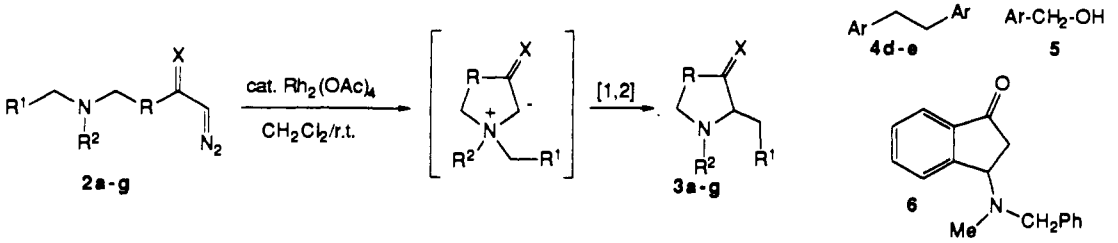
Table I. Treatment of ω-dialkylaminodiazoketones with $Rh_2(OAc)_4$[a]



substrate	R	X	R^1	R^2	[1,2] product (yield, %)[b]	other products[b]
2a	$(CH_2)_2$	O	Ph	Me	**3a** (99)	
2b	$(CH_2)_2$	O	Ph	Et	**3b** (91)	
2c	$(CH_2)_2$	O	CO_2Et	Me	**3c** (94)	
2d	$(CH_2)_2$	O	p-AcC_6H_4	Me	**3d** (71)	**4d** (25)
2e	$(CH_2)_2$	O	p-$MeOC_6H_4$	Me	**3e** (71)	**4e** (19)
2f	$(CH_2)_2$	O	p-$NO_2C_6H_4$	Me	**3f** (56)	**5** (5)
2g	o-C_6H_4	O	Ph	Me	**3g** (40)	**6** (23)

[a] Standard procedure: Substrates were dissolved in CH_2Cl_2 (0.05 M) and added dropwise by cannula to 3 mol % $Rh_2(OAc)_4$ in CH_2Cl_2 at room temperature over 0.5 h. After an additional 0.25 h, the reaction mixture was worked up and immediately chromatographed. [b] Isolated yields after chromatography. Satisfactory IR, ^1H and ^{13}C NMR spectra, and combustion analysis or HRMS data were obtained for substrates **2a-g** and their rearrangement products.

substrate **2g** gave a mixture of dihydroisoquinolone [1,2]-shift product **3g** and C-H insertion product **6**.

Importantly, complete migrating group selectivity was seen in all cases, consistent with the expectation that the carbon with the best radical stabilizing substituent will migrate.[13] As can be seen from the reaction of glycine derivative **2c**, migration was not limited to benzylic groups. Substrate **2b**, which proceeded through an *N*-ethylammonium ylide, showed no evidence of α′,β-fragmentation to generate ethylene and 1-benzyl-3-piperidone.[14] Those cases involving substituted benzyl migrating groups actually showed a diminished yield of [1,2]-shift product, apparently due to a greater tendency for the presumed benzylic radical intermediate[7e,13] to suffer escape from the solvent cage and undergo homocoupling to give **4d,e** or reaction with oxygen to give **5**. However, we were unable to isolate any of the corresponding bis(3-piperidone) dimers.[15]

Despite the availability of a five-membered C-H insertion transition state to carbenoids derived from substrates **2a-f**, 3-aminocyclopentanones from this pathway were not observed.[16] The one exception was **2g**, which gave 3-aminoindanone **6** as a substantial byproduct, perhaps due to enforced proximity resulting from ortho disposition of the benzylic methylene and the carbenoid. It should also be noted that none of the isomeric 2-aminoindanone which would derive from competing [1,2]-shift of the *endocyclic* benzyl carbon was seen. A comparable result observed by Ollis et al. when the same ylide was generated by quaternization/deprotonation[17a] was rationalized in terms of poor benzylic overlap with the incipient radical during endocyclic C-N homolysis.

In summary, we have demonstrated that the overall sequence of rhodium-catalyzed carbenoid generation/ammonium ylide formation/Stevens [1,2]-shift utilizing acyclic γ-dialkylamino diazo carbonyl substrates can be applied to the synthesis of six-membered nitrogen heterocycles in good to excellent yields. Starting materials are easily prepared in one step from secondary amines. The key step is exceedingly simple and does not require high-dilution conditions. The use of this transformation in the synthesis of alkaloid targets is currently being investigated and will be reported in due course.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We also acknowledge the National Institutes of Health (S07 RR07092) for partial support and the American Cancer Society for a Junior Faculty Research Award (F.G.W.).

