Reductive Demercuration in Deprotection of Trityl Thioethers, Trityl Amines, and Trityl Ethers

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A room-temperature deprotection method of trityl amines, -ethers, and -thioethers is presented, based on coupling of metal acid catalysis (HgX_2, with $X^- = Cl^-$ or OAc^-) and sodium borohydride reduction. The results of its application to monotritylated compounds (ethanethiol, ethanol, and piperidine) and to mono- and ditritylated 1,2-bifunctional compounds (mercaptoethanol, aminoethanethiol, and ethanolamine) are compared with those obtained with early methods based on the use of strong Brønsted acids (pure TFA and MeCN solutions of HCl). Trityl thioethers of simple thiols and amino and hydroxy thiols are promptly cleaved by reductive detritylation, and one-pot procedures can be employed to produce free thiols. In contrast, dilution with water of these same compounds in solutions of strong Brønsted acids leaves them unaffected. O−Tr and N−Tr bonds are broken by this latter treatment. However, trityl ethers are rapidly cleaved by even dilute HCl solutions, while cleaving of trityl amines is modulated by HCl concentration. Addition of $NaBH_4$ to solutions of monofunctional trityl ethers in $HgCl_2$/MeCN leads to complete deprotection. Monofunctional trityl amines are partially deprotected only if the complexation reaction is allowed to reach equilibrium. Combination of H^+- with HgX^+-catalyzed detritylation methods allows selective deprotection of pertritylated amino and hydroxy thiols. The results appear to be due to the strong difference in the affinity of the donor atoms present in the pertritylated substrates for H^+ and HgX^+. Catalysis based on Brønsted acids leads to cleaving of the N- and O-trityl bonds with recovering of the S-trityl group; that based on mercury salts allows recovering of N- and O-trityl groups with deprotection of the −SH function. Selectivity in deprotection of pertritylated amino alcohols seems to be severely hampered by similarity in the affinity of N- and O-atoms for H^+ and HgX^+, and, taking advantage of the lower HgX^+-complexation rate of the N-trityl with respect to the O-trityl group, only preservation of the N-trityl bond has been achieved.

Introduction

Triphenylmethyl is a common protecting group for hydroxyls and primary and secondary amino and thiol groups, and acidolysis represents the most practical method to remove it from the protected groups at the end of any desired reaction of the molecule under study. In principle, selective deprotection of pertritylated compounds, with at least two of the above listed functional groups protected, should be gained through controlled acidolysis, factors kinetically affecting the process being the strength of the Brønsted acid employed, its concentration, temperature, etc. However, data coming from the literature on deprotection times and temperatures of trityl thioethers, amines, and ethers[1] appear too much spread to put some confidence in selectively detritylating these groups. For example, S-detritylations with TFA have been performed at temperatures ranging from room to reflux temperature and required from 15 to 30 min.[2,3] Remarkably, the use of this as well as other strong protic acids has been found ineffective in many cases.[4] Further differences can be found in methods of working up the reaction mixture after deprotection. In analogous fashion, acid-catalyzed N- and O-detritylations are reported to be achieved in a variety of conditions.[1]

On the other hand, it is well-known that heavy metal ions displace trityl groups from trityl thioethers, both in protic and aprotic solvents, and in the former case, irrespective of the solvent acid strength.[1] With respect to acidolysis through a Brønsted acid, deprotection of trityl thioethers performed with the aid of metal ions introduces a further step, represented by the displacement of the metal from the mercaptide, usually performed by treatment with competing thiols or with acids, as HCl or H_2S, having anions giving rise to insoluble salts with the metal ion.[1,4] Furthermore, the use of metal ions in deprotecting trityl amines and trityl ethers appears to be much less investigated.

An early goal of this work was the characterization of the deprotection process of trityl thioethers, primarily with metal acids in aprotic solvents. Then, it was found that trityl amines and trityl ethers are detritylated by TFA at room temperature at a rate definitely higher than trityl thioethers, thus pointing to the concrete existence of methods of selective detritylation based on the kinetic control of the H^+-catalyzed reaction. In a further step, the encouraging results obtained in the recovery of thiols

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from their mercaptides by treatment with sodium borohydride prompted an extension of the method to trityl amines and trityl ethers.

This work reports the results of detritylation experiments on the substrates listed in the Experimental Section.[5] The idea was to compare the efficiency of early procedures with the detritylation method here investigated first on tritylated monofunctional compounds (ethylmercaptan, ethanol, and piperidine), then on trityl derivatives of compounds bearing two different functions (mercaptoethanol, ethanolamine, and mercaptoethylamine) at various levels of protection (for example, *S*- and *O*-tritylmercaptoethanol and *O*,*S*-ditritylmercaptoethanol). The behavior under detritylation of the bis-tritylated compounds has given information about selective deprotection, while that of the monotritylated substrates has shed light on the influence of the free group on the detritylation of the other (Tr-migration and so on).

As will be shown below, the results allow useful rules for selective detritylation to be drawn. The work herein reported encourages a broader investigation on selective protection or deprotection of multifunctional substrates under metal−acid catalysis, and experiments in this area are currently in progress in this laboratory.

Results

Detritylation requires the action of a nucleophile on the following general equilibrium, where **D** is the donor atom to be deprotected and $\mathbf{A}^+$ is the Lewis acid employed as catalyst:

$$\text{R-}\mathbf{D}\text{-Tr} + \mathbf{A}^+\text{X}^- \rightleftharpoons (\text{R-}\mathbf{D}^+(\mathbf{A})\text{-Tr})\,\text{X}^- \rightleftharpoons \text{R-}\mathbf{D}\text{-}\mathbf{A} + \text{TrX} \quad (1)$$

$$\text{TrX} \rightleftharpoons \text{Tr}^+ + \text{X}^-$$

($\mathbf{A}^+ = H^+, HgCl^+, HgOAc^+$; -**D** = -S, -NH or =N and -O; $X^- = TFAO^-, AcO^-, Cl^-$)

(reference to formalism introduced with eq 1 will be done throughout the following text). The experimental results indicate as fast the reactions involved in eq 1 when $\mathbf{A}^+ = H^+$, while $HgCl^+$ complexation by trityl amines appears to be slow (see below). Competition between the reactions of a given nucleophile with many substances taking part to equilibrium (1) is to be expected, and which route prevails depends on the equilibrium concentrations of $\mathbf{A}^+X^-$, Tr^+, TrX, of the adduct R-**D**-**A** and of the intermediate complex, on the nature of the employed nucleophile, and on the relative reaction rate of each of the species reacting with the given nucleophile. For a deeper insight in the results obtained in this work, the reactivity of each species taking part in eq 1, in particular with $NaBH_4$, has been accurately investigated.

In TFA, trityl derivatives of monofunctional amines, thiols, and alcohols give rise to yellow solutions whose rapid dilution with water at room temperature leads to prompt cleavage only of N−Tr and O−Tr bonds (heretofore, this procedure will be concisely indicated as TFA, H_2O; symbolism for this and other detritylation procedures is described in the Experimental Section). In contrast, trityl thioethers coming from simple thiols and amino and hydroxy thiols remain unaffected even after prolonged room-temperature treatment with TFA. AcOH does not deprotect trityl thioethers and, as an effect of its weakness, does not affect, as well, trityl amines and trityl ethers: dilution with water of AcOH solutions of these substrates provided only recovered starting material. Thus, even strong protic acids do not cleave S−Tr bonds, while only strong acids break N−Tr and O−Tr bonds. Remarkably, detritylation with TFA is one of the recommended methods for trityl thioethers.[1]

For the sake of comparison with the use of MeCN solutions of HgX_2 ($X = Cl^-, AcO^-$), described below, detritylation has been attempted also with HCl solutions in MeCN (procedure HCl/MeCN, H_2O). Trityl thioethers (Et-STr, ME-STr) were moderately detritylated only by strongly concentrated solutions of this acid, but with formation of secondary products. Trityl ethers (Et-OTr) were totally cleaved while cleaving of trityl amines (Pip-Tr and EA-NTr) is modulated from partial to complete by HCl concentration

A TFA or AcOH solution of a mercuric salt HgX_2 cleaves the S−Tr bond, and dilution with water gives rise to formation of the mercury mercaptide and TrOH. The acid strength does not affect the result, according to early successful quantitative S-detritylations with $Hg(OAc)_2$ in EtOH[4] and in MeOH.[2] Trityl amines or ethers are fully deprotected by HgX_2/TFA, H_2O, but this result seems to be due to the strength of TFA alone. The addition of the metal acid to AcOH (procedure HgX_2/AcOH, H_2O) gives rise to negligible traces of N- and O-detritylation. The introduction of the investigated substrates in a HgX_2/MeCN solution, followed by addition of water (HgX_2/MeCN, H_2O), gives rise to S-detritylation but leaves unaffected N−Tr and O−Tr bonds.

On passing to the use of $NaBH_4$ as nucleophile, it is clear that the final product of an its reaction on a given substrate does not necessarily depend on the substrate structure (known or merely hypothesized) in its solid state. Nevertheless, the investigation of reactions of this reductant with isolated and well characterized substances, taking part to equilibrium (1) or related with it, can throw light on the results reported in this paper. So, simple trityl derivatives are directly deprotected by reduction with $NaBH_4$/MeCN: TrCl and TrOAc have been rapidly converted into TrH. The same product has been reported as prevalent when $TrPF_6$ is reduced with $NaBH_4$ in THF.[6] This result has to be ascribed to Cl^- and AcO^- being good leaving groups. Accordingly, triphenylcarbinol and all the investigated substrates are not affected by this same treatment.

