J. Am. Chem. Soc. **1998,** *120,* 10372−10378

Solvent Effects on Carbocation−Nucleophile Combination Reactions: A Comparison of π-Nucleophilicity in Aqueous and Organic Solvents

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Received May 27, 1998

Abstract: The following selectivities are reported for partitioning of the α-(*N*,*N*-dimethylthiocarbamoyl)-4-methoxybenzyl carbocation $\mathbf{1}^+$ between nucleophilic addition of π-nucleophiles and a solvent of 50:50 (v:v) acetonitrile/water at 25 °C (nucleophile, $k_{\mathrm{Nu}}/k_{\mathrm{s}}$): pyrrole, 23 M^{-1}; 2-methoxythiophene, $\approx$2 M^{-1}. No nucleophile adducts (<2% of total products) were detected from the reaction of this carbocation in the same solvent containing the following carbon nucleophiles: thiophene (0.10 M), furan (0.10 M), ethyl 1-propenyl ether (0.10 M), amd 1-cyclohexenyl trimethylsilyl ether (0.01 M). These results show that only π-nucleophiles with Mayr nucleophilicity parameters greater than $N \approx 6$ are sufficiently reactive to compete with nucleophilic aqueous solvents for addition to $\mathbf{1}^+$, and they provide support for a simple relationship between the Ritchie N_+ scale of nucleophilicity in water and the Mayr N scale of nucleophilicity in weakly polar nonnucleophilic solvents.[2,3] Our data require a large effective molarity for the intramolecular addition of a trisubstituted alkene to an allylic carbocation.

In recent years there have been many determinations of rate constants for the addition of nucleophiles to carbocations in a variety of solvents, including weakly polar, aprotic, nonnucleophilic solvents such as dichloromethane;[2,3] polar, aprotic, and weakly nucleophilic solvents such as acetonitrile;[4] polar, protic, and weakly nucleophilic solvents such as 1,1,1,3,3,3-hexafluoro-2-propanol;[5,6] and polar, protic, and strongly nucleophilic solvents such as water.[7,8] An important conclusion from this work is that there are large decreases in the reactivity of anionic nucleophiles[4,9] and neutral amines[10] with increasing stabilization of the nucleophilic reagent by hydrogen bonding to solvent. This results from the requirement for the loss of these stabilizing hydrogen-bonding interactions on proceeding to the transition state for the nucleophile addition reaction.

The effect of polar protic solvents on the nucleophilic reactivity of alkenes and other π-nucleophiles has not been investigated in detail, but the lack of data in aqueous solvents might suggest that π-nucleophiles are simply too weakly nucleophilic to compete with nucleophilic solvents for addition to unstable carbocations. However, recent studies of photolytically generated ring-substituted diarylmethyl carbocations in acetonitrile have shown that the second-order rate constants for the addition of activated alkenes, such as vinyl ethers and silyl enol ethers, are significantly larger than that for addition of water.[11] These results suggest that it should be possible to study the addition of strongly activated nucleophilic alkenes to carbocations in an aqueous solvent, but we are not aware of any reports of such studies in the chemical literature.

We recently reported that the π-nucleophile **2** is 70 000-fold more reactive than a solvent of 50:50 (v:v) methanol/water toward the α-(*N*,*N*-dimethylthiocarbamoyl)-4-methoxybenzyl carbocation $\mathbf{1}^+$ (k_{alk}, Scheme 1),[12] generated as the intermediate of the stepwise reaction of α-(*N*,*N*-dimethylthiocarbamoyl)-4-methoxybenzyl pentafluorobenzoate (**1-PFB**) in aqueous solvents.[13] The reactivity of this highly activated π-nucleophile toward $\mathbf{1}^+$ is similar to that of the strongly nucleophilic azide ion.[12] These results show that π-nucleophiles can compete with an aqueous solvent for nucleophilic addition to carbocations, and they prompted the present work to determine the reactivity of other π-nucleophiles toward $\mathbf{1}^+$ in a solvent of 50:50 (v:v) acetonitrile/water. We report here the results of experiments that define the "threshold" π-nucleophile reactivity required for observing the formation of the π-nucleophile adduct to $\mathbf{1}^+$ in an aqueous solvent. This threshold is exceeded by pyrrole and 2-methoxythiophene, but not by thiophene, furan, or representative alkyl and silyl enol ethers, which are also activated for nucleophilic addition. A comparison of the data reported here, which define the relative nucleophilicity of π-nucleophiles toward $\mathbf{1}^+$ in aqueous solvents, and the extensive data from Mayr's laboratory,[2,3] which define the nucleophilicity of π-nucleophiles toward carbocations in aprotic organic solvents such as dichloromethane, shows that the effect of the very dramatic

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[2] Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−957.

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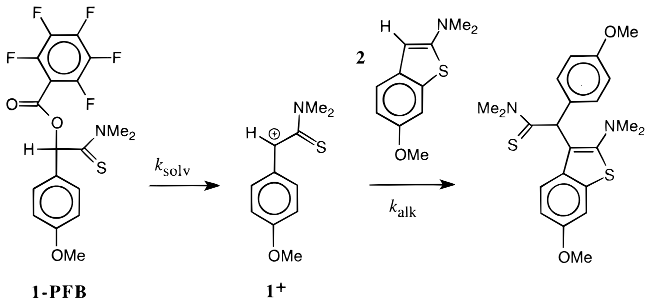
S0002-7863(98)01842-3 CCC: \$15.00

Scheme 1



change from an organic to an aqueous solvent on the relative reactivity of π-nucleophiles is small or negligible.

Experimental Section

Materials. Pyrrole (98%), thiophene (99+%), furan (99%), 1-cyclohexenyloxytrimethylsilane (99%), and ethyl 1-propenyl ether (98%, mixture of cis and trans isomers) were purchased from Aldrich. 2-Methoxythiophene (99%) was purchased from Lancaster Synthesis. Acetonitrile was HPLC grade from Fisher. All other organic chemicals and inorganic salts were reagent grade and were used without further purification. The water used in kinetic and product studies was distilled and then passed through a Milli-Q water purification system.

