Cancer Institute. We also thank the Syntex and Hoffmann-La Roche Corporations for financial support. Lastly, very special thanks to Drs. S. E. Normandin and C. S. Pogonowski for invaluable experiments which initiated this work.

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(1) For syntheses of confertin, see (a) J. A. Marshall and R. H. Ellison, *J. Am. Chem. Soc.*, **98**, 4312 (1976); (b) M. F. Semmelhack, A. Yamashita, J. C. Tomesch, and J. Hirotsu, *ibid.*, **100**, 5545 (1978); (c) P. A. Wender, M. A. Eissenstate, and M. P. Filosa, *ibid.*, **101**, 2196 (1979).
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(6) These hydrogenation conditions proved to be clearly superior, particularly with respect to the stereochemical course of reduction. The α-methyl analogue of **5** is produced in this reaction to the extent of ~5% and was removed by silica gel chromatography.
(7) Removal of the β proton at C_7 appeared to be the most likely experimental result given that **5** would occupy a minimal energy configuration at −78 °C and that carbon–hydrogen bond rupture would yield a filled p orbital anion) maximally oriented for interaction with the carbonyl residue.
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(10) We thank Professor Semmelhack for this sample and in addition thank Professor Paul Wender for an 80-MHz spectrum of confertin.
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(15) Again in our hands, hydrogenation with rhodium on alumina proved considerably superior to other reagent combinations.[1,2,b]
(16) We thank Professor Greico for a sample of synthetic damsin.

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Impregnated Reagents. Characterization of Sodium Cyanide on Alumina[1]

Sir:

Impregnated organic and inorganic reagents are emerging as valuable tools for the synthetic chemist.[2,3] Despite growing interest, however, no serious effort has yet been made to characterize these materials. Several fundamentally important questions need to be answered in order to provide a basis for understanding this chemistry and to define the limitations for practical organic synthesis: specifically, (1) whether the reagent is evenly distributed and is of uniform reactivity, (2) what the primary function of the support is in producing active species, and (3) how reactive the reagent is relative to "naked" [4] analogues in solution need clarification. In the present work one specific impregnated reagent, sodium cyanide on alumina ($NaCN/Al_2O_3$), has been carefully examined. From our results, cyanide ion is shown to be (1) evenly distributed between uniformly active and inactive sites, (2) reactive only at monolayer coverage, and (3) "half-naked".

Neutral alumina chosen for this study was commercially available and used as obtained.[5] It was pure γ-alumina having a surface area of 240 $m^2\ g^{-1}$ (BET, nitrogen adsorption) and possessing a total pore volume of 0.25 $cm^3\ g^{-1}$. Reproducibility of all of the data reported in this work was excellent and independent of the batch of alumina employed. A $NaCN/Al_2O_3$ reagent (**1**) was prepared using 5 mmol of NaCN/g of alumina based on procedures similar to those previously described.[6] The infrared spectrum of **1** (KBr pellet) showed a single and intense cyanide band at 2087 cm^{-1} and was identical with that of sodium cyanide powder. Assuming a tightly packed array of sodium and cyanide ions on the surface, this amount of salt corresponds approximately to that required for monolayer coverage. Reaction of **1** with an excess of 1-bromooctane in toluene at 90 °C revealed that ~60% of the cyanide present was reactive.[7] When the ratio of NaCN (mmol)/alumina (g) was increased by a factor of 2, the amount of reactive cyanide per gram of alumina remained unchanged; when it was decreased by a factor of 2, an approximately twofold reduction was observed. These results provide strong evidence that the salt is uniformly distributed between active and inactive sites and that only monolayer coverage is of practical synthetic value. Additional evidence for a uniform coating of NaCN on alumina comes from adsorption measurements of laurylamine onto **1** and neutral alumina. When 1.0 g of alumina was exposed to 20 mL of a 0.2 M solution of laurylamine in toluene at room temperature for 24 h, 0.35 mmol of the amine was adsorbed (GLC analysis of an aliquot of the liquid phase). In contrast, no detectable amine (±0.06 mmol) was adsorbed by either 1.0 g of **1** or pulverized NaCN. These data are consistent with a NaCN layer insulating the alumina surface from the bulk organic phase. The average pore diameter of the support is 40 Å (80% being <120 Å) and we tentatively attribute the inactive cyanide to material which is located in small pores, inaccessible to the organic halide.