The hydrochlorides of EA-NTr and Pip-Tr, as representative isolated intermediate complexes of trityl amines of the type $(\text{R-}\mathbf{D}^+(\text{H})\text{-Tr})Cl^-$, react with $NaBH_4$/MeCN or THF giving rise to hydrogen and to the parent trityl

(5) Notation: ME = mercaptoethanol; MEA = aminoethanethiol; EA = ethanolamine; TrCl = triphenylmethyl chloride; TrOH = triphenylcarbinol; TrOAc = triphenylmethyl acetate; TrH = triphenylmethane; Et-STr = trityl-ethanethiol; Et-OTr = trityl-ethanol; Pip-Tr = tritylpiperidine; ME-STr = *S*-tritylmercaptoethanol; ME-OSTr = *O*,*S*-ditritylmercaptoethanol; ME-OTr = *O*-tritylmercaptoethanol; MEA-STr: *S*-tritylaminoethanethiol; MEA-NSTr = *N*,*S*-ditritylaminoethanethiol; MEA-NTr = *N*-tritylaminoethanethiol; EA-NTr = *N*-tritylethanolamine; EA-NOTr = *N*,*O*-ditritylethanolamine; EA-OTr = *O*-tritylethanolamine; CYA-2Tr = *N*,*N*′-ditrityl-2-aminoethyl disulfide (*N*,*N*′-ditritylcystamine); MED = 2-hydroxyethyl disulfide; MED-2Tr = *O*,*O*′-ditrityl-2-hydroxyethyl disulfide; ME-SHgX, ME-OTrSHgX, MEA-SHgX and MEA-NTrSHgX (with X = Cl, OAc or OTFA) indicate mercaptides of ME, ME-OTr, MEA, and MEA-NTr, respectively.

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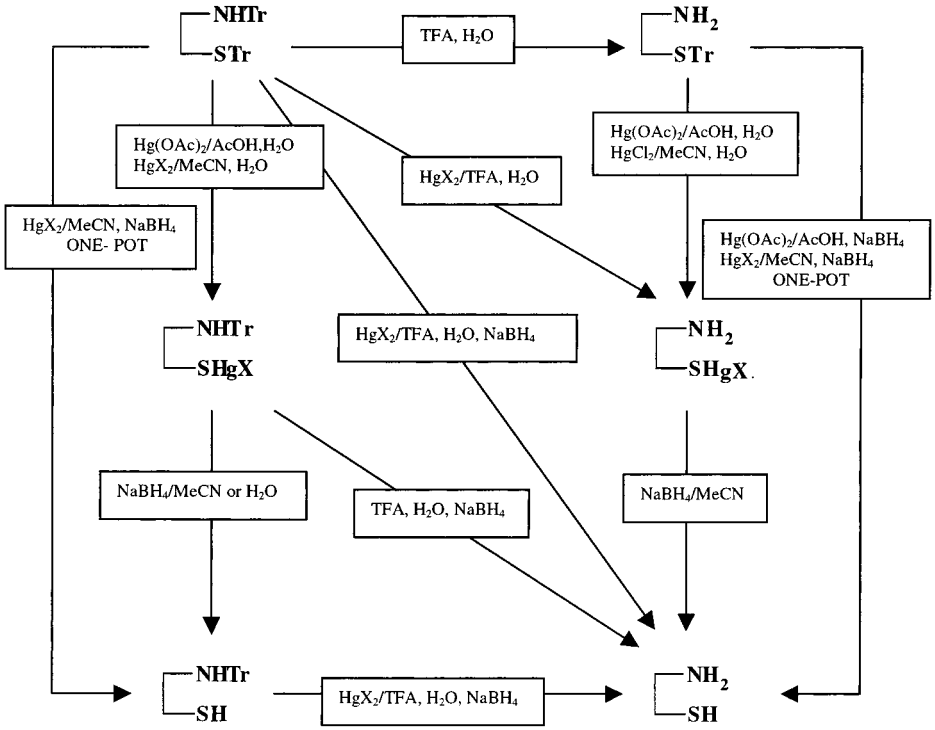

Figure 1. Deprotection pathways of tritylated derivatives of a representative 1,2-amino thiol (mercaptoethylamine).

amine, even in the presence of an excess of HCl. Dropping of a HCl/MeCN solution of a trityl ether into a $NaBH_4$/MeCN suspension leads to complete detritylation, but this result can be confidently referred to the catalytic effect of HCl alone. Trityl thioethers remain essentially unaffected by this same treatment. Remarkably, the procedure HCl/MeCN, $NaBH_4$ leaves unaffected the N−Tr bonds, while it leads to complete O-detritylation.

On addition to HgX_2/MeCN, all the investigated trityl derivatives give rise to coordination of mercury, and TLC can help in having an insight in relative amounts of species taking part to equilibrium (1) (see the Experimental Section). In many instances, complexation leads to heterolytic release of Tr^+ (as indicated by the more or less intense yellow color of the solution[7,8]). More generally, the resulting solutions are colorless. On the grounds of results coming from TLC controls, differences in rates of $HgCl^+$-complexing reactions have been revealed. It has been found that yellow solutions of trityl thioethers and colorless solutions of trityl ethers in $HgCl_2$/MeCN go rapidly to equilibrium, while trityl amines require hours to give a constant chromatogram. Reaction with $NaBH_4$ of freshly prepared solutions of Pip-Tr does not lead to detritylation. Solutions of Pip-Tr, left aside for 24 h, give rise to precipitation of a solid in which the presence of the moiety $(Pip^+(HgCl)\text{-}Tr)Cl^-$ can be confidently assumed (see the Experimental Section). In the solution in equilibrium with this solid the free substrate is practically absent. Reduction of both the suspension and of the isolated solid leads to only partial detritylation. A different result has been obtained for EA-NTr. In this case, complication is introduced by metal acid catalyzed Tr-migration: after 48 h from formation of the mixture, TLC shows disappearance of substrate, but appearance of EA-NOTr. However, reduction with $NaBH_4$ of this mixture has given only EA-NTr as final product, in agreement with the expectation that N-Tr groups are only slightly affected by this method.

As far as the reactivity of adducts of the type R-**D**-HgCl with $NaBH_4$ is concerned, ME-SHgCl, easily synthesized from ME in excess $HgCl_2$, reduced with $NaBH_4$ in MeCN, has given free ME and Hg^0. In contrast, attempts to prepare the adduct Pip-HgCl failed. However, the solid obtained by adding Pip to excess $HgCl_2$ in MeCN, having a composition corresponding to $(Pip^+(H)\text{-}HgCl)Cl^-$, is reduced by $NaBH_4$ to Pip and Hg^0. By comparison with the behavior of the hydrochloride $(Pip^+(H)\text{-}Tr)Cl^-$, reported above, it can be expected that, in the reaction with $NaBH_4$, protons would be first removed from $(Pip^+(H)\text{-}HgCl)Cl^-$, with production of hydrogen and of the adduct Pip-HgCl. Then, the attack on this compound should take place, with production of Hg^0 and Pip, as experimentally observed.

The addition of $NaBH_4$ to simple trityl thioethers and ethers (Et-STr and Et-OTr) in $HgCl_2$/MeCN (procedure $HgCl_2$/MeCN, $NaBH_4$, see the Experimental Section), completed with introduction of water in the reaction mixture, leads to quantitative deprotection. In contrast with this indication, the O-Tr group, in the presence of S-Tr or -SH moieties on the same molecule, remains unaffected by this same treatment: ME-OSTr is only S-detritylated by $NaBH_4$, with preservation of the O-Tr bond.

Figures 1−3 summarize the results of the application of procedures giving rise to effective detritylation in mono- and ditritylated 1,2-aminothiols, -hydroxythiols, and -amino alcohols, respectively. The results point to practical routes to selective detritylation of substrates bearing two different functions. So, the treatment of a

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(8) All the TFA solutions of the substrates under investigation and part of them in $HgCl_2$/MeCN have a bright yellow colour, due to the presence of the triphenylcarbenium ion. The solutions of these same substances in AcOH or $Hg(OAc)_2$/MeCN are colorless.

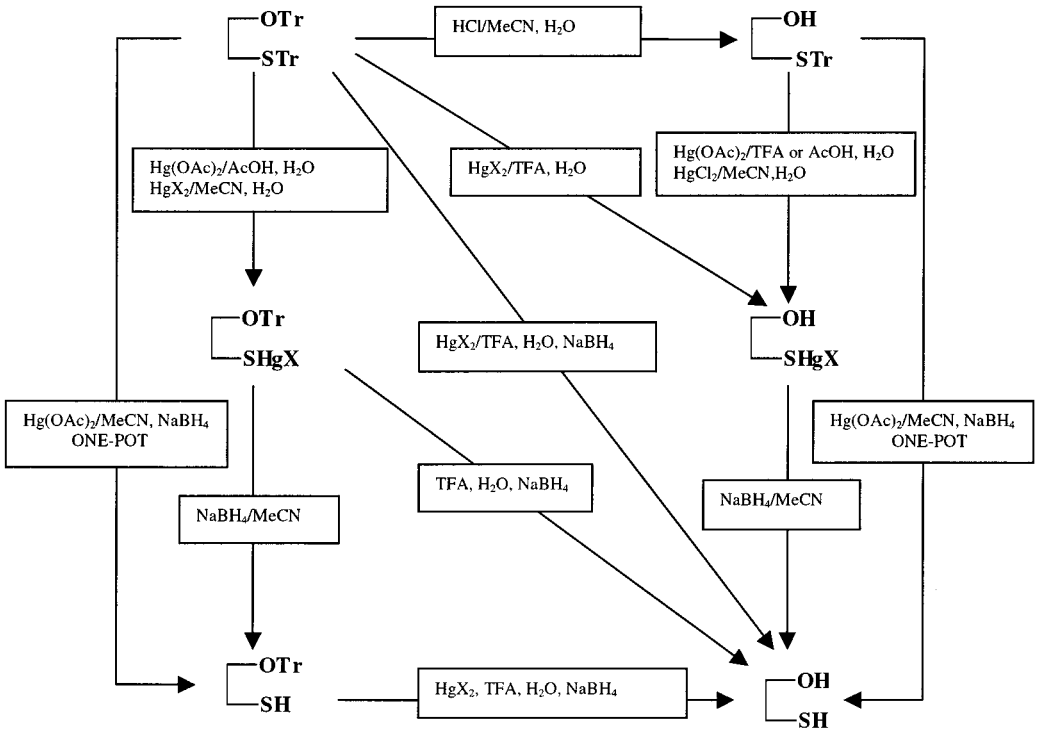

Figure 2. Deprotection pathways of tritylated derivatives of a representative 1,2-hydroxy thiol (mercaptoethanol).

