AMINE cationic liposomes,[1] by at least an order of magnitude.[14] Such an enhancement of cationic liposome gene delivery efficacy could have important implications for in vivo cationic liposome-mediated gene delivery.

In conclusion, we have devised a convergent synthesis for peptide mini-vectors, which were demonstrated to be able to mediate plasmid gene delivery in vitro. To the best of our knowledge, these are some of the smallest delivery vectors for nucleic acids yet reported and could be very useful tools for future gene therapy studies.

Experimental Section

All peptides were synthesized on an ABI 431A solid-phase batch peptide synthesizer. Unless otherwise stated above, syntheses were conducted on an 0.1-mmol scale with a fivefold excess of FMOC-protected L-amino acids (Novabiochem, Nottingham, UK) and FastMoc reagents 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate/hydroxybenzotriazole (HBTU/HOBt) (Alexis Corporation, Laufelfingen, Switzerland and SMPE Ltd, Croydon, UK) as the amide coupling agent. Coupling steps were carried out in *N*-methylpyrrolidinone (NMP) and dichloromethane (Rathburn, Walker-burn, UK) on super acid-labile 2-chlorotrityl resins (200–400 mesh; Novabiochem, Nottingham, UK) as the solid support. After synthesis, peptides were cleaved from the resin by trifluoroacetic acid (TFA) in dichloromethane (1% v/v), followed by treatment with pyridine (2.5 equiv) in methanol. Desalting was performed on a P2 biogel column (2×28 cm; Bio-Rad Laboratories, Herts., UK) attached to an FPLC system (Amersham Pharmacia Biotech UK, Bucks., UK) eluting with 0.1% aqueous TFA (0.75 ml min^{-1}; monitoring at 214 or 280 nm). Reverse-phase HPLC purification was usually carried out with a Vydac column (C18, 5μm, 2×25 cm; Hichrom Ltd, Berks., UK) attached to a Gilson HPLC system (Anachem, Beds., UK). Peptides were eluted with a gradient of acetonitrile in 0.1% aqueous TFA (5 ml min^{-1}; monitoring at 220–230 nm). Matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry was performed on a LaserMat 2000 (Thermobioanalysis Ltd, Herts., UK) with a matrix of α-cyano-4-hydroxycinnamic acid (α-CMC) (33 mM) in acetonitrile/methanol (Hewlett-Packard, Cheshire, UK).

Peptide **3** was synthesized as described above (Scheme 1). After final desalting, HPLC purification (eluting with acetonitrile at 53.5%, v/v) and lyophilization, **3** was obtained as a white powder. Overall yield: 8 mg (2.6 μmol, 3%); MS (MALDI-TOF) *m/z* calcd for $C_{136}H_{255}N_{46}O_{30}S_2$: 3078.9 $[M+H]^+$; found 3078.1. The sequence was further confirmed by amino acid composition and sequence analyses; homogeneity was judged to be greater than 95% by HPLC analysis.

Peptide **4** was synthesized as described above (Scheme 2). After final HPLC purification (eluting with acetonitrile at 96.5% v/v) and lyophilization, **4** was obtained as a white powder. Overall yield: 12 mg (2.7 μmol,3%); MS (MALDI-TOF) *m/z* calcd for $C_{206}H_{366}N_{53}O_{48}$: 4353.5 $[M+H]^+$, found 4353.8. The sequence was further confirmed by amino acid composition and sequence analyses; homogeneity was judged to be greater than 95% by HPLC analysis.

Peptides **3** and **4** (100 μg mL^{-1}) were dissolved in 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid, pH 7.3, containing 150 mM NaCl (HEPES buffered saline). The solution of **3** was then stirred for 16 h at room temperature in order to form an intramolecular disulfide bond. Bond formation was monitored by Ellman assay.[15] Finally, the gene delivery efficacies of oxidized **3** and/or **4** were tested as described previously.[8]

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Metathesis of Alkanes: Evidence for Degenerate Metathesis of Ethane over a Silica-Supported Tantalum Hydride Prepared by Surface Organometallic Chemistry**

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Here we report on evidence for a catalytic process in which ethane molecules mutually exchange a methyl group with one another on the silica-supported tantalum(III) hydride catalyst[1] ($\equiv SiO)_2Ta\text{-}H$ ($[Ta]_s\text{-}H$) (**1**) under mild conditions. We recently reported that the surface complex **1** catalyzes the metathesis of linear and branched alkanes and effectively