Kinetic experiments were performed in 50-mL culture tubes (Corning No. 9826, 13 × 100 mm) equipped with a Teflon-lined screw cap and a Teflon-coated stirring bar. In a typical kinetic run, the tube was charged with 1.25 g of **1** plus 2.5 mL of toluene containing 0.5 mmol of 1-bromooctane and 0.5 mmol of *n*-pentadecane (internal standard). The culture tube was placed in an oil bath maintained at 110 ± 0.5 °C and the contents were stirred vigorously. The reaction was followed by withdrawing 1-μL samples and monitoring the disappearance of the organic halide by GLC.[8] Clean pseudo-first-order kinetics was maintained over at least 3 half-lives and material balance (>95%) was good. A second-order specific rate constant, k_0, was calculated by dividing the observed first-order rate constant by the ratio of the number of moles of reactive cyanide to the volume of the organic phase and was equal to 4.2×10^{-4} L $mol^{-1}\ s^{-1}$.[9] When a similar reaction was conducted using an excess of organic halide relative to the reagent, pseudo-first-order kinetics was again followed over 3 half-lives.[10] A second-order rate constant obtained under these conditions by dividing the observed first-order rate constant by the concentration of 1-bromooctane in the organic phase was equal to 1.9×10^{-4} L $mol^{-1}\ s^{-1}$. Considering the heterogeneity of these systems and the treatment of NaCN on alumina as a "concentration", we regard the agreement between the two rate constants as satisfactory.

In order to put the reactivity of impregnated cyanide ion into perspective, we have also examined an analogous displacement carried out under liquid–liquid phase-transfer conditions. Thus, when 0.75 g of sodium cyanide dissolved in 1 mL of water with 3 mL of toluene containing 0.5 mmol of 1-bromooctane in the presence of 0.12 mmol of dicyclohexyl-18-crown-6 and 0.5 mmol of *n*-pentadecane (internal standard) was stirred, clean pseudo-first-order kinetics yielded a second-order rate constant of 4.0×10^{-2} L $mol^{-1}\ s^{-1}$ at 110 °C.[11] Based on the ~100-fold lower reactivity of **1** and the fact that pulverized NaCN showed no detectable reaction with 1-bromooctane under similar conditions, we view the impregnated reagent as being "half-naked"; i.e., the alumina exposes only a portion of the cyanide ion to the bulk organic phase.[12] Further studies aimed at establishing the generality of our findings are in progress.

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References and Notes

(1) Supported by the National Science Foundation (Grant No. CHE-77-28366).
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(7) In this experiment, 5 mL of 0.5 M 1-bromooctane in toluene was reacted with 0.5 g of **1** for 48 h at 90 °C and yielded 1.14 mmol of cyanooctane as determined by GLC. Further heating for 24 h did not change the yield significantly.
(8) Analyses were carried out on a Hewlett-Packard 5830 flame ionization instrument using a 2 ft × 0.125 in QF 1(10%) on Chromosorb W column at 160°C.
(9) Values of k_0 at 70, 90 and 100 °C were 2.1×10^{-5}, 6.9×10^{-5}, and 24.3×10^{-5} L mol^{-1} s^{-1}, respectively, and gave $\Delta H^{\ddagger} = 18.4 \pm 1.8$ kcal mol^{-1} and $\Delta S^{\ddagger} = -26.2 \pm 5$ eu.
(10) In this experiment, 0.25 g of **1** was reacted with 25 mL of 0.2 M 1-bromooctane in toluene at 110 °C.
(11) The observed first-order rate constant was 1.9×10^{-5} s^{-1}. The concentration of NaCN in the organic phase was 4.8×10^{-4} M (determined by reaction of an aliquot with excess 1-bromooctane at 100 °C).
(12) In principle, two fundamentally different mechanisms for displacement at the alumina surface can be envisaged. In the first, A, a soluble organic halide undergoes direct attack by an impregnated cyanide ion. In the second, B, the halide is adsorbed prior to displacement. While the observed first-order dependence on 1-bromooctane is in agreement with A, it is also consistent with B if the organic halide is weakly adsorbed. To the extent that alumina may assist the departure of bromide ion from the reactant, the apparent reactivity of cyanide must be regarded as a maximum value.

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Symmetrical Triamino-per-*O*-methyl-α-cyclodextrin: Preparation and Characterization of Primary Trisubstituted α-Cyclodextrins

Sir:

Exploitation of the unique geometry of cyclodextrins for the construction of models of receptor binding and of enzyme catalysis has been severely limited by the dearth of well-characterized polysubstituted derivatives. Thus, while the efficient modification of *all* of the primary hydroxyl groups of α- and β-cyclodextrins has been described[1] and numerous monosubstituted compounds have been reported,[2] no derivatives of intermediate substitution number have been described for which the positions of substitution are established.[3] We report here the preparation and characterization of 6,6″,6‴,6⁗-triamino-6,6″,6‴,6⁗-trideoxy-6′,6‴,6⁗,2,2′,2″,2‴,2⁗,2′′′′,3,3′,3″,3‴,3⁗,3′′′′-pentadeca-*O*-methyl-α-cyclodextrin (**1**) (= symmetrical triamino-per-*O*-methyl-α-CD), a trisubstituted α-cyclodextrin of known regiosubstitution that possesses a threefold axis of symmetry (Figure 1).