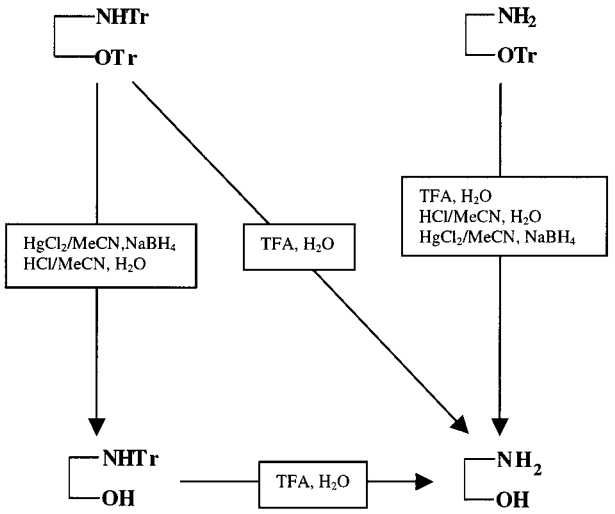

Figure 3. Deprotection pathways of tritylated derivatives of a representative 1,2-amino alcohol (ethanolamine).

pertritylated amino thiol, say MEA-NSTr, with TFA, H_2O (Figure 1) leads rapidly to the N-detritylated analogue. Further detritylation of this latter substrate can be achieved by treatment with $Hg(OAc)_2$/AcOH, H_2O or $HgCl_2$/MeCN, H_2O, followed by reduction with $NaBH_4$: the intermediate mercaptide MEA-SHgX can be isolated, then reduced by $NaBH_4$/MeCN, or the reaction can be realized in a one-pot procedure. The same pertritylated amino thiol can be S-deprotected by treatment with $Hg(OAc)_2$/AcOH or HgX_2/MeCN, followed by reduction with $NaBH_4$ of the isolated mercaptide, or in the one-pot procedure. The resulting NTr-aminothiol cannot be fully deprotected to the free aminothiol by TFA, H_2O, since acid-catalyzed Tr-migration to the S-atom occurs. Finally, the HgX_2/TFA, H_2O treatment on the pertritylated aminothiol MEA-NSTr gives the mercaptide MEA-SHgX, while the one-pot procedure HgX_2/TFA, H_2O, $NaBH_4$ treatment leads to the fully deprotected aminothiol.

In analogous fashion (see Figure 2), a pertritylated hydroxy thiol such as ME-OSTr, when treated with HCl/MeCN, H_2O, gives the S-tritylated hydroxy thiol, ME-STr. The low solubility of this substrate in TFA does not recommend the TFA, H_2O procedure for its O-detritylation. The thiol group of ME-STr can be deprotected by the one-pot procedure $Hg(OAc)_2$/MeCN, $NaBH_4$, or, step by step, through the isolation of the mercaptide ME-SHgX and further reduction with $NaBH_4$/MeCN. In contrast, O-tritylation can be preserved if the pertritylated substrate is first treated with $Hg(OAc)_2$/AcOH or MeCN, $NaBH_4$, and the resulting O-tritylated derivative is fully deprotected to the original hydroxy-thiol by treatment with HgX_2/TFA, H_2O, $NaBH_4$. The mercury mercaptide ME-SHgCl can be obtained from the pertritylated substrate by $HgCl_2$/HCl/MeCN, H_2O, while ME-OTrSHgOAc has been isolated by treatment of the same substrate with $Hg(OAc)_2$/AcOH, H_2O. Complete detritylation of ME-OSTr can be achieved by HgX_2/TFA, H_2O, $NaBH_4$.

Pertritylated amino alcohols appear to be less versatile substrates for selective detritylation. The N−Tr bond is preserved under treatment by $HgCl_2$/MeCN, $NaBH_4$, and the resulting N-protected amino alcohol is fully detritylated by TFA, H_2O. This same product, EA-NTr, has been obtained when EA-NOTr is treated with HCl/MeCN, H_2O. Complete deprotection of the pertritylated substrate is obtained by TFA, H_2O, and one has the same result when the substrate is EA-OTr. However, attempts to selectively detritylate −NTr in the presence of −OTr led always to mixtures of the N- and O-monotritylated derivatives, pointing to a preferential detritylation of the −OTr group.

Experimental Section

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. IR and ^1H NMR spectra of the

synthesized substrates have been found in agreement with the expectations and not reported. Thin-layer chromatography was carried out on Merck HF_{254} silica gel, using three systems as eluents: A, $CHCl_3$; B, $CHCl_3$/*n*-Heptane 1:1; C, $CHCl_3$/MeCN 4:1. Besides UV light, the spots have been characterized with ninhydrin (for amines and trityl amines), TFA vapors (which develop a bright yellow color in the presence of trityl-residues in the molecule), $NaBH_4$ in NaOH 3 M (which develops a black color in the presence of reducible mercury compounds), and $Ni(OAc)_2$/MeOH (which sprayed onto TLC plates, develops brown colors in the presence of thiol groups). For microanalyses, I am indebted to Dr. P. Galli of this same department, whose collaboration is gratefully acknowledged. All the commercial chemicals employed were of reagent grade, used, unless otherwise stated, without further purification and obtained from Merck, C. Erba, and Aldrich. Water was removed from commercial MeCN and ethanolamine by azeotropic distillation with benzene and fractionation. Diethyl ether was distilled from $LiAlH_4$ to remove moisture. THF was treated with NaOH pellets to remove peroxides and dried as for diethyl ether.

Substrates. 1. Tritylethanethiol (Et-STr). Ethanethiol (1.00 g, 16 mmol) was rapidly added under stirring to a suspension of 4.50 g (16 mmol) of triphenylmethyl chloride and 1.8 g (18 mmol) of TEA in 20 mL of MeCN. The mixture, left aside for 1 h, was poured into 200 mL of water, the resulting suspension was filtered off and the solid washed with water. The crude product (4.58 g, th. 4.91 g, 92.26%), slightly impure for TrOH, has been purified by crystallization from EtOH, mp 126−27 °C (lit.[9] mp 125 °C).

Anal. Calcd for $C_{21}H_{20}S$: C, 82.85; H, 6.62; S, 10.53. Found: C 82.76, H 6.71, S 10.44.

2. *S*-Tritylmercaptoethanol (ME-STr). Solid triphenylcarbinol (1.67 g, 6.4 mmol) was rapidly added, under stirring at room temperature, to a solution of 0.50 g of mercaptoethanol (6.4 mmol) and 0.63 g of HCl 37% in 8 mL of MeCN. The crystalline solid, precipitated from the clear solution, was stirred for 10 min, filtered, and washed with MeCN, obtaining 1.3 g of ME-STr chromatographically pure (th. 2.05 g, 63.41%). An analytical sample, obtained by further recrystallization from the same solvent, had mp 116−117 °C.

Anal. Calcd for $C_{21}H_{20}OS$: C, 78.71; H, 6.29; S, 10.00. Found: C, 78.62; H, 6.32; S, 9.92.

Alternatively, ME-STr has been obtained by detritylating ME-OSTr with HCl/MeCN: 1.00 g (1.8 mmol) of ME-OSTr was dissolved in 6 mL of HCl/MeCN 0.1 M and left aside at room temperature for 5 min, then the mixture was poured in water (120 mL) and the suspension neutralized with $NaHCO_3$, filtered, and the solid washed with water. The desired product was isolated from TrOH by washing the solid with cold MeOH and filtering the suspension. The addition of water 5:1 to the filtrate has given a crude solid which, after filtration and crystallization with MeCN produced a chromatographically pure ME-STr with a yield of 67%.

3. *O,S*-Ditritylmercaptoethanol (ME-OSTr). A 0.30 g portion of mercaptoethanol (3.8 mmol) was added to a solution of 2.30 g (8.8 mmol) of TrOH in 5 mL of TFA, and the mixture was kept under stirring for 3 h, poured under vigorous stirring in 100 mL of water, and neutralized with concentrated KOH. The mother liquor was decanted and the sticky paste washed with water, dissolved in 5 mL of hot MeCN, and left aside for 12 h. The crystalline solid, filtered and washed with MeCN (1.80 g, th. 2.49 g, 72.29%), contained only traces of ME-STr. The analytical sample was obtained by two crystallizations from MeCN, mp 173−175 °C.

Anal. Calcd for $C_{40}H_{34}OS$: C, 85.37; H, 6.09; S, 5.70. Found: C, 85.21; H, 6.15; S, 5.78.

4. *O*-Tritylmercaptoethanol (ME-OTr). A 0.50 g portion of ME-OSTr (0.9 mmol) was added to a solution of 1.0 g of $Hg(OAc)_2$ (3.1 mmol) in 6 mL of AcOH and left under stirring to complete dissolution. Then, 45 mL of water was added, and the resulting suspension was treated as described below for MEA-NTr. In an experiment, 0.8 mmol of TrOH was recovered. TLC analysis of the final product, along with ME-OTr, indicated the presence of ME-OSTr and ME-STr, coming from *O*- to *S*-trityl migration in ME-OTr. Since the reactivity of ME-OTr has prevented any further purification, its recovery has been accomplished by oxidation to its disulfide, MED-2Tr. The crude product was dissolved in Et and oxidized with I_2/Et in the presence of stoichiometric TEA (0.9 mmol). The final mixture was extracted with water, and the Et solution was dried and evaporated. The crude product was crystallized from MeCN, obtaining 0.18 g of MED-2Tr (th. 0.29, 64.07%), mp 93−94 °C.