α-(*N,N*-Dimethylthiocarbamoyl)-4-methoxybenzyl pentafluorobenzoate (**1-PFB**) was prepared as described previously.[13]

2-[α-(*N,N*-Dimethylthiocarbamoyl)-4-methoxybenzyl]pyrrole (**1-(2-Pyr)**) was prepared by the reaction of **1-PFB** (10 mg) in 2 mL of 70:30 (v:v) trifluoroethanol/water containing 1 M pyrrole at room temperature for 3 h. The products were separated by HPLC using a semipreparative octadecylsilane column from YMC and eluting with 80:20 (v:v) methanol/water. The fractions which contained the pyrrole adduct were pooled, and the product was extracted into chloroform. Evaporation of the solvent gave **1-(2-Pyr)** (50%) as a brown solid: ^{1}H NMR (500 MHz, CD_3OD): δ 7.09 (2H, d, $J = 8.5$ Hz, Ar), 6.81 (2H, d, $J = 8.5$ Hz, Ar), 6.69 (1H, dd, $J_{45} = 3.0$ Hz, $J_{35} = 1.5$ Hz, pyrrole H-5), 6.00 (1H, t, J_{34}, $J_{45} = 3.0$ Hz, pyrrole H-4), 5.86 (1H, dd, $J_{34} = 3.0$ Hz, $J_{35} = 1.5$ Hz, pyrrole H-3), 5.71 (1H, s, ArCH), 3.77 (3H, s, OCH_3), 3.35 (3H, s, $N(CH_3)_2$), 3.31 (3H, s, $N(CH_3)_2$); MS found 274.1140, $C_{15}H_{18}N_2OS$ requires 274.1140.

Product Analyses by HPLC. Product studies of the reactions of **1-PFB** were carried out in 50:50 (v:v) acetonitrile/water at $I = 0.50$ ($NaClO_4$) and 25 °C. Solutions were prepared by mixing equal volumes of an aqueous solution containing the appropriate salt at $I = 1.0$ ($NaClO_4$) with acetonitrile containing the appropriate π-nucleophile. Reactions were initiated by making a 100-fold dilution of a solution of **1-PFB** in acetonitrile into the reaction mixture to give a final substrate concentration of 6×10^{-5} M. Fluorene or 9-hydroxy-9-methylfluorene [$(2-8) \times 10^{-5}$ M] was used as an internal standard to correct for small variations in the HPLC injection volume. HPLC analysis of a solution of 2-methoxythiophene (0.1 M) in 50:50 (v:v) acetonitrile/water with peak detection at 271 nm revealed several contaminant peaks that interfered with the analyses of the products of the reaction of **1-PFB**. The use of a larger concentration of 3×10^{-4} M **1-PFB** for the reactions in the presence of 2-methoxythiophene allowed for a reduction in the sample volume used for HPLC analysis, and this minimized problems resulting from the presence of small amounts of UV-absorbing contaminants in 2-methoxythiophene.

The products of the reactions of **1-PFB** were separated by HPLC and identified as described in earlier work,[14−16] with peak detection at 271 nm (which is λ_{max} for **1-OH**)[12,13] using a Waters 996 diode array detector. The pyrrole adduct **1-(2-Pyr)** was identified by comparison of its HPLC retention time with that for authentic material, prepared as described above. The products were generally analyzed after a reaction time of 40 min, which is ca. 7 halftimes for the reaction of **1-PFB**. The π-nucleophile adducts were shown to be stable for at least 2 days under the conditions used for their generation.

The ratios of the yields of the nucleophile adducts were calculated using eq 1, where (A_{RNu1}/A_{RNu2}) is the ratio of the HPLC peak areas of two adducts RNu1 and RNu2 and ($\epsilon_{RNu2}/\epsilon_{RNu1}$) is the ratio of the extinction coefficients of these adducts at 271 nm. The ratio of the extinction coefficients for the adducts of azide ion and water to $\mathbf{1}^+$ has been shown to be 1.0.[12,13] The ratio for the adducts of propionate ion and water to $\mathbf{1}^+$ is also assumed to be 1.0 because the extinction coefficients for the carboxylate ion and solvent adducts of several ring-substituted 1-phenyl-2,2,2-trifluoroethyl carbocations at λ_{max} for the corresponding alcohols are identical.[16] A value of $\epsilon_{RNu}/\epsilon_{ROH} = 1.1$ at 271 nm was calculated for the pyrrole and solvent adducts using eq 2, where ΔA_{RNu} and ΔA_{ROH} are the changes in the HPLC peak areas for the pyrrole adduct **1-(2-Pyr)** and the solvent adduct **1-OH**, respectively, determined for reaction of a fixed concentration of **1-PFB** in the presence of increasing concentrations of pyrrole.

$$[\mathrm{RNu1}]/[\mathrm{RNu2}] = (A_{\mathrm{RNu1}}/A_{\mathrm{RNu2}})(\epsilon_{\mathrm{RNu2}}/\epsilon_{\mathrm{RNu1}}) \tag{1}$$

$$\epsilon_{\mathrm{RNu}}/\epsilon_{\mathrm{ROH}} = \Delta A_{\mathrm{RNu}}/\Delta A_{\mathrm{ROH}} \tag{2}$$

$$k_{\mathrm{Nu1}}/k_{\mathrm{Nu2}} = [\mathrm{RNu1}][\mathrm{Nu2}]/[\mathrm{RNu2}][\mathrm{Nu1}] \tag{3}$$

$$k_{\mathrm{Nu}}/k_{\mathrm{s}}\ (\mathrm{M}^{-1}) = \sum[\mathrm{RNu}]/[\mathrm{ROH}][\mathrm{Nu}] \tag{4}$$

The yields of the products of the reaction of **1-PFB** with 2-methoxythiophene were too low to allow for an accurate determination of the relative extinction coefficient of the 2-methoxythiophene adduct. Therefore, an approximate value of $\epsilon_{RNu}/\epsilon_{ROH} = 1$ was used in the calculation of the yield of this adduct.