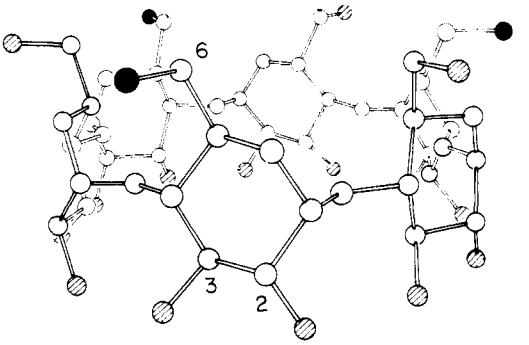
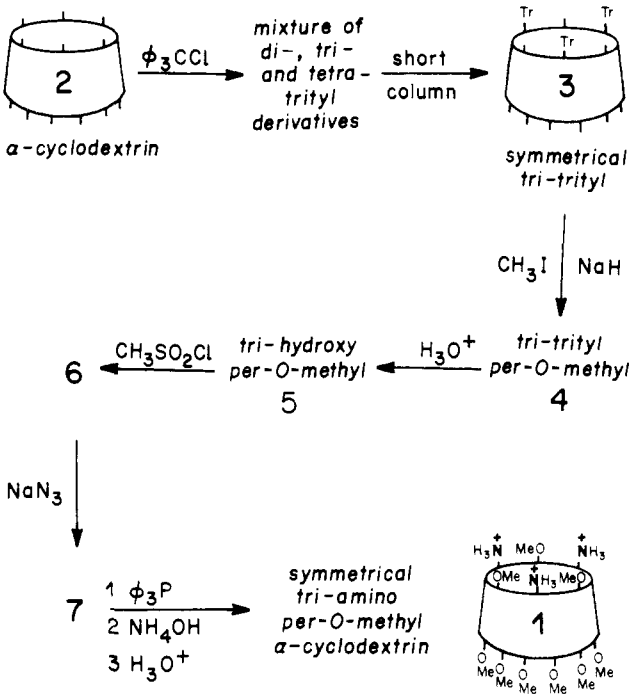


Figure 1. Drawing of symmetrical triamino-per-*O*-methyl-α-cyclodextrin (**1**). The coordinates used for the cyclodextrin skeleton were based on crystal structure data summarized by Saenger.[11] The shaded circles represent methoxyl groups and the full circles represent ammonium groups.

Scheme I. Synthetic Route to Symmetrical Triamino-per-*O*-methyl-α-cyclodextrin (**1**)



Synthesis. The synthesis of **1** is outlined in Scheme I. Reaction of purified[4] α-cyclodextrin **2** with 3.3 equiv of trityl chloride in pyridine (55 °C, 24 h) gave a multitude of products.[5] Thin-layer chromatography (TLC) on silica gel (butanone-water-3-methylbutan-1-ol, 7:1:1) showed six major products, having R_f values of 0.37, 0.28, 0.26, 0.23, 0.20, and 0.14, and about 12 minor products. The desired symmetrically substituted 6,6″,6⁗-tri-*O*-trityl-α-cyclodextrin **3** (R_f of 0.28) was isolated in 23% yield after "short column chromatography"[6] on silica gel eluting with butanone-water-3-methylbutan-1-ol, 100:10:1.[7] The product was identified by ^{1}H and ^{13}C NMR spectroscopy (vide infra).[8] Methylation of the 15 hydroxyl groups of **3** was accomplished using methyl iodide and *crystalline* sodium hydride in dimethylformamide (DMF).[1] Removal of the three trityl groups, by brief treatment of **4** in a two-phase system (concentrated hydrochloric acid–chloroform), gave **5**. Reaction of the three free hydroxyl groups with methanesulfonyl chloride in pyridine, followed by displacement of the sulfonate groups with sodium azide in DMF, gave the symmetrical triazido-per-*O*-methyl-α-cyclodextrin (**7**). Reduction of **7** with triphenylphosphine and ammonia in dioxane[9] gave the desired product **1**, isolated as its trihydrochloride salt. Each of the five reactions from **3** to **1** went in yields between 94 and 97%, and **1** was isolated in 19% overall yield from α-cyclodextrin **2**.

In a similar fashion, mono-6-amino-6-deoxy-6′,6″,6‴,6⁗,6′′′′,2,2′,2″,2‴,2⁗,2′′′′,3,3′,3″,3‴,3⁗,3′′′′-heptadeca-*O*-methyl-α-cyclodextrin hydrochloride (**8**) (= monoamino-per-*O*-methyl-α-CD) was prepared in 24% overall yield, beginning with the preparation of mono-6-*O*-trityl-α-cyclodextrin.[2a]

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