$ , Table II) as a function of the duration of the reaction were established in the following reactivity sequence: tetrahydrofuran < benzene < diethyl ether < acetonitrile < dichloromethane < N,N-dimethylformamide. The reactivity appears to be in accord with the Lewis acid and Lewis base properties. Again, the results obtained in this particular system indicate a trend; more thorough investigations are needed before general conclusions can be drawn.

#### Catalysed vs. non-catalysed silanization reaction

In series 4a and b, *n*-octadecyl bonded phases were prepared with a solvent and a base (a) and without either of these catalysts (b). The ligand density,  $\alpha_{\text{exp}}$ , plotted against the reaction time is shown in Fig. 1. Apparently, in all instances the kinetics follow two different rate constants, with an intermediate range around the inflection point. The limited data on the initial steep part (curve a) do not allow any apparent rate constants to be derived. However, it can be assumed that the reaction in the first region is pseudo-first order, *i.e.*, proportional to the actual concentration of the silanization reagent. The second region probably obeys kinetics that are dif-

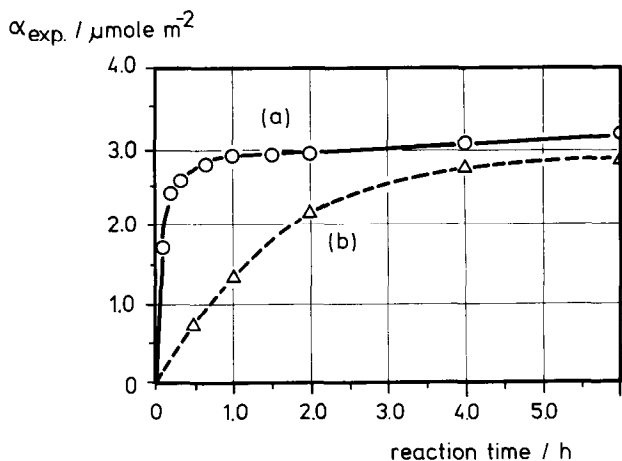


Fig. 1. Kinetics of (a) catalysed and (b) non-catalysed silanization reaction. *n*-Octyldimethylchlorosilane, silica of 15 nm pore size (see series 4a and b). (a) solvent dichloromethane, 2,6-lutidine, reaction temperature 323°K; (b) silane only, reaction temperature 433°K.

fusion controlled. Although a direct relative comparison of the reaction rate cannot be made owing to the differences in the reaction temperatures [(a) at 323°K and (b) at 433°K], the course of the curves clearly demonstrates the benefit of the catalysts: under the given conditions and with a batch size of 10 g, 90% of the total conversion takes place within 1 h in the presence of the catalysts. Scale-up preparations were made of the catalytic reaction with batch sizes from 100 g to 4 kg and a reproducibility of the ligand density of  $\pm 0.1 \mu\text{mole m}^{-2}$ . In order to achieve maximum ligand density of *n*-octadecyl-bonded groups, an amount of  $5 \mu\text{mole m}^{-2}$  of silane was applied in the starting solution. Compared with the non-catalysed silanization, the reaction temperature can be kept low, and the procedure permits economic consumption of the silane.

Ligand densities below the maximum cannot be adjusted via the reaction time in the catalysed case but only by applying a calculated amount of the silane required. It is worth mentioning that the precise achievement of a certain  $\alpha_{\text{exp}}$  value is strongly dependent on the purity of the silane employed.

## CONCLUSIONS

Of the various dependences documented, the solvent appears to exert a more pronounced effect than the base in the given silanization reaction. Although a full mechanistic description of the silanization reaction cannot yet be given, the principal question centres on whether and to what extent these differences in  $\alpha_{\text{exp}}$  values are associated with the chromatographic properties, *i.e.*, retention and selectivity of solutes. Clearly, the answer will be highly dependent on the eluent composition and the molecular structure of the solutes, *i.e.*, their hydrophobic, hydrophilic and ionic character. In addition, the highly reactive system employed offers the opportunity of controlling (via the reaction conditions) the homogeneity of the bonded layer across the internal surface and the porous particle. However, this has yet to be substantiated by physico-chemical and chromatographic measurements.

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