Values of k_{Nu1}/k_{Nu2} (dimensionless) for partitioning of **1-PFB** between reaction with Nu1 and Nu2 were determined from the ratios of the yields of the corresponding nucleophile adducts using eq 3. Values of k_{Nu}/k_s (M^{-1}) for partitioning of **1-PFB** between reaction with nucleophilic reagents and solvent were determined using eq 4, where $\sum$[RNu] corresponds to the sum of the HPLC peak areas for all the products of reaction of the nucleophile with **1-PFB**. The rate constant ratios k_{Nu1}/k_{Nu2} and k_{Nu}/k_s (M^{-1}) determined from product analyses in different experiments were reproducible to better than ±10%.

Results

The yields of the products of the reaction of **1-PFB** in 50:50 (v:v) acetonitrile/water ($I = 0.50$, $NaClO_4$) at 25 °C in the presence of five concentrations of sodium propionate in the range 0.05−0.25 M and a fixed concentration of 0.50 mM sodium azide were determined by HPLC analyses. The data gave $k_{az}/k_{prop} = 840 \pm 40$ for partitioning of **1-PFB** between reaction with azide and propionate ions, which is the average of these five determinations calculated using eq 3. The yields of the products of the reaction of **1-PFB** in 50:50 (v:v) acetonitrile/water ($I = 0.50$, $NaClO_4$) at 25 °C containing 0.01 M sodium propionate gave $k_{prop}/k_s = 120$ M^{-1} for partitioning of **1-PFB** between reaction with propionate ion and solvent, were calculated using eq 4.

The yields of the products of the reaction of **1-PFB** in 50:50 (v:v) acetonitrile/water ($I = 0.50$, $NaClO_4$) at 25 °C in the presence of five concentrations of pyrrole in the range 0.01−0.10 M were determined by HPLC analyses. The data gave $k_{Nu}/k_s = 23$ M^{-1} (Table 1) for partitioning of **1-PFB** between reaction with pyrrole and solvent, calculated using eq 4. The calculated ratio k_{Nu}/k_s (M^{-1}) does not change as the concentration of pyrrole is increased from 0.01 to 0.10 M, which shows

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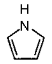
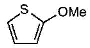
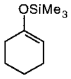
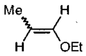
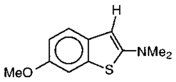
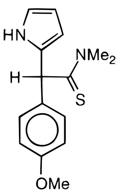
Table 1. Rate Constant Ratios for the Partitioning of **1**+ between Reaction with Added Nucleophilic Reagents and Solvent in 50:50 (v:v) Acetonitrile/Water (Scheme 2) and Estimated Values of the Nucleophilicity Parameters N_+ and N[a]

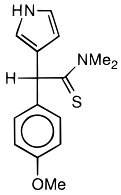
Nucleophile	k_{Nu}/k_s (M^{-1}) [b]	k_{Nu}/k_{HOH} [c]	N_+ [d]	N_{calc} [e]
	23 [f]	640	1.4	7.2 (7.3) [g]
	≈ 2 [h]	≈ 60	≈ 0.3	≈ 6.1
	< 0.2 [i]	< 6	< -0.70	< 5.1
	< 0.2 [i]	< 6	< -0.70	< 5.1
	< 2 [j]	< 60	< 0.30	< 6.1 (5.6) [k]
	< 0.2 [i]	< 6	< -0.70	< 5.1
	70 000 [l]	1.9 x 10^6	4.8	10.6
N_3^-	100 000 [m]	2.4 x 10^6		

[a] At 25 °C and I = 0.50 (NaClO$_4$). [b] Rate constant ratio for partitioning of $\mathbf{1}^+$ between reaction with the nucleophile and solvent, determined from analysis of the products of the reaction of **1-PFB** as described in the Experimental Section. [c] Dimensionless ratio of second-order rate constants calculated from k_{Nu}/k_s (M^{-1}) and [H$_2$O] = 27.8 M in 50:50 (v:v) acetonitrile/water. [d] Estimated value of the Ritchie nucleophilicity parameter N_+, calculated using eq 6 of the text. [e] Estimated value of the Mayr nucleophilicity parameter N, calculated from the value of N_+ using eq 8 of the text. [f] Average of values determined at five concentrations of pyrrole in the range 0.01−0.10 M. [g] Value calculated by Mayr (ref 34) from data for the reaction of pyrrole with the tricarbonylcyclohexadienyliron cation in nitromethane (refs 2 and 35). [h] Approximate value, see Experimental Section. [i] Upper limit based on the assumption that a 2% yield of the nucleophile adduct could have been detected from reaction of **1-PFB** in the presence of 0.10 M π-nucleophile. [j] Upper limit based on the assumption that a 2% yield of the nucleophile adduct could have been detected from reaction of **1-PFB** in the presence of 0.01 M π-nucleophile. [k] Data from ref 2. [l] Data from ref 12. [m] Calculated as $k_{az}/k_s = (k_{az}/k_{prop})(k_{prop}/k_s)$, see Results section.

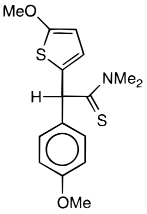
that there is no significant general base catalysis of the reaction of solvent by pyrrole.[17,18] The product of the reaction of pyrrole was prepared independently from the reaction of **1-PFB** in 70:30 (v:v) trifluoroethanol/water and was isolated by semipreparative HPLC, as described in the Experimental Section. ^{1}H NMR analysis showed that each of the three C−H protons of the pyrrole ring is coupled to at least one vicinal proton, which requires that the three protons are attached to adjacent carbons and identifies the product as **1-(2-Pyr)** rather than **1-(3-Pyr)**. The formation of **1-(2-Pyr)** is consistent with the known to be much greater nucleophilic reactivity of pyrrole at C-2 than at C-3.[19]



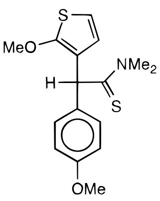
1-(2-Pyr)



1-(3-Pyr)



1-(5-MeOTh)



1-(3-MeOTh)