Anal. Calcd for $C_{42}H_{38}O_2S_2$: C, 78.96; H, 5.99; S, 10.04. Found: C, 78.58; H, 5.81; S, 9.87.

An authentic sample of MED-2Tr was synthesized through I_2 oxidation of an Et solution of ME in the presence of solid $NaHCO_3$. The final mixture was filtered off, the solid was thoroughly washed with Et, and the Et solution was evaporated under vacuum. An oil was obtained (MED) which, dissolved in Py, along with a small excess of TrCl, was left aside for 3 days at rt and then poured into 150 mL of water. The suspension was slightly acidified with HCl and the solid filtered off and washed with water.

5. *S*-Tritylaminoethanethiol (MEA-STr). Aminoethanethiol hydrochloride (2.00 g, 17.6 mmol) was dissolved in 5 mL of TFA. Triphenylcarbinol (4.58 g, 17.6 mmol) was added to the solution portionwise, under stirring at room temperature, until the solution became clear. The reaction mixture, a dense deeply red liquid, was left aside for 1 h and then poured in 200 mL of water under vigorous stirring. The suspension of the white solid was alkalanized with TEA and filtered and the solid washed with water alkaline for TEA. After drying, 5.60 g of the crude solid, slightly impure for TrOH, was obtained (th. 5.62 g). Purification was achieved by dissolving the crude product in HCl/MeCN and rapidly diluting 1:10 with commercial Et the clear solution, obtaining a white fibrous solid, the monohydrated hydrochloride (Anal. Calcd for $C_{21}H_{24}ClNOS$: C, 67.45; H, 6.47; N, 3.75; S, 8.57. Found: C, 67.63; H, 6.63; N, 3.73; S, 8.48). The base can be obtained from this solid, after filtration and washing with Et, by stirring an its suspension in Et/concentrated KOH. When both phases were clear, the organic layer was isolated and dried. The solid obtained by evaporation of the Et solution was chromatographically pure. An analytical sample was obtained by further crystallization from MeCN, mp 91−93 °C (lit.[4] mp 90−93 °C).

Anal. Calcd for $C_{21}H_{21}NS$: C, 78.95; H, 6.63; N, 4.38; S, 10.04. Found: C, 78.85; H, 6.68; N, 4.41; S, 9.92.

Alternatively, MEA-STr has been prepared by selective detritylation of MEA-NSTr with TFA: 1.00 g (1.8 mmol) of the pertritylated MEA was dissolved in 5 mL of TFA and left aside for 3 min. Then, water was added (10:1) and the resulting suspension was alkalanized with concentrated KOH and filtered off. The solid, an equimolar mixture of MEA-STr and TrOH, was purified as before through the formation of the hydrochloride. Melting point and analytical data have been found consistent with those reported above.

6. *N,S*-Ditritylaminoethanethiol (MEA-NSTr). A 5.34 g (53 mmol) portion of TEA was added to a solution of 2.00 g (18 mmol) of aminoethanethiol hydrochloride in 10 mL of DMF. To the obtained suspension, kept under stirring, 10.32 g (37 mmol) of TrCl was added portionwise. Then, the mixture was left aside for 4 h. After the mixture was poured into 200 mL of water, the liquid was decanted and the sticky paste washed with water and triturated with EtOH, giving rise to a white solid, whose weight, after filtration, washing with EtOH, and drying, was 21.88 g (th. 29.78 g, 73.49%). The analytical sample was obtained after two crystallizations from MeCN, mp 161−63 °C.

Anal. Calcd for $C_{40}H_{35}NS$: C, 85.52; H, 6.28; N, 2.49; S, 5.71. Found: C, 85.23; H, 6.37; N, 2.60; S, 5.80.

MEA-NSTr was prepared also by addition of triphenylmethyl chloride (0.87 g, 3.1 mmol) to a solution of 1.00 g (3.1 mmol) of MEA-STr and 0.32 g of TEA (3.2 mmol) in 4 mL of DMF. The mixture was allowed to react under stirring at room temperature, and then it was poured in 100 mL of water and

(9) Fischer, P. *J. Prakt. Chem.* **1910**, *82* (2), 523.

TEA was added up to pH 10. The solid was filtered, washed with water/TEA, dried, and crystallized from DMF (1.00 g, th 1.76 g, 57.0%).

7. *N*-Tritylaminoethanethiol (MEA-NTr). MEA-NSTr (0.63 g, 1.1 mmol) and 1,80 g of $Hg(OAc)_2$ (5.6 mmol) were dissolved in 20 mL of AcOH, the clear solution was stirred for 2 min, and then water was added to a volume of 120 mL. The resulting suspension of MEA-NTrSHgOAc and TrOH was neutralized with concentrated KOH and filtered off. The solid, washed with water and dried under vacuum, was suspended in Et until triphenylcarbinol disappeared and then filtered off. The Et solution, passed through silica gel and evaporated, gave 1.0 mmol of chromatographically pure TrOH. The residue was suspended in 20 mL of MeCN, and solid $NaBH_4$ was added under stirring to this suspension. The reaction was considered to be complete 15 min after the start. After the addition of 10 mL of Et, water was introduced cautiously and the suspension left under stirring until gas evolution was almost completely ceased. Then, borine complexes were destroyed with HCl 1:1, the pH was adjusted to 7−8 with KOH and AcONa, and the mixture was filtered off. The two-phase filtrate was transferred in a separatory funnel and the organic layer was isolated, dried on Na_2SO_4 and rapidly evaporated under vacuum. TLC analysis on the crude solid, along with MEA-NTr as the principal product, pointed to the presence of MEA-NSTr and MEA-STr, coming from N to S trityl migration in MEA-NTr.

Owing to the reactivity of this substrate, its recovering has been accomplished by oxidation to its disulfide, CYA-2Tr. The crude residue was dissolved in Et and titrated with I_2/Et. Soon in the course of titration, a yellow solid precipitated (the hydroiodide of CYA-2Tr), which, filtered and washed with Et, suspended in Et and kept under stirring in the presence of concentrated KOH has given rise to an ethereal solution of CYA-2Tr. After this organic solution was dried, CYA-2Tr was recovered chromatographically pure by solvent evaporation (0.23 g, th. 0.35 g, 65.8%).

The solid was found identical with an authentic sample prepared from cystamine hydrochloride by treatment with TrCl/DMF in the presence of TEA. CYA-2Tr, crystallized from MeCN, had mp 141−142 °C, and an analytical sample has given the following data. Anal. Calcd for $C_{42}H_{40}N_2S_2$: C, 79.20; H, 6.33; N, 4.40; S, 10.07. Found: C, 79.08; H, 6.43; N, 4.59; S, 9.88.

In an attempt to prepare MEA-NTr through a one-pot procedure, $NaBH_4$ was directly added to the neutralized water suspension of MEA-NTrSHgOAc. However, this procedure led to negligible reduction of the mercaptide, which has been recovered as a black gummy solid at the end of reaction. For one-pot S-detritylations of MEA-NSTr, see below in the detritylation experiments section.

8. *N,O*-Ditritylethanolamine (EA-NOTr). Ethanolamine hydrochloride (0.30 g, 3.1 mmol) was added to a mixture of 1.80 g of TrCl (6.5 mmol) and 1.00 g of TEA (9.9 mmol) in 6 mL of MeCN. The suspension was refluxed for 1 h, cooled to room temperature, and kept at − 4 °C for 2 h. After filtration, the solid was washed with MeCN, water and once again with MeCN, dried under vacuum, obtaining 0.90 g of chromatographically pure crystals (th. 1.68 g, 53.57%) with mp 168−70 °C dec. The analytical sample has been obtained by one crystallization from MeCN.

Anal. Calcd for $C_{40}H_{35}NO$: C, 88.04; H, 6.46; N, 2.57. Found: C, 87.83; H, 6.51; N, 2.61.

9. *N*-Tritylethanolamine (EA-NTr). This compound has been obtained by addition of 1.00 g (3.6 mmol) of TrCl to a large excess of ethanolamine in 5 mL of MeCN. The mixture was kept under stirring at rt for 0.5 h and then poured in 100 mL of water. The crude solid, obtained by filtration, washed with water, and dried (0.90 g, th. 1.09 g, 82.6%), was dissolved in anhydrous Et and precipitated as hydrochloride with gaseous HCl (platelets, mp 185−87 °C).

Anal. Calcd for $C_{21}H_{22}ClNO$: C, 74.22; H, 6.52; N, 4.12. Found: C, 73.95; H, 6.84; N, 4.24.

10. *O*-Tritylethanolamine (EA-OTr). Excess of ethanolamine hydrochloride (6.00 g, 61.5 mmol) was added to a solution of 6.00 g (21.5 mmol) of TrCl in 20 mL of anhydrous Py. The mixture was stirred at room temperature for 3 days and then poured under vigorous stirring in 250 mL of water. The resulting suspension was filtered and the solid washed with water, dried under vacuum, and dissolved in ether. This solution, transferred in a separatory funnel, was treated rapidly with HCl/H_2O 3 M, and the obtained solid was filtered off, washed with water, thoroughly dried, and washed with Et. EA-OTr was regenerated by stirring the suspension of the solid in Et/concentrated KOH. The clear organic phase was washed with water, dried and evaporated, obtaining 3 g of chromatographically pure solid (th. 6.52 g, 46.0%) with mp 89−92 °C, employed as analytical sample.

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.16; H, 6.98; N, 4.62. Found: C, 82.98; H, 7.29; N, 4.52.