Supplementary Material Available: Representative procedures for the synthesis of diazo ketones **2a** and **2g** and piperidone **3a** along with physical data for all substrates and their [1,2]-shift products (5 pages). Ordering information is given on any current masthead page.

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Molecular Sieving by a Perforated Langmuir-Blodgett Film[1]

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Molecular separations, via the use of synthetic membranes, are beginning to yield new and more energy-efficient methods for chemical processing.[2] Further advances in this area will require the creation of novel materials that exhibit high permeation selectivity (permselectivity) and high permeation rates.[3] We have previously outlined a strategy for the synthesis of perforated monolayers, based on the use of porous surfactants.[4,5] We have also proposed that such assemblies could be used to construct composite membranes that distinguish permeants on the basis of their molecular size. Here, we provide experimental verification of this concept. Specifically, we describe the synthesis and permeation characteristics of Langmuir-Blodgett (LB) multilayers

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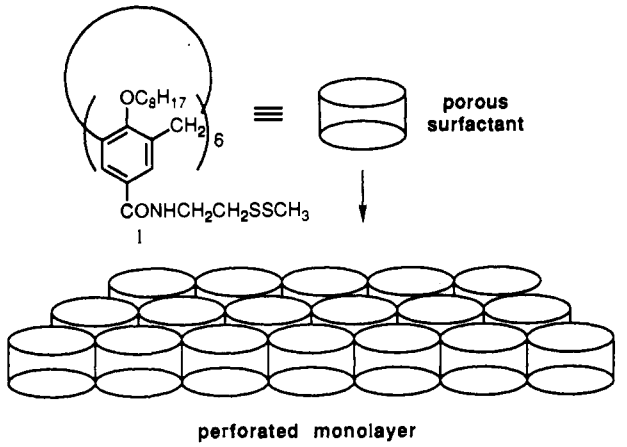
Table I. Flux of He, N_2, and SF_6 across Membrane Composites[a]

membrane	monolayers of I[b]	pressure (atm)	flux ($cm^3/cm^2 \cdot s \cdot cm$ Hg)		
			He	N_2	SF_6
Celgard	0	0.03	2800×10^{-4}	1100×10^{-4}	540×10^{-4}
Celgard/I	26	0.03	31×10^{-4}	24×10^{-4}	14×10^{-4}
Celgard/I	50	0.09	11×10^{-4}		5.2×10^{-4}
Nuclepore	0	0.03	630×10^{-4}	250×10^{-4}	130×10^{-4}
Nuclepore/I	26	0.20	9.6×10^{-4}	4.0×10^{-4}	1.9×10^{-4}
PTMSP	0	0.70	530×10^{-6}	540×10^{-6}	310×10^{-6}
PTMSP/I	12	0.70	96×10^{-6}	5.8×10^{-6}	$<0.22 \times 10^{-6}$
PTMSP/I	24	0.70	54×10^{-6}	4.0×10^{-6}	$<0.22 \times 10^{-6}$
PTMSP/I	24	0.70	47×10^{-6}	2.0×10^{-6}	$<0.22 \times 10^{-6}$
PTMSP/I[c]	24	0.70	20×10^{-6}	1.9×10^{-6}	1.9×10^{-6}
PTMSP[d]	0	0.70	150×10^{-6}	14×10^{-6}	4.1×10^{-6}

[a] Normalized for pressure and area (1.2 cm^2). In all cases, the permanent pressure was applied to the calixarene side of the membrane. [b] Transfer ratios of Celgard were 1.09 ± 0.05 and 0.90 ± 0.02 on the up and down trips, respectively; for Nuclepore membranes, they were 1.07 ± 0.03 and 1.02 ± 0.03, respectively. The up and down transfer ratios for PTMSP were 1.07 ± 0.03 and 0.98 ± 0.06, respectively. [c] UV-treated composite. [d] UV-treated support.

Scheme I



of I that have been assembled onto poly[1-(trimethylsilyl)-1-propyne] (PTMSP) film (Scheme I).[6] Our results not only demonstrate the feasibility of creating LB composites that exhibit high permselectivity but also show that such selectivity is critically dependent on the use of supports that possess a continuous surface.