HPLC analysis of the products of the reaction of **1-PFB** in 50:50 (v:v) acetonitrile/water (I = 0.50, NaClO$_4$) at 25 °C in the presence of 2-methoxythiophene (0.01−0.10 M) showed that there are two products of the reaction of 2-methoxythiophene with similar retention times and peak areas. We were unable to isolate and characterize these two products owing to their low overall yields and similar HPLC retention times. However, the relatively large activation of 2-methoxythiophene for nucleophilic addition and the observation of two products from the reaction of this π-nucleophile with **1-PFB** are consistent with the assignment of **1-(5-MeOTh)** and **1-(3-MeOTh)** as the structures of the two products. If this assumption is correct then the greater nucleophilic reactivity of C-2 than of C-3 at unsubstituted thiophene[20] is balanced here by the larger activation of C-3 than of C-5 at 2-methoxythiophene by the electron-donating methoxy group. The data gave $k_{Nu}/k_s \approx 2$ M^{-1} (Table 1) for partitioning of **1-PFB** between reaction with 2-methoxythiophene and solvent, calculated using eq 4, where the total yield of the nucleophile adduct, $\sum$[RNu], was obtained from the sum of the HPLC peak areas for the two products of the reaction of 2-methoxythiophene.

The reactions of **1-PFB** in 50:50 (v:v) acetonitrile/water (I = 0.50, NaClO$_4$) at 25 °C in the presence of thiophene (0.10 M), furan (0.10 M), or ethyl 1-propenyl ether (0.10 M, mixture of cis and trans isomers) resulted in no detectable formation of products of the reaction of these nucleophiles with **1-PFB** and no decrease in the yield of the solvent adduct **1-OH**, as determined by an internal standard. An upper limit of $k_{Nu}/k_s <$ 0.2 M^{-1} (Table 1) for partitioning of **1-PFB** between reaction with these alkenes and the solvent was calculated with the assumption that at least a 2% yield of the nucleophile adduct could have been detected in these experiments. This 2% detection limit is conservative and was established by inspection of HPLC chromatograms, in which peaks with 2% of the area of the solvent adduct **1-OH** were easily detected.

The low solubility of 1-cyclohexenyl trimethylsilyl ether in 50:50 (v:v) acetonitrile/water restricted our studies of this alkene to concentrations of ≤0.01 M. HPLC analysis of the products of reaction of **1-PFB** in 50:50 (v:v) acetonitrile/water (I = 0.50, NaClO$_4$) at 25 °C in the presence of 1-cyclohexenyl trimethylsilyl ether (0.01 M) showed a peak with an early retention time that was also present as a contaminant of the starting alkene. However, the yield of the solvent adduct **1-OH** remained constant when the concentration of this alkene was increased from zero to 0.01 M, and no nucleophile adducts were detected by HPLC analysis. Therefore, an upper limit of $k_{Nu}/k_s <$ 2.0 M^{-1} (Table 1) for partitioning of **1-PFB** between reaction with 1-cyclohexenyl trimethylsilyl ether and solvent was calculated with the assumption that a 2% yield of the nucleophile adduct could have been detected in these experiments.

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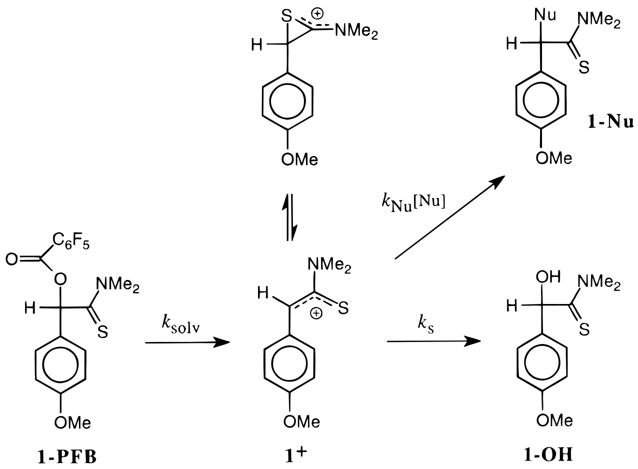
Scheme 2



Discussion

Formation and Reaction of the Carbocation Intermediate $\mathbf{1}^+$. We have shown previously that the reactions of α-(*N*,*N*-dimethylthiocarbamoyl)-4-methoxybenzyl derivatives (**1-X**) in mixed aqueous/organic solvents proceed by a $D_N + A_N$ (S_N1)[21] mechanism through the free α-thioamide-substituted 4-methoxybenzyl carbocation intermediate $\mathbf{1}^+$ (Scheme 2), and that this carbocation exhibits an exceptionally large kinetic stability and selectivity toward added nucleophilic reagents.[12,13] Therefore, the partitioning ratios determined in this work from analysis of the products of the reaction of **1-PFB** in the presence of added nucleophiles (see Results) represent rate constant ratios for partitioning of the carbocation intermediate $\mathbf{1}^+$ (Scheme 2).

The rate constant ratio for partitioning of $\mathbf{1}^+$ between reaction with azide ion and a solvent of 50:50 (v:v) acetonitrile/water ($I = 0.50$, NaClO$_4$) can be calculated from the partitioning ratios for reaction of $\mathbf{1}^+$ with azide and propionate ions and propionate ion and solvent determined in this work as $k_{\mathrm{az}}/k_{\mathrm{s}} = (k_{\mathrm{az}}/k_{\mathrm{prop}})(k_{\mathrm{prop}}/k_{\mathrm{s}}) = (840)(120\ \mathrm{M}^{-1}) = 100\ 000\ \mathrm{M}^{-1}$ (Table 1). This is similar to $k_{\mathrm{az}}/k_{\mathrm{s}} = 70\ 000\ \mathrm{M}^{-1}$ determined for partitioning of $\mathbf{1}^+$ in 50:50 (v:v) methanol/water,[12,13] with the difference reflecting the larger nucleophilicity of methanol/water than of acetonitrile/water. This very large selectivity of $\mathbf{1}^+$ toward azide ion in 50:50 (v:v) acetonitrile/water can be used to establish an upper limit of $k_{\mathrm{s}} < 5 \times 10^4\ \mathrm{s}^{-1}$ for the reaction of solvent with $\mathbf{1}^+$, because the reaction of azide ion cannot exceed the diffusion limit of $k_{\mathrm{az}} = 5 \times 10^9\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$.[22] Absolute values of $k_{\mathrm{az}} = 1.0 \times 10^7\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ and $k_{\mathrm{s}} = 230\ \mathrm{s}^{-1}$ ($k_{\mathrm{az}}/k_{\mathrm{s}} = 45\ 000\ \mathrm{M}^{-1}$) for the reaction of $\mathbf{1}^+$ in 50:50 (v:v) methanol/water have been determined directly for reactions at 20 °C, by the generation of $\mathbf{1}^+$ using laser flash photolysis of **1-PFB**, so that the reaction of azide ion with $\mathbf{1}^+$ is in fact well below the diffusion-controlled limit.[23] A value of 180 s^{-1} has been determined for the reaction of $\mathbf{1}^+$, generated by laser flash photolysis at 20 °C, with a solvent of 50:50 (v/v) acetonitrile/water.