11. Tritylethanol (Et-OTr). A mixture of excess anhydrous EtOH, 2.00 g of TrCl (7.2 mmol), and 0.90 g of TEA (8.9 mmol) was left aside for 24 h. Then, the liquid was distilled under vacuum. The addition of 5 mL of MeOH to the sticky solid residue gave rise to the formation of 0.8 g of chromatographically pure crystals (th. 2.07 g, 38.7%). The analytical sample was obtained by further crystallization from EtOH, mp 81−83 °C (lit.[4,10] mp 79−82 °C and 84−85 °C, respectively).

Anal. Calcd for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.46; H, 7.21.

12. Tritylpiperidine (Pip-Tr). Piperidine (0.70 g, 8.0 mmol) was added to a hot solution of 1.00 g of TrCl (3.6 mmol) in 3 mL of MeCN, and the mixture was left aside for 30 min and then poured under stirring in 150 mL of water. The resulting suspension was extracted with Et. The organic extract, after drying over Na_2SO_4, was evaporated and the residue crystallized by trituration with 3 mL of MeCN (yield, 1.00 g, th. 1.18 g, 85.0%). An analytical sample was obtained by two crystallizations from MeCN, mp 156−57 °C (lit.[9] mp 153 °C).

Anal. Calcd for $C_{24}H_{25}N$: C, 88.03; H, 7.69; N, 4.28. Found: C, 87.97; H, 7.74; N, 4.42.

Detritylation Procedures. For the sake of rate comparison, unless otherwise stated, all the detritylations have been performed at room temperature and stopped, for Brønsted acids and HgX_2 solutions in these acids, with the addition of water 1 min after complete substrate dissolution. When use was made of the reductive procedure with HgX_2/MeCN, care has been employed in adding $NaBH_4$ just once the lowest substrate concentration has been reached in the complexing solution, that is 5 min after the reaction mixture has become clear and until TLC monitoring has shown constant chromatograms (for trityl-amines only). TLC, with $CHCl_3$ as eluent, shows disappearance or attenuation of the substrate spot, as due to complexation along with the presence of a very intense spot at the origin, due to excess HgX_2, the intermediate *-onium* complex and the mercury-adduct of the detritylated parent compound (see eq 1). The relative amount of the *-onium* complex and the adduct in the mixture is monitored by the intensity of the TrX-spot. Presence and intensity of this spot appears to be related with the yellow color of the substrate solution in HgX_2/MeCN. The presence of the *-onium* complex in the spot at 0.0 is indicated by the more or less intense yellow color developed by this spot in the presence of TFA vapors, as due to Tr residues. Absence of this chromatic reaction, accompanied by lack of the spot of the original substrate, points to complete detritylation and conversion to the mercury adduct of the parent compound, as observed in Et-STr. All these mercury compounds give black spots when sprayed with $NaBH_4$ in water.

In a typical experiment, 1×10^{-4} mol of the substrate were dissolved in 1 mL of the Brønsted acid or 5 mL of the HCl/MeCN or HgX_2/MeCN solution. The metal acid has been employed in a molar ratio up to 10:1 with respect to the substrate, to avoid dimerization of the type **-D**-Hg-**D**- and to ensure high equilibrium concentrations of the *-onium* complex and of the detritylated mercury adduct. All the operations have

(10) Smith, H. A.; Smith, R. J. *J. Am. Chem. Soc.* **1948**, *70*, 2400.

been performed in a nitrogen atmosphere, under stirring and cooling with ice the reaction vessel.

Detritylation was assumed to be complete when the substrate spot was not visible in the TLC of the final collected solid or organic solution. Whenever TrOH or TrH have been isolated, these compounds were determined gravimetrically and a substantial agreement with chromatographic indications was obtained. Figures for partial deprotection have not been determined. Procedures employed in this work are summarized below.

(A) Detritylation with Pure Brønsted Acids (TFA or AcOH, H_2O) or Their Solutions in Aprotic Solvents (HCl/MeCN, H_2O). The HCl solution was prepared by bubbling dry HCl in anhydrous MeCN. Reaction with excess $AgNO_3$ in water has been employed to determine HCl concentration. The highest concentration employed was 0.2 M, that is the $HgCl^+$ concentration in the detritylation experiments with the highest $HgCl_2$/substrate molar ratio. Water was added to the substrate solution in the acidic mixture up to complete precipitation of the solid. The resulting suspension was neutralized or alkalanized with $NaHCO_3$ or concentrated KOH, then filtered off or extracted with Et or $CHCl_3$.

(B) Detritylation with Solutions of HgX_2 in Brønsted Acids (HgX_2/TFA or AcOH, H_2O). In the case of tritylamines and trityl ethers, once the solution was clear, it has been left under stirring for 1 min, then water was added, the resulting suspension was filtered off, and the solid was washed thoroughly with water. Trityl thioethers, under these conditions, gave rise to mercury mercaptides, more or less soluble in organic solvents, thus interfering with gravimetric determination of TrOH. In these cases, filtration of the Et solution through silica gel has led to isolation of pure TrOH.

Free thiols were obtained by cautious addition of sodium borohydride (portionwise as solid or as concentrated solution in H_2O) to the crude alkaline suspension obtained as described previously (procedure HgX_2/TFA or AcOH, H_2O, $NaBH_4$). Extraction with Et or $CHCl_3$ of the neutral or basic suspension in which all the borine complexes were destroyed dissolved TrOH and any organic solid present. The final mixture consisted of two clear phases, with mercury settled on the bottom of the reaction vessel. Alternatively, the alkaline suspension was filtered off, and the solid was washed with water, dried, and reduced by $NaBH_4$/MeCN.

(C) Reductive Detritylation with Solutions of HgX_2 in MeCN (HgX_2/MeCN, $NaBH_4$). The substrate was dissolved in $HgCl_2$/MeCN, and the solution was left under stirring up to constant chromatogram. Then, solid $NaBH_4$ was added cautiously portionwise to the solution, obtaining precipitation of a gray, dense solid releasing bubbles of gas. Gradually, the solid darkened and settled (this same behavior characterizes the reaction of $NaBH_4$ with pure $HgCl_2$ and $Hg(OAc)_2$). At this stage, whenever complete detritylation occurred, stoichiometric TrH was recovered from the solution (see, for example, Et-OTr in detritylation experiments section) and both the substrate and its parent compound have disappeared. The end of reaction has been assumed when gaseous bubbling was ceased.

Small portions of water were added cautiously to the suspension of the gray solid, giving rise to intense production of gas. Then, 1:1 HCl was dropped into the reaction mixture up to complete destruction of borine complexes and Et was added, for the sake of obtaining two clear phases, with mercury settled on the bottom of the reaction vessel. Further addition of concentrated KOH or AcONa led to regeneration of organic bases and their extraction in the organic phase.

Reactivity of $NaBH_4$ with Isolated Species in Equilibrium (1). With the only exception of TrCl and TrOAc (see below), all the tritylated substrates investigated in this work have been lost unaltered by treatment with $NaBH_4$ in any protic or aprotic solvent.

To clarify the catalytic effect of protons on the nucleophilic attack of the hydride ion on a tritylamine, the hydrochlorides of Pip-Tr and EA-NTr have been treated with $NaBH_4$. The addition of the reactant to the MeCN or THF solution of these hydrochlorides gave rise to production of hydrogen and dilution with water of the mixture produced only recovering of the original tritylated amine. The same results have been obtained when the hydrochlorides were suspended in HCl/MeCN or THF. The addition of $HgCl_2$ to the water phase at the end of the reduction procedure in THF did not produce any precipitation, pointing to absence of Pip.

Examples of reductive demercuration of adducts of thiols and of complexes of amines are as follows.

Reductive Demercuration of Chloromercury(II) Hydroxyethylmercaptide with $NaBH_4$/MeCN. The substrate ME-SHgCl has been prepared by adding under stirring 1.0 mL (0.0128 mol) of ME in 20 mL of EtOH to a hot solution of 4.0 g (0.0148 mol) of $HgCl_2$ in 150 mL of EtOH. When the addition of thiol was completed, the obtained suspension was refluxed for 5 min, then left aside for 1 h and filtered off. The solid was washed with EtOH and Et (3.66 g, th. 4.00 g, 91.5%). The analytical sample was obtained by crystallization from EtOH, in the presence of a small amount of $HgCl_2$, mp 161−163 °C (lit.[11] mp 135−140 °C).

Anal. Calcd for $C_2H_5ClOSHg$: C, 7.67; H, 1.61; S, 10.24. Found: C, 7.45; H, 1.63; S, 9.88.

In three experiments, solid $NaBH_4$ was added portionwise under stirring to a suspension of about 200 mg of ME-SHgCl in 5 mL of MeCN. Weighting of the produced Hg^0 has furnished an average value for Hg % of 63.82 (th. 64.05).

Reductive Demercuration of Two $HgCl_2$ Complexes of Pip. (a) The addition of 0.182 mL of Pip (1.8 mmol) to a solution of 1.00 g of $HgCl_2$ (3.7 mmol) in 5 mL of MeCN has given rise to precipitation of a microcrystalline solid with mp 161−63 °C and composition corresponding to Pip·$HgCl_2$. Anal. Calcd for $C_5H_{11}Cl_2HgN$: C, 16.84; H, 3.11; N, 3.93. Found: C, 16.74; H, 3.35; N, 3.87.

(b) A well-crystallized compound of formula Pip·$HgCl_2$·HCl was prepared by addition of 2.33 g of $HgCl_2$ (8.6 mmol) to a suspension of 1.00 g of piperidine hydrochloride (8.2 mmol) in 5 mL of a 0.7 M solution of HCl in MeCN. The resulting clear solution was kept at 0 °C for 4 h and then filtered off. The crystalline solid, washed with the cold HCl/MeCN solution and ether, was dried under vacuum and employed as analytical sample (0.93 g, th. 3.37 g, 27.6%), mp 108−9 °C. Anal. Calcd for $C_5H_{12}Cl_3HgN$: C, 15.29; H, 3.08; N, 3.58. Found: C, 15.42; H, 2.97; N, 3.48.