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converts a given alkane into a mixture of higher and lower molecular weight alkanes. For example, ethane can be converted to methane, propane, and to a lesser extent, heavier alkanes [Eq. (1)].[2]

$$2\,C_2H_6 \xrightarrow{\mathbf{1}} CH_4 + C_3H_8 + (\varepsilon\,C_{4+}) \qquad (1)$$

This unprecedented catalytic reaction involves both cleavage and formation of C–C bonds of alkanes,[3] which may occur simultaneously or stepwise at the metal center. In the case of olefins, the metathesis reaction was discovered in the late 1960s and was the subject of numerous studies since then.[4] In particular, it was shown that a degenerate process that scrambles the reagent occurs together with the productive process. For example, the production of bideuterated ethylene from a mixture of tetra- and undeuterated ethylene over various catalysts constituted a proof for the existence of a degenerated process in the case of unlabeled olefins. We have now discovered the occurrence of a similar process in alkane metathesis by using ^{13}C-monolabeled ethane ($^{13}CH_3$–CH_3).

The metathesis of ^{13}C-monolabeled ethane in the presence of **1** was carried out in a batch reactor at 150 °C; the gas phase was analyzed by GC and the isotopic distribution of ethane was monitored by GC/MS. After 1 h the expected metathesis products methane, propane, isobutane, butane, and traces of pentane and isopentane were evolved. After 100 h, the conversion of ethane into metathesis products reached 11 %, which correspond to about 13 turnovers (Figure 1 a). Under these reaction conditions, the activity and the selectivity for the products (see Experimental Section) were the same regardless of whether labeled or unlabeled ethane was used.

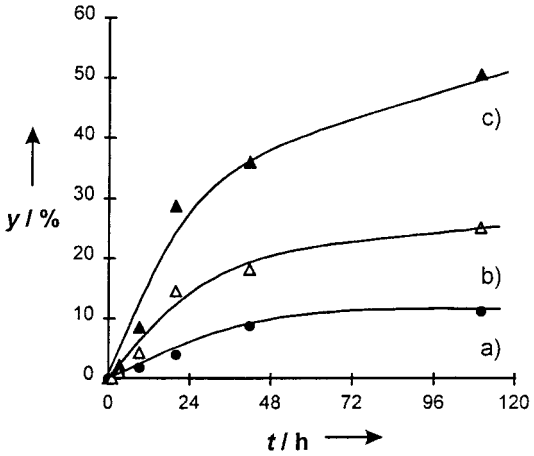


Figure 1. Amounts y of monolabeled ethane converted into a) other alkanes (methane, propane, butanes), b) unlabeled and dilabeled ethane (detectable degenerate metathesis), and c) unlabeled, monolabeled, and dilabeled ethane (calculated degenerate metathesis) versus time.

Analysis of the gas phase by GC/MS reveals an additional process that occurs in parallel to the formation of higher alkanes: monolabeled ethane is converted to its unlabeled and dilabeled isotopomers in similar amounts (Figure 2). The initial rate of this new process (Figure 1 b) is about 2.5 times higher than that of the metathesis reaction (Figure 1 a). This ratio does not change during the reaction, and after 100 h, 25 % of the monolabeled ethane was converted to a 1/1 mixture of ethane and dilabeled ethane, whereas only about 11 % was transformed into other alkanes.