The large selectivity of $\mathbf{1}^+$ toward azide ion in aqueous solvents ($k_{\mathrm{az}}/k_{\mathrm{s}} = 100\ 000\ \mathrm{M}^{-1}$) and the low reactivity of this carbocation ($k_{\mathrm{s}} = 180\ \mathrm{s}^{-1}$) stand in sharp contrast to the relatively small azide ion selectivities ($k_{\mathrm{az}}/k_{\mathrm{s}} \approx 100\ \mathrm{M}^{-1}$) and large rate constants for reaction with solvent ($k_{\mathrm{s}} \approx 5 \times 10^7\ \mathrm{s}^{-1}$) observed for a series of α-substituted 4-methoxybenzyl carbocations in 50:50 (v:v) trifluoroethanol/water, in which the α-substituents ranged from strongly electron-donating (α-OMe) to strongly electron-withdrawing (α-CF$_3$).[24] The remarkable kinetic stability of $\mathbf{1}^+$ may be partly or wholly due to the formation of a “closed” carbocation with sulfur bridging (Scheme 2).[13] However, the absence of neighboring group participation by the α-thioamide group in the ionization of **1-X**[13] provides good evidence that, if important, the closed species is formed *after* the initial ionization of **1-X** to give the “open” carbocation. The principle of microscopic reversibility requires that the same pathway be followed for the ionization of **1-PFB** to give $\mathbf{1}^+$ and pentaflourobenzoate ion and the addition of pentafluorobenzoate ion to $\mathbf{1}^+$ to give **1-PFB**. The reversible ionization of **1-N$_3$** is also expected to proceed through the open form of $\mathbf{1}^+$ (Scheme 2) because there is no obvious imperative that the change from an azide ion to a pentafluorobenzoate leaving group/nucleophile results in a change in the mechanism for reaction of **1-X**.

Reactivities of π-Nucleophiles. The primary goal of this work was to establish the extent of nucleophilic activation by electron-donating atoms or groups that is required for observation of the reaction of a π-nucleophile with a carbocation in aqueous solution. The relatively low solubility of alkenes in water required that the aqueous solvent used here contain 50% acetonitrile as a cosolvent. However, a change in solvent from 50:50 (v:v) acetonitrile/water to 100% water results in only very small changes in the observed first-order rate constants for the reaction of ring-substituted triarylmethyl and diarylmethyl carbocations with solvent.[25]

The relatively high reactivity of water as a nucleophile on one hand and as a Brønsted acid on the other necessarily restricted our studies to a small group of π-nucleophiles. This is because the majority of π-nucleophiles are either too unreactive (see below) to compete with the aqueous solvent for nucleophilic addition to $\mathbf{1}^+$ or they are so strongly activated that they are expected to undergo competitive protonation by water during the generation of $\mathbf{1}^+$ as an intermediate in the solvolysis of **1-PFB** in acetonitrile/water (Scheme 2).[26] This requirement that this work in aqueous solution be restricted to a small group of π-nucleophiles suggests that very low yields will be obtained from most Friedel−Crafts-type alkylation reactions in this solvent.

The activation of the π-system of pyrrole by electron donation from the annular nitrogen results in a nucleophilic reactivity at C-2 toward the carbocation $\mathbf{1}^+$ that is significantly greater than the reactivity of a solvent of 50:50 (v:v) acetonitrile/water ($k_{\mathrm{Nu}}/k_{\mathrm{s}} = 23\ \mathrm{M}^{-1}$, Table 1). Similarly, the activation of the substituted benzothiophene **2** (Scheme 1) at C-3 by electron donation from the annular sulfur and the α-nitrogen results in a highly nucleophilic species ($k_{\mathrm{Nu}}/k_{\mathrm{s}} = 70\ 000\ \mathrm{M}^{-1}$ in 50:50 (v:v) methanol/water).[12] The annular sulfur and α-oxygen of 2-methoxythiophene provide a smaller activation of the π-system of 2-methoxythiophene, and the reactivity of this carbon nucleophile is similar to that of solvent ($k_{\mathrm{Nu}}/k_{\mathrm{s}} \approx 2\ \mathrm{M}^{-1}$, Table

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[21] Guthrie, R. D.; Jencks, W. P. *Acc. Chem. Res.* **1989**, *22*, 343−349.

[22] McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1991**, *113*, 1009−1014.

[23] McClelland, R. A. Personal communication.

[24] Amyes, T. L.; Stevens, I. W.; Richard, J. P. *J. Org. Chem.* **1993**, *58*, 6057−6066.

[25] McClelland, R. A.; Kanagasabapathy, V. M.; Steenken, S. *J. Am. Chem. Soc.* **1988**, *110*, 6913−6914. McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 3966−3972.