Samples of both these compounds were reduced with $NaBH_4$ as suspension in THF or solution in H_2O, obtaining Hg^0. Free Pip has been revealed in water solution with ninhydrin or with $HgCl_2$, obtaining a white precipitate at pH 7.

Detritylation Experiments. The most representative detritylation experiments are reported below (see also, Figures 1−3).

Catalyzed and Uncatalyzed Reductive Detritylation of TrCl, TrOAc, and TrOH to TrH. TrCl and TrOAc[12] were quantitatively and rapidly reduced to TrH by portionwise addition of solid $NaBH_4$ to their MeCN solutions.[13] TrOH remained unaffected by this same treatment, but more or less relevant quantities of TrH were produced by addition of $NaBH_4$ to solutions of this substrate in HCl/MeCN or TFA and vice versa.

Solutions of TrCl in $HgCl_2$/MeCN are reduced by $NaBH_4$ to TrH. TrOH is reduced to TrH if $NaBH_4$ is added portionwise to an its solution in $HgCl_2$/MeCN and vice versa. The use of $Hg(OAc)_2$ in these same procedures has left this substrate unaltered.

Detritylation of Monofunctional Substrates. Detritylation of Pip-Tr with $HgCl_2$/MeCN, $NaBH_4$. On adding Pip-Tr to $HgCl_2$/MeCN, the colorless mixture became rapidly turbid. TLC taken 5 min after mixing showed an intense substrate spot. Reduction of this solution with $NaBH_4$ gave

(11) Bennett, G. K. *J. Chem. Soc.* **1922**, 2139.

(12) TrOAc has been prepared in situ by mixing equimolar AgOAc and TrCl in anhydrous MeCN.

(13) The $NaBH_4$ reduction of halides capable of forming stable carbenium ions is a well-known reaction but it is reported to be very slow in absence of water. See: (a) Brown, H. C.; Bell, H. M. *J. Org. Chem.* **1962**, *27*, 1928. (b) Bell, H. M.; Brown, H. C. *J. Am. Chem. Soc.* **1966**, *88*, 1473.

back Pip-Tr. When the mixture was left aside for 48 h, a considerable amount of a white solid was produced and Pip-Tr disappeared from TLC of the solution. The solid, filtered and washed with cold MeCN and Et, had a mp 131−133 °C dec. The elemental analysis pointed to Pip-Tr·$6HgCl_2$ as its simplest molecular formula (Anal. Calcd for $C_{24}H_{25}Cl_{12}Hg_6N$: C, 14.73; H, 1.29; N, 0.27. Found: C, 15.03; H, 1.30; N, 0.39). Addition of $NaBH_4$ to the suspension or either to the isolated solid or the filtrate led to mixtures of Pip-Tr and TrH. The presence of Pip in water has been revealed by addition of $HgCl_2$, which gave rise to precipitation of a white insoluble solid.

Detritylation of EtO-Tr with $HgCl_2$/MeCN, $NaBH_4$. (a) A colorless solution of 0.0997 g (0.35 mmol) of Et-OTr in 15 mL of a MeCN solution of 0.9453 g (3.5 mmol) of $HgCl_2$ was reduced with $NaBH_4$ just 5 min after mixing. TLC monitoring before reduction showed permanence of the substrate spot and lack of TrCl. The 0.0 intense spot did not develope any color when exposed to TFA vapors. After the rapid addition of $NaBH_4$, the substrate disappeared from TLC and only TrH was detected in the eterogeneous solution. Water was added 2 min after the addition of the reductant was completed. At the end of the treatment, the TLC of the organic layer, with system B as eluent, showed only the TrH spot. Evaporation of the organic layer has given 0.0789 g (th. 0.0845 g) of crystals with mp 91−94 °C (TrH). (b) In a second experiment on 0.1050 g of Et-OTr, the suspension obtained after the addition of $NaBH_4$, after the dark-gray solid was settled, was filtered off and the solid washed with MeCN and Et. Water was added to filtrates, and after destruction of the borine complexes, the evaporation of the organic layer gave 0.0810 g of TrH, 91.1%. (c) In a third experiment, the Et-OTr solution in $HgCl_2$/MeCN was left aside for 4 days, then treated as before, obtaining similar results.

Detritylation of Et-STr with $HgCl_2$/MeCN, $NaBH_4$. (a) A yellow solution of 1×10^{-4} mol of Et-STr and 1×10^{-3} mol of $HgCl_2$ in 3 mL of MeCN has given TLC($CHCl_3$) showing a very weak substrate spot and an intense one due to TrCl; the 0.0 spot remains almost colorless on exposure to TFA vapors. After addition of $NaBH_4$ and settling of the dark-gray solid, the suspension was treated as described above for Et-OTr under (a) and (b), obtaining in both cases quantitative recovering of TrH. (b) A solution of 1×10^{-4} mol of both Et-STr and $HgCl_2$ in 3 mL of MeCN has given a TLC($CHCl_3$) with spots at 0.0, 0.6 (TrCl) and 0.9 (Et-STr). (c) In a further experiment, 1×10^{-4} mol of this same substrate were dissolved in a solution of 1×10^{-3} mol of $Hg(OAc)_2$ in 3 mL of MeCN. The most relevant difference with respect to the results obtained with $HgCl_2$ was the presence in TLC($CHCl_3$) of a tail 0.0−0.6, which became yellow with TFA vapors. The other results were similar to those obtained with $HgCl_2$.

Detritylation of Bifunctional Monotritylated Substrates. (i) S-Detritylation of MEA-STr to MEA with $Hg(OAc)_2$/AcOH, H_2O (See Figure 1). A solution of 32.0 mg of MEA-STr (1×10^{-4} mol) and of an excess of $Hg(OAc)_2$ in 1 mL of AcOH was stirred for 5 min at room temperature, and then water was added (10 mL). The suspension was filtered off, and the solid was washed with water and dried (TrOH chromatographically pure, 22.3 mg, th. 26.0, 85.8%). The filtrate, treated with $NaBH_4$, HCl, and $NaHCO_3$ up to pH 7−8, was titrated with 0.45×10^{-4} mol of I_2. Care was taken in controlling the complete destruction of $NaBH_4$. In a blank, an equal quantity of the reductant was dissolved in water and the solution treated as described above: the final mixture did not reduce I_2/H_2O or a $HgCl_2$ solution in water.

(ii) N-Detritylation of MEA-NTr to MEA-STr and to MEA (See Figure 1). Owing to its instability, this substrate, obtained by detritylation of MEA-NSTr with the procedure described below, has not been isolated and its behavior under detritylation has been monitored only by TLC. Its R_f($CHCl_3$) is 0.75 and the spot becomes red-brownish when sprayed with $Ni(OAc)_2$/MeOH. In the organic phase obtained at the end of the MEA-NSTr detritylation, MEA-NTr is always accompanied by MEA-NSTr, MEA-STr and TrOH as impurities. Once the organic solution has been distilled under vacuum, treatment of the solid residue with TFA, H_2O led to disappearance of the spots due to MEA-NTr and MEA-NSTr and to permanence of that due to MEA-STr. Formation of free MEA has been excluded, since the water phase did not react with I_2, nor give any chromatic reaction with $Ni(OAc)_2$. Treatment of the same residue with HgX_2/TFA, H_2O and addition of $NaBH_4$ to the water suspension, leading to complete detritylation of all the MEA-derivatives, gave rise to a water solution with an 80% of the expected reducing power.

(iii) S-Detritylation of ME-STr to ME with $Hg(OAc)_2$/AcOH, H_2O (One-Pot Procedure, See Figure 2). A solution of 32.0 mg of ME-STr (1×10^{-4} mol) and of an excess of mercury acetate in 1 mL of AcOH was stirred at room temperature for 5 min, then 10 mL of water was added and the resulting suspension was brought to pH 7−8 and reduced with $NaBH_4$. At the end of the treatment, Et was added and the suspension was extracted three times. Drying and evaporation of the Et solution gave 21.0 mg of TrOH (th. 26.0 mg, 80.8%) and the water solution was rapidly titrated with 4.1 mL of I_2/H_2O 0.01 M (0.41×10^{-4} mol), according to Zervas and Photaki.[2,3]

(iv) Lack of Detritylation of ME-STr with TFA, H_2O. A yellow solution of ME-STr in TFA, kept under stirring at room temperature for 5 min, diluted with water 1:10 gave a sticky solid whose TLC points to the prevalent presence of the original compound, with TrOH and *S*-trityltrifluoroacetylmercaptoethanol as impurities.

(v) O-Detritylation of ME-OTr to ME with HgX_2/TFA, H_2O, $NaBH_4$ (See Figure 2). As in the case of MEA-NTr, ME-OTr was not isolated as such and the effects of detritylation procedures have been merely monitored by TLC. With $CHCl_3$ as eluent, ME-OTr has $R_f = 0.85$ and its spot becomes brown when sprayed with $Ni(OAc)_2$/MeOH. The crude solid obtained from S-detritylation of ME-OSTr cannot be O-detritylated with TFA, H_2O, because this treatment gives rise to migration. Free ME from ME-OTr has been obtained only by the procedure HgX_2/TFA, H_2O, $NaBH_4$.

(vi) Detritylation of EA-NTr with $HgCl_2$/MeCN, $NaBH_4$. The TLC($CHCl_3$) of a colorless solution of EA-NTr in $HgCl_2$/MeCN showed three spots overlapped at the origin. This solution was reduced five minutes after its formation and the result was recovering of unaltered EA-NTr. Another similar solution, left aside for 48 h, besides the two intense spots due to $HgCl_2$ and the complex, showed spots due to TrCl and EA-NOTr, this latter recognized by a chromatic reaction with ninhydrin. Reduction with $NaBH_4$ produced EA-NTr and TrH. Lack of EA-OTr in the mixture before reduction was revealed in the following way. One milliliter of this solution was poured in a solution of KOH/H_2O 2 M and the resulting suspension was extracted with Et. TLC($CHCl_3$) of the organic layer, besides TrOH and EA-NOTr, revealed only EA-NTr. In contrast, EA-NTr was rapidly detritylated by the TFA, H_2O procedure, with quantitative recovery of TrOH.