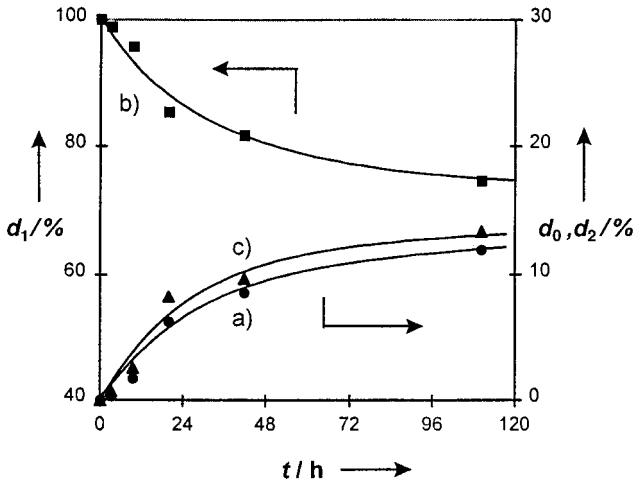
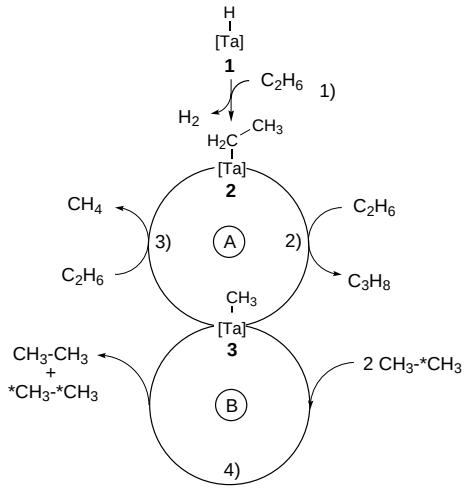


Figure 2. Degenerate metathesis of ethane, studied using $^{13}CH_3$–CH_3. Contribution of a) unlabeled (d_0), b) monolabeled (d_1), and c) dilabeled (d_2) ethane to the isotopomer distribution versus time.

The metathesis of alkanes over **1** has some similarities with olefin metathesis. Indeed, in most cases, the latter reaction involves two processes: one that converts the substrate to its lower and higher homologues, and one that leads to its scrambling. By analogy, we refer to the conversion of ethane into other alkanes as *productive* metathesis, and the conversion of monolabeled ethane to its isotopomers as *degenerate* metathesis. In contrast to ethylene metathesis, which is an exclusively degenerate process, ethane metathesis involves both productive and degenerate processes.

Productive and degenerate metatheses both require C–C bond cleavage of monolabeled ethane and formation of a new C–C bond. In the proposed mechanism for productive metathesis (Scheme 1 Ⓐ), two intermediates were proposed: $(\equiv SiO)_2Ta$–Et (**2**) and $(\equiv SiO)_2Ta$–Me (**3**).[2] The surface complex **2** reacts with ethane in a C–C bond-activation process (2) to form C_3H_8 and **3**. The surface complex **3** is implicated in a C–H bond-activation process (3) which



Scheme 1. Catalytic cycle for ethane metathesis. Ⓐ Productive metathesis, Ⓑ degenerate metathesis.

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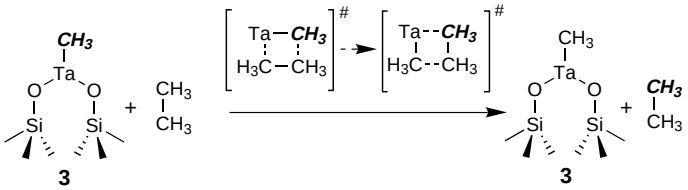
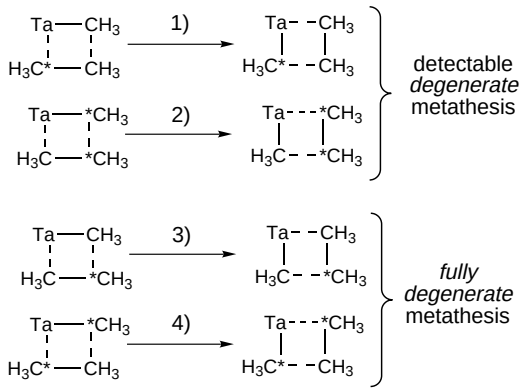
regenerates **2**. This simple catalytic scheme can be extended to explain the degenerate metathesis of ethane. Since the surface complexes **2** and **3** are very similar, **3** should be able to perform C–C bond activation of ethane, which would lead to exchange of a methyl group with an incoming molecule of ethane (Scheme 2).



Scheme 2. σ-Bond metathesis: C–C bond activation of ethane by the surface complex **3**.