[26] For example, the first-order rate constant for the protonation of 1,1-dimethoxyethene by water at 25 °C is $5.9 \times 10^{-2}\ \mathrm{s}^{-1}$ [Kresge, A. J.; Leibovitch, M. *J. Am. Chem. Soc.* **1992**, *114*, 3099−3102] and the corresponding rate constants for protonation of simple enamines range from $10^{-3}\ \mathrm{s}^{-1}$ to $\geq 80\ \mathrm{s}^{-1}$ [Keeffe, J. R.; Kresge, A. J. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1994]. By comparison, the rate constant for solvolysis of **1-PFB** in 50:50 (v:v) methanol/water ($I = 0.50$, NaClO$_4$) at 25 °C is $k_{\mathrm{solv}} = 5.3 \times 10^{-3}\ \mathrm{s}^{-1}$.[13]

1). By contrast, electron donation from the lone annular sulfur at thiophene does not result in a π-nucleophile that is sufficiently nucleophilic to compete with solvent for addition to $\mathbf{1}^+$ ($k_{Nu}/k_s < 0.2$ M^{-1}, Table 1). Similarly, the following π-nucleophiles, each of which are activated by only a single oxygen, are insufficiently nucleophilic to compete with a solvent of 50:50 (v:v) acetonitrile/water for addition to $\mathbf{1}^+$ (Table 1): furan ($k_{Nu}/k_s < 0.2$ M^{-1}); 1-cyclohexenyl trimethylsilyl ether (a representative silyl enol ether, $k_{Nu}/k_s < 2$ M^{-1}); and ethyl 1-propenyl ether (a representative vinyl ether, $k_{Nu}/k_s < 0.2$ M^{-1}).

The partitioning ratio $k_{Nu}/k_s = 23$ M^{-1} for reaction of pyrrole and solvent with $\mathbf{1}^+$ in 50:50 (v:v) acetonitrile/water can be combined with [H_2O] = 27.8 M in this solvent to give the dimensionless ratio of second-order rate constants $k_{Nu}/k_{HOH} = 640$ (Table 1). Thus, despite the lower Brønsted basicity of pyrrole (p$K_a = -3.8$)[27] than of water (p$K_a = -1.7$), C-2 of pyrrole is 640-fold more reactive than water toward $\mathbf{1}^+$. This is consistent with the known preference of "soft" acids and bases (e.g., $\mathbf{1}^+$ and the π-system of pyrrole) and "hard" acids and bases (e.g., the proton and water) to react with one another, and it can be rationalized within the framework developed to explain this general trend of organic and inorganic reactivity.[28]

The partitioning of the benzyl carbocation, generated from the decomposition of *N*-benzyl-*N*-nitrosobenzamide or the protonation of phenyldiazomethane by benzoic acid, between nucleophilic addition of solvent and trapping by benzoate ion within an ion pair results in a higher yield of the solvent adduct in a solvent of pyrrole than in a solvent of methanol.[29] This observation is in qualitative agreement with the results reported here that pyrrole is more reactive than the hydroxylic solvent water toward $\mathbf{1}^+$. However, despite the early report of the facile formation of pyrrole adducts from the reaction of triarylcarbinols with pyrrole in acetic acid,[30] there have been surprisingly few reports of the preparation of benzylated pyrroles via nucleophilic addition of pyrrole to carbocations generated in nucleophilic media.

A comparison of the upper limits on the rate constant ratios k_{Nu}/k_{HOH} for the reaction of representative vinyl and silyl enol ethers and water with $\mathbf{1}^+$ in 50:50 (v:v) acetonitrile/water (Table 1) with the corresponding rate constant ratios calculated from the second-order rate constants determined for reaction of these alkenes and water with ring-substituted diarylmethyl carbocations generated by laser flash photolysis in acetonitrile[11] shows that the change from an aqueous solvent to acetonitrile results in either little change or in an increase in k_{Nu}/k_{HOH}. For example, the values of $k_{Nu} = 1.3 \times 10^8$ M^{-1} s^{-1} for the reaction of 1-cyclohexenyl trimethylsilyl ether[11] and $k_{HOH} = 4.3 \times 10^6$ M^{-1} s^{-1} for the reaction of water[25] with the diarylmethyl carbocation $(4\text{-MeAr})_2CH^+$ give $k_{Nu}/k_{HOH} = 30$, which is consistent with $k_{Nu}/k_{HOH} < 60$ in 50:50 (v:v) acetonitrile/water determined in this work (Table 1). Similarly, $k_{Nu}/k_{HOH} \approx 6$ estimated for reaction of a 1:1 mixture of the cis and trans isomers of ethyl 1-propenyl ether and water with $(4\text{-ClAr})_2CH^+$ [31] is consistent with $k_{Nu}/k_{HOH} < 6$ in an aqueous solvent (Table 1).

Structure−Reactivity Correlations. Mayr and co-workers have shown that most or all of the rate constants, k_{Nu}, for the activation-limited reactions of nucleophilic reagents with resonance-stabilized carbocations show a good fit to a three-parameter equation (eq 5).[2] In this equation, N is the Mayr nucleophilicity parameter, E is the electrophilicity parameter, which has an arbitrary value of 0 for the bis(4-methoxyphenyl)-methyl carbocation, and s is the sensitivity of the nucleophilic addition reaction to changes in the sum of E and N, which has an arbitrary value of 1 for the "standard" alkene 2-methyl-1-pentene.[2] Equation 6 describes the *constant* selectivity relationship for electrophile−nucleophile combination reactions established by Ritchie,[32] where k_s is the rate constant for reaction of the electrophile with water (or an aqueous solvent) and N_+ is the Ritchie nucleophilicity parameter. The relatively unreactive carbocation $\mathbf{1}^+$ is expected to adhere, at least approximately, to the Ritchie N_+ scale, provided its reactions with nucleophiles are activation limited, with rate constants below the diffusion-controlled limit. This criterion is met for the alkenes examined in this work, because the selectivities k_{Nu}/k_s (M^{-1}) for their reaction with $\mathbf{1}^+$ in 50:50 (v:v) acetonitrile/water are at least 10^3-fold smaller than $k_{az}/k_s = 100\,000$ M^{-1}, and the rate constant for the reaction of $\mathbf{1}^+$ with azide ion in 50:50 (v:v) methanol/water is $k_{az} = 1.0 \times 10^7$ M^{-1} s^{-1}.[23]