(vii) O-Detritylation of EA-OTr to EA with $HgCl_2$/MeCN, $NaBH_4$ (See Figure 3). EA-OTr was easily deprotected by the procedure $HgCl_2$/MeCN or THF, $NaBH_4$, with traces of migration and formation of EA-NTr and EA-NOTr. TrH was the secondary product.

Detritylation of Bifunctional Ditritylated Substrates: MEA-NSTr (Figure 1). **(i) S-Detritylation of MEA-NSTr to MEA-NTr with $HgCl_2$/MeCN, H_2O, $NaBH_4$.** A 0.20 g (0.4 mmol) portion of the substrate was dissolved in a solution of 0.90 g of $HgCl_2$ (3.3 mmol) in 8 mL of MeCN. The yellow solution readily gave rise to precipitation of a white solid. TLC monitoring indicated presence of TrCl and absence of substrate. Water was added to this suspension up to solid dissolution and reprecipitation. Portionwise addition of solid $NaBH_4$ and treatment as reported above, gave rise to two clear phases. The organic phase, equilibrated against the water solution at pH = 8, was isolated, dried on Na_2SO_4, and evaporated under vacuum. Et was added to the solid residue and the Et solution was treated with iodine according to the previously described procedure (see substrates, no. 7), giving rise to 0.08 g of chromatographically pure CYA-2Tr (th. 0.11 g, 72.7%).

(ii) S-Detritylation of MEA-NSTr to MEA-NTr with $Hg(OAc)_2$/MeCN, $NaBH_4$. Starting from the same quantity of the substrate, CYA-2Tr have been obtained, with a higher yield (81.8%) with respect to the treatment with $HgCl_2$. This result can be ascribed to the fact that in the $HgCl_2$ procedure, the strong acid produced during the $NaBH_4$ addition catalyzes Tr-migration from N- to S-atom.

(iii) NS-Detritylation of MEA-NSTr through MEA-SHgX with HgX_2/TFA, H_2O, $NaBH_4$ (One-Pot Procedure). When water was added to a yellow solution of MEA-NSTr in HgX_2/TFA, a solid was obtained (a mixture of MEA-SHgX and TrOH, by TLC) which has been reduced with $NaBH_4$ directly in the suspension, once the solution was neutralized. After reduction, 91% of free thiol was detected with I_2 titration of the water phase. An analogous result has been obtained on isolating the solid mixture and reducing it with $NaBH_4$/MeCN.

Detritylation of Bifunctional Ditritylated Substrates: ME-OSTr (Figure 2). **(i) S-Detritylation of ME-OSTr to ME-OTr with $Hg(OAc)_2$/MeCN, $NaBH_4$ (**One-Pot Procedure). A 0.5610 g portion of ME-OSTr (0.10 mmol) was added to a suspension of excess $Hg(OAc)_2$ in 6 mL of MeCN, and the mixture was left under stirring for 5 min, then solid $NaBH_4$ was added portionwise. At the end of the treatment, the organic phase was rapidly titrated with I_2/Et in the presence of a small amount of a concentrated solution of $NaHCO_3$: 0.04 mmol of I_2 was employed, yield 88.0%. After separation and washing with water, the organic solution was dried over Na_2SO_4 and then evaporated to dryness (0.0280 g, th. 0.0320, 87.5%). The disulfide has been crystallized from MeCN.

(ii) O-Detritylation of ME-OSTr to ME-STr with TFA and HCl/MeCN, H_2O. Quenching by water of a yellow solution of ME-OSTr in TFA led to mixtures of unreacted ME-OSTr, ME-STr, and TrOH. Addition of water to an uncolored solution of this same substrate in a moderately concentrated solution of HCl in MeCN led to rapid detritylation to ME-STr.

(iii) OS-Detritylation of ME-OSTr to ME-SHgX with $Hg(OAc)_2$/ TFA, H_2O. The procedure was as above for N,S-detritylation of MEA-NSTr to MEA-SHgX with HgX_2/TFA, H_2O. The yield in thiol was 86% in the one-pot procedure (see below) and less when the mercaptide was isolated and reduced in MeCN suspension.

(iv) OS-Detritylation of ME-OSTr to ME with HgX_2/ TFA, H_2O, $NaBH_4$ (One-Pot Procedure). ME-OSTr was dissolved in TFA containing excess $Hg(OAc)_2$, giving a yellow solution. After addition of water and neutralization, the suspension was reduced with $NaBH_4$, giving rise to two clear final phases. The organic phase gave almost quantitative recovery of 2 equiv of TrOH. The $Ni(OAc)_2$/MeOH test was negative for the organic layer. In contrast, addition of $Ni(OAc)_2$/H_2O to the inorganic layer at pH 8 produced an intense red-brownish color.

Detritylation of Bifunctional Ditritylated Substrates: EA-NOTr (Figure 3). **(i) O-Detritylation of EA-NOTr with $HgCl_2$/MeCN, $NaBH_4$.** The colorless solution of 0.1046 g of EA-NOTr in excess $HgCl_2$/MeCN, 5 min after its formation, had TLC($CHCl_3$) showing absence of TrCl and permanence of the uncomplexed substrate (however, spots at 0.0 became yellow in the presence of TFA vapors). Once this solution was reduced with $NaBH_4$, the final alkaline water suspension was thoroughly extracted with Et, and after drying, the extracts were distilled under vacuum. The solid residue was dissolved in Et and the resulting solution was filtered off. Bubbling of dry HCl produced 0.0554 g of EA-NTr·HCl (th. 0.0652 g, 84.9%) which was isolated by filtration. EA-NTr was obtained by extraction with concentrated KOH of an Et suspension of this solid, and recognized by TLC. The filtrate, after solvent evaporation, has given off 0.0415 g of TrH (th. 0.0468 g, 88.7% for a detritylation of only one group).

(ii) O-Detritylation of EA-NOTr with HCl/MeCN, H_2O. EA-NOTr, sparingly soluble in MeCN, dissolved rapidly in the presence of HCl, soon giving a suspension of the hydrochloride of EA-NTr from which EA-NTr has been recovered by treatment with Et/concentrated KOH.

Discussion

In principle, the addition of a nucleophile stronger than X^- to the equilibrium mixture (1) favors the formation of the deprotected substrate R-**D**-**A** by attack on triphenylcarbenium ion, on TrX and on the Tr-residue of the intermediate complex (R-$\mathbf{D}^+$(**A**)-Tr)X^-, this last species appearing to be more suitable for substitution than R-**D**-Tr itself for having a better leaving group. When :Nu = H_2O or $NaBH_4$, TrOH and TrH are expected as final secondary products, respectively. A further factor favoring deprotection, when $\mathbf{A}^+$ is HgX^+ and $NaBH_4$ is employed as nucleophile, is the reducibility of R-**D**-HgX to R-**D**-H. Competition of the nucleophile and the intermediate complex for the Lewis acid $\mathbf{A}^+$, has to be taken into account as unfavorable factor in detritylation, because abstraction of $\mathbf{A}^+$ from the complex produces not reducible R-**D**-Tr.

As previously said, the yellow color assumed in many instances by the catalyzed mixtures indicate an high degree of shifting of equilibrium (1) toward R-**D**-A and TrX, for it being due to free Tr^+ or ionic couples with triphenylcarbenium ion.[7,14] Whenever this color is seen, its formation rate is always high, pointing to rapid reactions producing and consuming species taking part to eq 1. Further information can be obtained on observing the quenching effects produced on these colored solutions by addition of the nucleophile. The first one is that quenching not always accompanies detritylation. Monofunctional trityl ethers, -amines and -thioethers give rise to deeply yellow TFA solutions, but rapid addition of water to these produces only O- and N-detritylation. It can be guessed that only in the first two cases loss of color is due to the transformation of Tr^+ and TrX into TrOH, while for a trityl-thioether it is apparently an effect of reversion of equilibrium (1) toward R-**D**-Tr. The second information is that the irreversible production of TrOH from Tr^+ and TrX cannot be the only driving force of detritylation, otherwise, trityl-thioethers as well should be detritylated by TFA, H_2O. The third information is that, since fading is rapid, reactions with water leading to quenching are fast.

Of these same monofunctional substrates, only Et-STr gives rapidly rise to a yellow solution when dissolved in $HgCl_2$/MeCN. Addition of water to the solution of Et-STr gives rise to rapid fading and to S-detritylation, while this same treatment of the Pip-Tr and of the Et-OTr solutions leads essentially back to the unreacted substrates. In this case, as well, detection of Tr^+ does not ensure detritylation. Furthermore, in S-detritylation, rates of reactions in equilibrium (1) and of those between species in eq 1 and water are rapid. Furthermore, solutions of the same substrates in $Hg(OAc)_2$/MeCN or AcOH are colorless, but, addition of water leads to detritylation of trityl-thioethers alone. Hence, the efficiency of the procedure does not depend on the degree of shifting of eq 1.

In the procedure TFA, H_2O, proton exchange between H_2O and $\mathbf{A}^+X^-$ seems to be ineffective on detritylation; otherwise, trityl ethers, trityl amines, and trityl thioethers should exhibit the same behavior. Analogous consideration can be extended to cases in which $\mathbf{A}^+$ = HgX^+. Thus, neither the nucleophilic attack onto Tr^+ or

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TrX nor competition of H_2O and $\mathbf{A}^+X^-$ for $\mathbf{A}^+$ determine the result of detritylation procedures such as TFA, H_2O and HgX_2/MeCN, H_2O.