Alkylation of 37,38,39,40,41,42-hexahydroxycalix[6]arene[7] with 1-bromooctane gave the corresponding hexakis(*n*-octyloxy) ether; sequential Friedel–Crafts acylation (CH_3COCl), haloform oxidation, acid chloride formation, and condensation with 2-methyldithiaethylamine afforded calixarene I in 18% overall yield.[8]

The surface pressure–area isotherm that was recorded for I at the air–water interface was similar to that of an analogous mercurated calix[6]arene;[4,5] the limiting area and collapse pressure were 200 ± 10 $Å^2$/molecule and 55 dyn/cm, respectively. Brief exposure to UV light (254 nm, 7 min) resulted in disulfide disproportionation and cross-linking, as evidenced by surface viscosity measurements;[4] i.e., unlike nonirradiated monolayers of I, which readily flowed through a canal viscometer (slit width of 4 mm), the UV-treated film fully maintained a surface pressure of 8 dyn/cm for >2 h. Transfer of 21 nonpolymerized monolayers of I to a silicon wafer via vertical dipping (24.0 dyn/cm) afforded uniform Y-type (head to head, tail to tail) LB films having a repeat thickness of 18 ± 1 Å/monolayer (ellipsometry). Subsequent UV treatment resulted in a ca. 20% decrease in film thickness and an assembly that was essentially nonremovable by $CHCl_3$.

Similar transfer of 26 monolayers of I to 25 μm thick Celgard supports[9] resulted in a composite that exhibited reduced permeability toward He and SF_6 (Table I); an analogous membrane, made from 50 layers of I, showed a further reduction in permeability. The overall changes in He/SF_6 selectivity that were observed in both cases, however, were only modest. Similar results were obtained using Nuclepore membranes having macropores that were 300 Å in diameter. Careful examination of each composite, by use of a JEOL 6300 scanning electron microscope (equipped with a field emission source), revealed the presence of film defects. Apparently, the transferred monolayers are unable to effectively traverse all of the macropores that are present on the surface of the film.

In an effort to minimize defect formation, PTMSP was then examined as support material.[10] Cast films of this polymer are known to possess extraordinarily high permeability (due to a high internal free volume and a glassy state) and a continuous surface.[11] Transfer of 12 monolayers of I to 14 μm thick cast films of PTMSP gave composites having barrier properties toward He, N_2, and SF_6, which are also presented in Table I. In striking contrast to those membranes that were prepared from the macroporous supports, *a significant decrease in permeability was accompanied by a substantial increase in permselectivity*. The He/SF_6 selectivity, which was >440 for the 12-layer composite, is particularly noteworthy.[12] The fact that the ratios of He/SF_6 (>440) and He/N_2 (17) are much higher than those predicted by Graham's law (i.e., $He/SF_6 = 6$; $He/N_2 = 2.6$) provides compelling evidence that the pores are of molecular dimensions and that permeation is governed by a sieving action of the composite and not by Knudsen diffusion.[13] Examination of CPK models indicates that SF_6 is too large to pass through the pore of I. Thus, all of the SF_6 that does pass through this composite must diffuse across interstitial pores. In contrast, nitrogen and helium have diameters which should permit their passage through I. Although we cannot presently assign the fractions of He and N_2 that diffuse across molecular versus interstitial pores, the selectivity features of this composite clearly show that its pore structure is unique compared with standard LB films made from stearic acid, which do not exhibit sieving properties.[14]

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Efforts that have been made to stabilize PTMSP/I by UV treatment (254 nm, 7 min) have led to a significant reduction in permselectivity and permeation rates (Table I). Apparently, the integrity of the LB suprastructure cannot be fully maintained under these conditions; i.e., defects are created as a consequence of the two-dimensional polymerization and/or the photodecomposition of the support.

Our demonstration that molecular sieving can be achieved with LB composites, made from a combination of porous surfactants and highly permeable supports possessing a continuous surface, should lead the way to novel and potentially exploitable membranes for molecular separations. Efforts aimed at exploring such possibilities are now under intensive investigation.

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Nucleotides Bearing a Cleavable Genotoxic Group on the Phosphate

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N-Nitrosopyrrolidine (NPYR), a rodent carcinogen,[1] is a promutagen requiring enzymic conversion, presumably to its α-hydroxylated derivative, to exhibit its mutagenic activity.[2] Earlier studies from our laboratory have shown that NPYR and *N*-nitrosomorpholine can be converted into their α-phosphate esters on near-ultraviolet (UVA) irradiation in the presence of inorganic phosphate and that these α-phosphate derivatives are directly mutagenic toward bacteria.[3-7] Furthermore, direct mutagenicity was observed for UVA-irradiated mixtures of *N*-nitrosomorpholine and nucleotides (in place of inorganic phosphate), and the mutagenic components formed were found in distinctive zones in paper chromatography, depending on the nucleotide used.[3] It is likely, therefore, that in this process the nucleotides were linked to the *N*-nitrosodialkylamine at the α-carbon. Such compounds seemed to us to be worthy of exploration for their properties. We wish to report here the synthesis of this new class of nucleotide derivatives using NPYR. These nucleotides are directly mutagenic to *Salmonella*, and they can be cleaved in vitro under mild conditions at the phosphoester–NPYR linkage. With near-ultraviolet irradiation, this cleavage takes place and, when a strand of DNA is present in the reaction mixture, the DNA undergoes single strand breaks.