Since the methyl group of **3** can be labeled or unlabeled[5] and monolabeled ethane is an unsymmetrical molecule, four reaction pathways can be envisaged (Scheme 3). The formation of unlabeled and dilabeled ethanes is the only detectable



Scheme 3. Degenerate (1, 2) and fully degenerate (3, 4) ethane metathesis.

part of the reaction [detectable degenerate metathesis, reactions 1 and 2]; it should also be accompanied by the undetectable production of monolabeled ethane from monolabeled ethane [fully degenerate metathesis, reactions 3 and 4]. Experimental measurements show that unlabeled and dilabeled ethane are produced in a 1:1 ratio (Figure 2). No measurable isotopic effects occur in these processes, and all the reaction pathways (1) – (4) have the same probability. Consequently, the rate of fully degenerate metathesis should be equal to the rate of detectable degenerate metathesis, which in turn is equal to the sum of the rates of formation of unlabeled and dilabeled ethane. After 100 h, ethane and dilabeled ethane are formed in equal amounts and correspond to 12.5 % of the initial quantity of monolabeled ethane. We can then calculate that about 50 % of the monolabeled ethane underwent a degenerate metathesis reaction (Figure 1c), while the degree of conversion to productive metathesis products was about 11 %. Under these experimental conditions degenerate metathesis is on average five times faster[6] than productive metathesis, and this is consistent with the lower steric hindrance of $(\equiv SiO)_2Ta-Me$ (**3**) relative to $(\equiv SiO)_2Ta-Et$ (**2**).

We have discovered a new catalytic process, that can be referred to as degenerate metathesis, that leads to the isotopomeric redistribution of labeled ethane [Eq. (2)]. This

$$4\,{}^{13}CH_3{-}CH_3 \xrightarrow{\mathbf{3}} H_3C{-}CH_3 + 2\,{}^{13}CH_3{-}CH_3 + {}^{13}CH_3{-}{}^{13}CH_3 \qquad (2)$$

process is about five times faster than productive metathesis. These results allow us to complete the catalytic cycle proposed for alkane metathesis (Scheme 1 Ⓑ) and demonstrate again the high activity of our tantalum catalyst[7] in the cleavage and formation of C–C bonds of alkanes.

Experimental Section

The reactions were carried out in the absence of solvent under inert atmosphere or vacuum. The product mixture and the isotopomer distribution were monitored at different stages of the reaction: the reaction vessel was cooled to room temperature, an aliquot was allowed to expand in a small volume, brought to atmospheric pressure with hydrogen, and analyzed by gas chromatography (HP 5890 apparatus, Al_2O_3/KCl on fused silica column (50 m × 0.32 mm)) and GC/MS (HPG 1800A apparatus). Elemental analyses were performed at the CNRS Central Analysis Service of Solaize. Ethane (Air liquide) and monolabled ethane (Cambridge Isotope Laboratories) were dried over freshly regenerated molecular sieves (3 Å) and deoxo traps immediately before addition. Silica (Degussa, 200 $m^2 g^{-1}$) was dehydroxylated under vacuum at 500 °C for 15 h.

An IR cell, in which the supported tantalum hydride was previously synthesized[1] (60 mg, 6.77 wt % Ta) was charged with 100 % monolabeled ethane. ($p = 16$ kPa, substrate/catalyst ratio ≈ 120:1). The reaction was carried out at 150 °C. After 100 h, the conversion of ethane was about 11 % (calculated from the consumption of ethane), and the selectivities for the products were as follows: methane 70, propane 27, isobutane 1.6, butane 1.2, and pentanes 0.2 %.

Determination of the isotopomer distribution of ethane: The mass spectrum of a mixture of variously labeled ethanes was evaluated for the peak distribution between m/z 24 and 33. The spectrum of unlabeled ethane has a peak distribution between m/z 24 and 31. It is assumed that the same distribution of peaks is shifted by one unit mass to a higher value for each ^{13}C atom in the molecule. A theoretical spectrum was calculated in which the parameters represent the relative amount of unlabeled, monolabeled, and dilabeled ethane, and the sums of the squares of the differences between corresponding peaks of the theoretical and experimental spectra were minimized with the computer program Excel solver.

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[5] The methyl group in $(\equiv SiO)_2Ta-Me$ (**3**) necessarily comes from a reaction between monolabeled ethane and **2**. Since no isotopic effect was observed, the CH_3 group in **3** has equal probability of being labeled or unlabeled.

[6] In a batch reactor, secondary reactions between unlabeled and dilabeled ethanes and **3** can occur; the statistical 1:2:1 distribution of unlabeled, monolabeled, and dilabeled molecules is not affected by such a process. Consequently, the value calculated for the ratio of rates of degenerate/productive metathesis is underestimated.