$$\log k_{Nu} = s(E + N) \tag{5}$$

$$\log (k_{Nu}/k_s) = N_+ \tag{6}$$

$$N = \frac{N_+ + \log k_s - sE}{s} \tag{7}$$

$$N_{calc} = N_+ + 5.8 \tag{8}$$

Equations 5 and 6 can be combined to give eq 7, which relates the Mayr and the Ritchie scales of nucleophilicity. The reactivity of the bis(4-methoxyphenyl)methyl carbocation, for which $E = 0$, toward a solvent of 1:2 (v:v) acetonitrile/water is $k_s = 1.3 \times 10^5$ s^{-1},[25] which is somewhat larger than $k_s = 180$ s^{-1} for the reaction of $\mathbf{1}^+$ with a solvent of 50:50 (v:v) acetonitrile/water.[23] These values of k_s can be substituted into the expressions given by eq 5 for the reactions of $\mathbf{1}^+$ and the bis(4-methoxyphenyl)methyl carbocation to give $E = [\log (180/(1.3 \times 10^5))]/0.80 = -3.57$ as the electrophilicity parameter for $\mathbf{1}^+$, where $s = 0.80$ is the sensitivity parameter for reaction of the nucleophile water.[2] The values of $\log k_s = 2.26$ and $E = -3.57$ for $\mathbf{1}^+$, together with $s = 1.0$ determined for the reactions of many π-nucleophiles,[2] can then be substituted into eq 7 to give eq 8.[33] This equation provides values of N_{calc}, the estimated Mayr nucleophilicity parameter for the reaction of π-nucleophiles with the carbocation $\mathbf{1}^+$ in the *aqueous* solvent 50:50 (v:v) acetonitrile/water (Table 1).

The selectivity of $\mathbf{1}^+$ for reaction with pyrrole ($k_{Nu}/k_s = 23$ M^{-1}, Table 1) gives an estimated value of $N_+ = 1.4$ for this π-nucleophile (eq 6) that can be substituted into eq 8 to give $N_{calc} = 7.2$ as the estimated Mayr nucleophilicity parameter for pyrrole in an aqueous solvent (Table 1). This is in good

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[27] Chiang, Y.; Whipple, E. B. *J. Am. Chem. Soc.* **1963**, *85*, 2763. The thermodynamically favored position of protonation of pyrrole is C-2: Joule, J. A.; Smith, G. F. *Heterocyclic Chemistry*; Van Nostrand: London, 1972; pp 194−195.

[28] *Hard and Soft Acids and Bases*; Pearson, R. G., Ed.; Dowden, Hutchinson and Ross: Stroudsberg, PA, 1973. Pearson, R. G. *Chemical Hardness*; John Wiley & Sons: New York, 1997.

[29] Darbeau, R. W.; White, E. H. *J. Org. Chem.* **1997**, *62*, 8091−8094.

[30] Khotinsky, E.; Patzewitch, R. *Ber.* **1909**, *42*, 3104−3106.

[31] Calculated using $k_{Nu} = 1 \times 10^9$ M^{-1} s^{-1} for reaction of a mixture of the *cis* and trans isomers of ethyl 1-propenyl ether, which is an average of the values of $k_{Nu} = 7.7 \times 10^8$ M^{-1} s^{-1} and $k_{Nu} = 1.3 \times 10^9$ M^{-1} s^{-1} for reaction of the cis and trans isomers, respectively, and $k_{HOH} = 1.7 \times 10^8$ M^{-1} s^{-1}.[11]

[32] Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348−354. Ritchie, C. D. *Can. J. Chem.* **1986**, *64*, 2239−2250.

agreement with $N = 7.3$ that can be calculated[34] from data for the reaction of pyrrole with the tricarbonylcyclohexadienyliron cation in nitromethane,[2,35] but is somewhat larger than $N = 6.2$ for *N*-methylpyrrole,[34] whose nucleophilic reactivity should be similar to that of pyrrole.

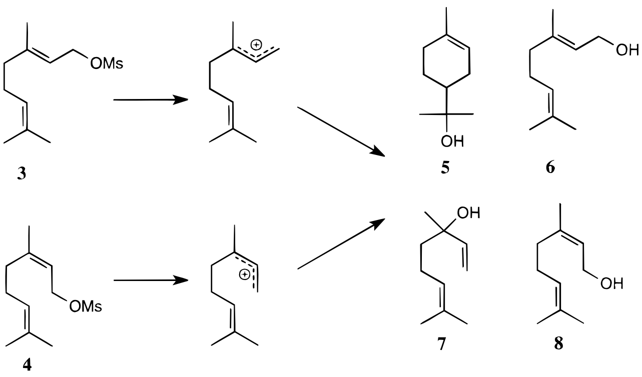
The value of log $(k_{az}/k_s) = 5.0$ for partitioning of $\mathbf{1}^+$ between reaction with azide ion and solvent is smaller than the value of log $(k_{az}/k_s) = 6.0$ determined for partitioning of the bis(4-methoxyphenyl)(4-methylphenyl)methyl carbocation in 1:2 (v:v) acetonitrile/water, for which $k_s = 86\ \mathrm{s}^{-1}$.[22] The small difference in the selectivities of these two carbocations, which show similar chemical reactivities toward addition of solvent, is not understood. A similar proportional difference in the values of the nucleophile selectivities log (k_{Nu}/k_s) [Nu = pyrrole] for the reactions of $\mathbf{1}^+$ and carbocations which follow the N_+ scale is possible, but would not result in a large change in the value of N_{calc} for the reaction of pyrrole calculated from eq 8.

The data in Table 1 give $N_+ \approx 0.3$ (eq 6) and $N_{calc} \approx 6.1$ (eq 8) for 2-methoxythiophene and $N_+ = 4.8$ and $N_{calc} = 10.6$ for the strongly activated π-nucleophile **2**.[12] By contrast, thiophene and furan, and the representative enol ethers and silyl enol ethers examined in this work, are too weakly nucleophilic to compete with the aqueous solvent 50:50 (v:v) acetonitrile/water to give detectable yields of the corresponding adducts to $\mathbf{1}^+$. However, the upper limits on the values of N_{calc} for these nucleophiles in an aqueous solvent (Table 1) are consistent with the Mayr parameters *N* for these nucleophiles in organic solvents.[2]

The derivation of eq 8 from Ritchie's N_+ in eq 6 and Mayr's in eq 5 assumes that the change from the solvent water used in the development of the N_+ scale to the organic solvents used in the development of the *N* scale has no effect on nucleophile selectivity (k_{Nu}/k_s). The fair agreement between the values of $N_{calc} = 7.2$ for pyrrole calculated in this work using data for reactions in water and $N = (6.2-7.3)$ determined for reactions in organic solvents provides support for this assumption, and for the suggestion of Mayr that the rate constants for reactions of π-nucleophiles with carbocations are not strongly affected by the change from nonpolar organic solvents to water.[2] These data are consistent with the conclusion that the relative activation barrier for addition of π-nucleophiles to carbocations is insensitive to the polarity and hydrogen-bonding properties of the solvent, and that the dispersion of positive charge that occurs on proceeding from the carbocation and π-nucleophile reactants to the transition state for the nucleophilic addition does not result in a large differential stabilization of these species by interaction with the polar protic solvent water.