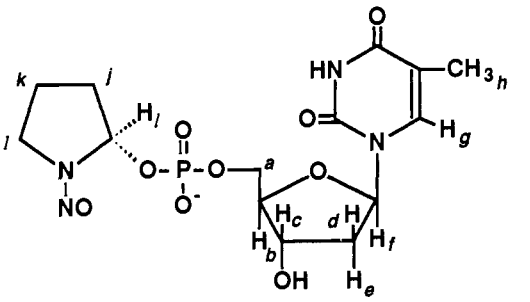

Figure 1. Structure of NPYR-dpT.

Table I. Preparation and Properties of NPYR Nucleotides

compd[a]	yield,[b] %	PPC[c] R_f	PPC[c] R_f of parent nucleotide	PEP[d] M_{pX}	UV in H_2O[e] λ_{max}, nm
NPYR-dpT	9	0.70	0.37	0.54	266
NPYR-dpC	15	0.62	0.21	0.51	272
NPYR-dpA	11	0.62	0.27	0.52	259
NPYR-dpG	12	0.44	0.12	0.51	248
NPYR-dpCpT	8	0.33	0.19	0.74	268
NPYR-pA	14	0.62	0.26	0.47	258
NPYR-Up	4	0.53	0.22	0.51	259

[a] dpX represents deoxyribonucleoside 5′-phosphate, pA is adenosine 5′-phosphate, and Up is uridine 2′(and 3′)-phosphate. [b] The yields were from α-acetoxy-NPYR used and are calculated on the basis of UV absorbance of the isolated material. Molar absorbances at the λ_{max} are the calculated sums of those for nucleotides and α-acetoxy-NPYR. The yield for NPYR-dpCpT was from dpCpT, for which α-acetoxy-NPYR was used in excess. [c] Paper chromatography was run ascendingly on Toyo filter paper 51C, with propanol–concentrated NH_4OH–H_2O (6:3:1, v/v) as solvent. [d] Paper electrophoresis was run in 0.03 M sodium phosphate buffer at pH 7.4 (200 V, 80 min). M_{pX} represents mobility relative to that of the parent nucleotide. [e] A feature in the spectra of these NPYR nucleotides was that the A_{240} values are elevated from those of their parent nucleotides due to the intramolecular presence of an equimolar NPYR moiety.

A solution of thymidine 5′-phosphate Na_2 (dpT) (8 mg) and α-acetoxy-NPYR (2 mg)[8] in water (16 μL) was heated at 75 °C for 20 min. The product, thymidine 5′-phosphate mono(1-nitroso-2-pyrrolidinyl) ester (NPYR-dpT, Figure 1), was isolated by use of TLC on cellulose [solvent: 2-propanol–concentrated NH_4OH–H_2O (7:1:2)] followed by paper chromatography [solvent: propanol–concentrated NH_4OH–H_2O (6:3:1)]. The NMR spectra (^1H, ^{31}P, ^1H–^1H COSY, and ^1H–^{31}P HSQC) of this material supported the expected structure and its diastereomeric mixture: ^1H NMR (500 MHz, D_2O) δ 1.87 (s, h), 1.92 (s, h), 2.09–2.28 (m, j + k), 2.28–2.41 (m, d + e), 3.48–3.74 (m, l), 3.97–4.19 (m, a + b), 4.51–4.58 (m, c), 6.30–6.38 (m, f), 6.53–6.58 (m, i), 7.70 (s, g), and 7.72 (s, g); ^{31}P NMR (202.35 Hz, D_2O) δ −2.44 and −2.83. The proton-detected ^1H–^{31}P heteronuclear two-dimensional correlation spectrum (^1H–^{31}P HSQC) confirmed the assignment that the phosphate is linked to the α-carbon of NPYR: both H(i) and H(a + b) were correlated with the ^{31}P.

The mass spectrum gave signals corresponding to the assigned structure: *m/z* 421 (free acid), 438 (NH_4 salt), and 443 (Na salt). The UV spectrum in water was close to the sum of the spectra for dpT and α-acetoxy-NPYR [the ε values of which are 6850 at 229 nm (λ_{max}), 5250 at 240 nm, and less than 100 at 280 nm and longer wavelengths]; the spectrum at pH 12, which was stable, showed a maximum at 265 nm with a 20% lower absorbance from that in water, as expected for a thymine nucleotide. At pH 2, the spectrum showed a rapid change, as monitored by the decrease in absorbance at 240 nm, to give, after 5 min, a spectrum identical to that of dpT, a phenomenon suggesting the cleavage of the NPYR moiety. On treatment with snake venom phosphodiesterase, NPYR-dpT gave dpT, as identified by paper chroma-

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