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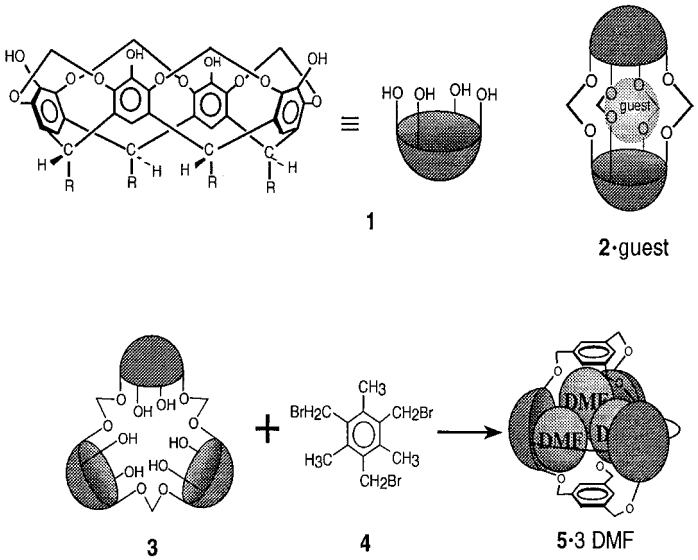
A Giant Carceplex Permanently Entraps Three Organic Molecules**

Naveen Chopra and John C. Sherman*

A current trend in supramolecular chemistry is the creation of large hosts that can accomodate several guests or one large guest. Particularly exciting is the possibility of encapsulating several molecules within molecular vessels and thus facilitating the study of a "microsolvent". The formation of such a species could allow a sophisticated study of templation versus solvent effects, as several molecules may have to be displaced by several others. To date, carceplexes, which permanently entrap molecules within their confines,[1] were only shown to entrap single small guest molecules.[2, 3] We report here the preparation of a carceplex roughly triple the size of any reported previously. We demonstrated the clean and selective permanent entrapment of three molecules of DMF and probed the properties of the entrapped microfluid medium. Such a system should provide a novel opportunity to study complex template effects.

Many large host systems have been reported[4] that could potentially be used to bind several guests: The holand by Reinhoudt et al. is a very large and rigid macrocycle of four concave host units.[3b] It has a huge cavity with correspondingly large holes; although it has not been shown to retain or complex guests, related species have been shown to bind steroids.[4f] The resorcinarene hexamer of Atwood and MacGillivray is a noncovalent assembly that may contain several solvent molecules according to electron density found in the crystal structure; no definitive characterization of encapsulated guests has been reported, nor has the assembly been shown to retain guests in solution.[5] Rebek and Conn encapsulated single large guests in their capsules, and in one case two guests were complexed; the reversible complex formation indicates rapid guest exchange.[6] Cram et al. reported several large hemicarceplexes, in which large portals allow guests to escape and preclude the retention of small molecules.[7] In contrast, the host reported here is unique in that it irreversibly retains several guest molecules.

In designing a large carceplex, certain criteria must be met, including structural rigidity and an effectively closed surface. Cavitands such as tetrol **1** (Scheme 1) are rigid bowl-shaped



Scheme 1. Schematic representation of the synthesis of carceplexes containing guest molecules. R = CH_2CH_2Ph. For clarity, methyl groups are omitted from the caps of **5**·3DMF.

molecules with an enforced cavity and are hence attractive building blocks for the construction of carceplexes. Indeed, two molecules of tetrol **1** were linked to create the small carceplex **2**.[3a] We recently reported the synthesis of a cyclic trimer of bowls (**3**),[8] which is a rigid barrel-shaped molecule with an enforced cavity. Trimer **3** seems ideally suited as a precursor for a large carceplex, and hence it was combined with cap **4** in DMF with K_2CO_3 as base in the presence of KI at ambient temperature for 24 h. The product was identified as carceplex complex **5**·3DMF (36% yield). The complex **5**·3DMF is readily soluble in $CHCl_3$ and was easily isolated from polymeric side products by chromatography on silica gel. The matrix-assisted laser desorption/ionization (MALDI) mass spectrum of **5**·3DMF showed a single predominant peak (m/z: 3641; calcd for **5**·3DMF·Na^+: 3642), which

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