There is only a relatively small difference in the second-order rate constants for addition of water to the benzhydryl carbocation in acetonitrile ($k_{HOH} = 1.2 \times 10^8\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$)[11] and for the nucleophile addition reaction in 2/1 (v/v) water/acetonitrile ($k_{HOH} = k_s/[\mathrm{HOH}] = 9 \times 10^8\ \mathrm{s}^{-1}/37\ \mathrm{M} = 2.4 \times 10^7\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$).[25] This shows that the aqueous solvent provides nearly equal stabilizing solvation of the reactants (water and $\mathrm{Ph_2CH^+}$) and the transition state for nucleophile addition so that there is only a small solvent effect on the barrier for formation of this transition state. Similarly, the change from aqueous to organic solvents has a relatively small effect on the rate constants for concerted Diels−Alder reactions of alkenes.[36]

Scheme 3



Intramolecular Reactions of Alkenes. The solvolysis of geranyl methanesulfonate (**3**) in 9:1 (v:v) acetone/water proceeds by a stepwise $\mathrm{D_N} + \mathrm{A_N}$ mechanism[21] through an allylic carbocation intermediate that partitions to give a 17% yield of α-terpineol (**5**), via intramolecular nucleophilic addition of the trisubstituted alkene to the cationic center, and a total yield of 83% of the products of the direct nucleophilic addition of solvent without cyclization (3% of **8**, 27% of **6**, and 53% **7**).[37] The conversion of **3** to **5** and **8** with net *cis*−*trans* isomerization of the C-2 alkene provides strong evidence for formation of an allylic carbocation intermediate that is sufficiently long-lived to undergo rotation about the C2−C3 bond. The solvolysis of neryl methanesulfonate (**4**) under the same conditions gives an even larger yield of 45% of **5**.[37] These results show that the barriers for the intramolecular nucleophilic addition of an alkene and the bimolecular addition of an aqueous solvent to an allylic carbocation are similar.

By contrast, our data show that a threshold value of $N \approx 6$ is required for observation of alkene nucleophile adduct in mostly aqueous solvents, so that trisubstituted alkenes, which have relatively small Mayr nucleophilicities (e.g., $N = 0.70$ for 2-methyl-2-butene),[2] are far too weakly nucleophilic to compete with an aqueous solvent for intermolecular reactions with stable carbocations that follow the Ritchie N_+ scale. The observed intramolecular trapping of an allylic carbocation by a weakly nucleophilic trisubstituted alkene (the formation of **5** from **3** or **4**, Scheme 3)[37] is therefore consistent with a large "effective molarity" for this nucleophilic alkene addition reaction[38] and, possibly, to a decrease in the selectivity of the highly reactive allylic carbocation[39] toward solvent and the alkene due to a Hammond effect.[7,16]

Summary. Only a limited set of highly nucleophilic π-nucleophiles are sufficiently reactive to compete with an aqueous solvent of 50:50 (v:v) acetonitrile/water for nucleophilic addition to the moderately stable carbocation $\mathbf{1}^+$ (Table 1), and only small yields of the nucleophile adduct are observed for π-nucleo-

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[33] This analysis is complicated by the uncertainty in the fraction of $\mathbf{1}^+$ that is present in the "open" and "closed" forms (Scheme 2). The limits $1.0 \geq f_{open} \geq 0.002$ can be set for the fraction of $\mathbf{1}^+$ in the open form, where $f_{open} = 1.0$ is the value assumed in the derivation of eq 8. The lower limit of $f_{open} \geq 0.002$ was calculated from the *limiting* rate constant $k_{az} = 5 \times 10^9\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ for the diffusion-controlled reaction of azide ion with carbocations[22] and the *observed* rate constant $k_{az} = 1 \times 10^7\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ for the reaction of azide ion with $\mathbf{1}^+$.[23] If $f_{open} = 0.002$, then the rate constant for the reaction of solvent with the open carbocation is $k_s = 180\ \mathrm{s}^{-1}/0.002 = 9.0 \times 10^4\ \mathrm{s}^{-1}$, $E \approx 0$ for $\mathbf{1}^+$ and the expression for eq 8 becomes $N_{calc} = N_+ + 5.0$. However, the resulting uncertainty in the values of N_{calc} (±0.4 unit) does not affect any of our interpretations.

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[38] Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183−278.

[39] The value $k_s = 4 \times 10^9\ \mathrm{s}^{-1}$ for reaction of an allylic carbocation with a solvent of 1:3 (v:v) acetonitrile/water [Thibblin, A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 313−319] is much larger than the values of k_s for the stable carbocations that follow the Ritchie N_+ scale.[32]

philes with Mayr nucleophilicities smaller than $N \approx 6$. This would include all simple aliphatic alkenes, substituted benzenes, simple enol ethers and most silyl enol ethers, and simple allyl stannanes and allyl silanes.[2] Our data also show that the proposed relationship (eqs 7 and 8) between the Ritchie N_+ scale of nucleophilicity in aqueous solution and the Mayr N scale of nucleophilicity in organic solvents holds for nucleophile addition reactions of pyrrole.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (GM 39754). We are grateful to Herbert Mayr for advice on the use of the N scale for correlations of nucleophile reactivity, to R. A. McClelland for his determination of the rate constant for reaction of $\mathbf{1}^+$ with 50:50 (v/v) acetonitrile/water, and to Tina Amyes for helpful discussion.

JA981842P