In the H^+-catalyzed procedures employing H_2O as nucleophile, of the remaining two factors affecting detritylation, competition of H_2O and (R-$\mathbf{D}^+$(H)-Tr)X^- for H^+ seems to be the most effective in explaining the reported behavior of trityl ethers, trityl amines, and trityl thioethers. In general, the attack of the nucleophile on the intermediate *onium*-complex can produce both $\mathbf{A}^+$- and Tr^+-abstraction, according to the following equilibrium:

$$\text{R-}\mathbf{D}\text{-Tr} + \mathbf{A}\text{-Nu}^+ \rightleftharpoons \text{R-}\mathbf{D}^+(\mathbf{A})\text{-Tr} + :\text{Nu} \rightleftharpoons \text{R-}\mathbf{D}\text{-}\mathbf{A} + \text{Tr-Nu}^+$$

If, as reasonably expected, in eq 2 proton abstraction is much faster than detritylation, the deprotonation equilibrium is rapidly reached. If the affinity of the nucleophile for $\mathbf{A}^+$ is higher than that of the complex, an overall reversion of equilibrium (2) toward R-**D**-Tr should be expected. In contrast, if the $\mathbf{D}^+-\mathbf{A}$ bond is preserved, the trityl-residue can be removed by attack on Tr^+ and TrX. In other words, when $\mathbf{A}^+ = H^+$, the equilibrium concentrations are determined by the relative affinity of **D** and :Nu for H^+, this decreasing along the series N > O > S. Consistently, in the H^+-catalyzed detritylation procedures, nucleophiles having oxygen as donor atom (water or alcohols) cannot compete with nitrogen for protons, so that the addition of water to TFA solutions of trityl amines gives rise to trityl-displacement. In contrast, the more acidic S^+-H moieties easily lose protons, so that water addition to TFA solutions of trityl thioethers causes recovering of the unaltered substrate. Addition of mercaptans to TFA solutions of trityl thioethers gives rise to equilibria based on the trityl migration from the original to the added mercaptan. Accordingly, the presence of a free thiol group in the molecule of a trityl ether or trityl amine gives rise to H^+-catalyzed Tr migration, as observed for ME-OTr and MEA-NTr. On passing to ditritylated bifunctional substrates, procedures TFA, H_2O and HCl/MeCN, H_2O give results in substantial agreement with those reported above for monotritylated substrates.

Finally, as the last factor favoring detritylation, nucleophilic substitution of H_2O on Tr-groups of the complex itself, for steric reasons, should have a rate lower than attacks on Tr^+ and TrX. However, contribution of this reaction to detritylation cannot be excluded, whenever proton exchange between :Nu and (R-$\mathbf{D}^+$(H)-Tr)X^- allows significant equilibrium concentrations of the complex.

Metal acids, introduced in a solution of a trityl-derivative in a protic solvent, compete with protons for the central atom in the -onium complexes and overwhelm protons themselves as acceptors when the solvent is a weak Brønsted acid. The nucleophile added to these solutions and, of course, to those in aprotic solvents, has to compete with the -onium complex for $\mathbf{A}^+ = HgX^+$, a soft metal acid[15] for which the affinity scale to be followed should be S > N > O.[16] So, the introduction of HgX_2 into a TFA, AcOH, or MeCN solution of any S-trityl derivative, leads invariably to the isolation of the metal mercaptide and triphenylcarbinol, if water is employed as nucleophile. Trityl ethers and trityl amines are detritylated by HgX_2/TFA, H_2O, but, since they remain unaffected by treatment with $HgCl_2$/MeCN, H_2O, these results indicate that detritylation is due to the strength of the Brønsted acid employed.

On passing to the use of $NaBH_4$ as nucleophile, the comparison of the results obtained on adding the reductant to $HgCl_2$/MeCN solutions of Et-STr and Et-OTr may elucidate many questions. The former substrate gives a yellow solution, the latter a colorless one. TLC-monitoring confirms that Et-STr is practically absent in the equilibrium mixture, while Et-OTr is negligibly complexed. However, both are completely deprotected by $NaBH_4$, thus pointing to the fact that the reactions producing TrH and consuming Tr^+, TrCl and R-**D**-HgCl goes to completion just because reactions in equilibrium (1) are fast when **D** = S or O. Partial detritylation of Pip-Tr allows to experience a different situation. When Pip-Tr is in equilibrium in $HgCl_2$/MeCN, lack of free substrate and presence of only traces of TrCl in the heterogeneous mixture should indicate that the prevalent species is the complex. Furthermore it cannot be said if the production of Tr^+, TrCl and PipHgCl is fast, but it can be supposed as such, on grounds of steric repulsion among the four bulky groups in the complex. Thus, the production of mixtures of Pip-Tr and TrH by addition of $NaBH_4$ has to be ascribed to competition between the production through eq 1 of species reducible to TrH and the reduction of the ammonium-complex. Furthermore, it should be remembered that the complex can be reduced through two different routes. The first one, in analogy with the reduction of PipTr · HCl, leads to Hg^0 and Pip-Tr, the second one produces first TrH and Pip-HgCl, which, in turn, is reduced to Pip and Hg^0. This latter is a second route to detritylation, but its contribution to the production of TrH appears quite dubious.

Different possible mechanisms can be proposed for the reduction of TrX (X = −Cl or −OAc). In the S_N1 mechanism, the first step consists of the production of triphenylcarbenium ions and BH_4^- acts merely as a scavenger of these ions.[17] A second mechanism requires an S_N2 backside attack on TrX, while a third one, a four-center mechanism, requires the presence of a polar bond in the molecule and proceeds through attack of the nucleophilic hydrogen of BH_4^- onto the electrophilic center, while the borine atom accepts electronic charge coming from the nucleophilic center in the bond.[18] If this last would be the mechanism, lack of detritylation by simple attack of $NaBH_4$ on the other tritylated substrates under examination in this work should be referred to the low polarity of the $\mathbf{D}-Tr$ bond. However, besides bond polarity, steric hindrance due to the bulky Tr-moiety should prevent easy formation of four-center activated states. Even in case of TrCl, so structurally simple with respect to the other trityl-derivatives investigated, it appears more conceivable a backside attack on Tr− or, better, quenching of Tr^+, rapidly produced by the substrate itself. Furthermore, although charge separation in TrOH (and in the remaining tritylated substrates) should not be very different with respect to that in TrCl or TrOAc, $NaBH_4$ in pure MeCN leaves unaltered TrOH. In the reaction of TrX with $NaBH_4$, instead of bond

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(17) This mechanism is assumed as predominant by Olah (ref 6) in the hydrogen transfer reaction between $NaBH_4$ and $Tr^+PF_6^-$, MeCN being a solvent favouring the formation of Tr^+.
(18) Dessy, R. E.; Paulik, F. *J. Chem. Educ.* **1963**, *40*, 185.

polarization, it seems the nature of good leaving groups of Cl^- and OAc^- to determine production of TrH. Hence, the four-center mechanism does not appear a conceivable route for cleaving bonds with trityl groups.

Both complexation with H^+ or $HgCl^+$ increases charge separation in the Tr-**D** bond, transforming R-$\mathbf{D}^+$ in a leaving group better than in the uncomplexed substrate. Thus, nucleophilic substitution by hydride-ions could be expected, as for TrX. In contrast, in these cases the experimental evidence indicates that the Tr-N^+ bond is not cleaved. The reaction with $NaBH_4$ of the hydrochlorides of Pip-Tr and EA-NTr produces H_2 instead of TrH. For hydrochlorides, this result supports the concerted-type mechanism already proposed for the reaction of $NaBH_4$ with weak acids [19,20] and, in particular, with trimethylammonium ion. [21] In the tritylammonium complexes investigated in this work, the electrophilic center approached by the hydride ion is the hydrogen-atom and never the central carbon atom of the Tr-group. Thus, the concerted-type mechanism does not allow any detritylation to occur by attack of the reductant on the intermediate ammonium-complexes. As shown above, this statement can be extended to intermediate HgX^+-ammonium complexes of tritylated amines, with the only possible exception of Pip-Tr.

Et-OTr and Et-STr, as examples of substrates where the presence of a lone pair on $\mathbf{D}^+$ allows bonding with electrophilic borine and the concerted-type mechanism to appear more suitable than for ammonium-complexes, are fully detritylated by $HgCl_2$/MeCN, $NaBH_4$. In contrast, the same procedure, when applied to ME-OSTr or ME-OTr, leads to recovery of ME-OTr. This result seems to convincingly support the four-center model for the reduction mechanism. Both these substrates in $HgCl_2$/MeCN are essentially solutions of ME-OTrSHgCl, a mercaptide in which the O-atom, for its β-position with respect to S, should be strongly coordinated to the metal atom, that is its lone pair is strongly involved in this bond with the only metal atom present in the molecule. When $NaBH_4$ is employed, electrophilic borine prefers the much more nucleophilic center on sulfur with respect to that on oxygen, thus leaving uncleaved the O-Tr bond.

The four-center model for the transition state in the $NaBH_4$ reduction receives further support by reduction of HgX_2 and R-**D**-HgX. In the first case, the gray to black solid produced by addition of $NaBH_4$ to a solution of HgX_2 in MeCN should be the four-center complex itself, which slowly decomposes producing the unstable hydride H-Hg-X, which, in turn, gives rise to formation of HX and Hg°, according to well-established studies.[22,23] In reduction of the adducts R-**D**-HgX the substrate has two different nucleophilic sites to be approached by the electrophilic counterpart $-BH_3^-$, the X atom or the donor atom **D**. Approaching to X should prevent any HX to be released and induces formation of R-$\mathbf{D}^-$ ions, while approaching to **D** gives rise to production of free HX and leads to the formation of borine-complexes of the type $((R\mathbf{D})_xH_y)B^-$, which in a further step, in the presence of water, decompose giving free thiols, amines or alcohols, as effectively observed.

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