a significant difference between the effect of the $-C{=}O^{+}-$ group and the $-C{=}C-$ group. The energy differences between the five- and six-membered rings are similar to those observed by Sorensen.[26]

The substituent effect indicated by the relative heat of formation of the 1,3-dimethyltetrahydrofuranonium ion IX is not easy to rationalize. The heat of formation is 3.1 kcal/mol less exothermic than that of the corresponding 1,3,3-trimethyl-substituted ion VII after correcting for the difference in energy of the olefinic bond in the starting esters. Thus replacing a hydrogen in the 3 position by a methyl increases the stability of the ion by 3.1 kcal/mol in spite of a steric interaction expected to decrease the stability by *ca.* 0.4 kcal/mol. Thus there must be a net inductive and/or resonance stabilization of about 3.5 kcal/mol. Replacing the 2-hydrogen in 4,4-dimethyldioxolenium ion by a methyl group results in an increased stabilization of 3.6 kcal/mol (see Table I). It is hard to see why a 3-methyl group in the monooxonium ion should have as large a stabilizing effect as a 2-methyl group in the dioxolenium ion.

It is also of interest that formation of the monooxonium ions from ketones is more exothermic than formation of the dioxonium ions by 2–4 kcal/mol. The ion with the charge spread over two oxygen atoms is expected to be thermodynamically more stable. We believe this apparent contradiction is due to a greater increase in the stabilization of the ground-state ester than of the ion when a methylene group is replaced by an oxygen. The difference in heats of formation (gas phase) of 2-pentanone and ethyl acetate is 44.04 kcal/mol[30] with ethyl acetate being more stable. If replacing the methylene group in the 5 position in ion VII by an oxygen yielding ion V increases the stability of the ion by *ca.* 40 kcal/mol, the relative heats of formation will be as observed. The heat of protonation of ethyl acetate is larger than that for 2-pentanone, by 0.6 kcal/mol,[31] and can be rationalized on the same basis. Arnett[31] has rationalized the decrease in heat of protonation as alkyl groups are replaced by phenyl using a similar argument.

There are many unexpected substituent effects on the stability of the oxonium ions discussed here. It is obvious that many factors not explicitly considered in the rationalization of substituent effects on solvolytic reactivities must be playing a significant role in stable ions in strong acid media. The substituent effects on the stabilities of cations observed in strong acids are large, and the development of the calorimetric technique means that a variety of systems not readily studied using acidity function techniques can be handled nicely. Our studies of the relative heats of formation of a variety of cationic systems are proceeding in order to explore some of these substituent effects.

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(31) Table I, footnote *b*.

Protolysis Kinetics of *N*-Benzyl-*N'*-methylurea

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Abstract: Protolysis of the title compound is specific acid–base catalyzed and the rate constants are reported. Both NH groups are base catalyzed to the same extent, but differ under acid catalysis. Acid and base catalysis of the title compound is explained qualitatively on the basis of polar substituent effects (σ^*) and steric effects (E_s). The energy of activation for protolysis was only obtainable under basic conditions and is reported. The protolysis kinetics of *N*-methylpropionamide under identical conditions is reported and is used as a comparison.

The study of proton exchange kinetics of NH-bearing compounds has provided a number of examples of compounds differing in mechanism and rates of protolysis.[1–6] Steric and polar influences of proton exchange, however, have not been extensively studied. This paper reports our study of the protolysis kinetics of *N*-benzyl-*N'*-methylurea, a compound whose two NH groups exhibit protolysis kinetic differences as a result only of influences by their respective substituents. The title compound allows one to qualitatively assess steric and polar influences on NH exchange rates. To our knowledge no similar study has been reported, nor has the protolysis of a disubstituted urea previously been reported.

In this paper the technique employed was to follow by high-resolution pmr the rate of collapse of the NCH_3 and NCH_2 doublets as a function of pH. The methyl and methylene doublets arise from coupling by the protons of the urea nitrogens which becomes discernible under slow proton exchange conditions. *N*-Methylpropionamide was also studied under the same conditions for comparison. Rate constants for acid- and base-catalyzed protolysis of the title compound and the

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Table I. Rate Constants[a] for NH Proton Exchange and Energies of Activation[b]

Compound	k_{-OH}, M^{-1} sec^{-1}	k_{H^+}, M^{-1} sec^{-1}	E_a (base), kcal/mol
$CH_3NHCO\mathit{NH}CH_2Ph$	$2.45 \pm 2.0 \times 10^4$	$3.31 \pm 1.16 \times 10^5$	7.37 ± 0.7
$CH_3\mathit{NH}CONHCH_2Ph$	$2.45 \pm 2.0 \times 10^4$	$2.41 \pm 0.90 \times 10^6$	7.37 ± 0.7
$CH_3CH_2CONHCH_3$	$2.78 \pm 0.140 \times 10^5$	$6.33 \pm 0.58 \times 10^2$	

[a] Rate constants were determined on 0.5 M solutions in 16 mol % *tert*-butyl alcohol in CO_2-free water at 34°. [b] Energies of activation were not obtainable under acidic conditions for either compound or basic conditions for the amide because of decomposition at elevated temperatures.

comparison amide were obtained, and the influences of steric and polar effects on the observed catalyzed protolysis rate constants are discussed.

Experimental Section

Nmr Spectra. All spectra in this study were obtained in the frequency sweep–external lock mode on a Hitachi Perkin-Elmer R20A high-resolution nmr spectrometer operating at 60 MHz, and equipped with a variable temperature probe and digital frequency counter. All spectra except those used to determine energy of activations were determined at 34 ± 1°. All temperatures are within ±1° and were calibrated with ethylene glycol. Spectra were determined at 30 Hz sweep width and 1000-sec sweep time. Instrument settings were checked to assure saturation did not occur; homogeneity was adjusted every other spectrum.

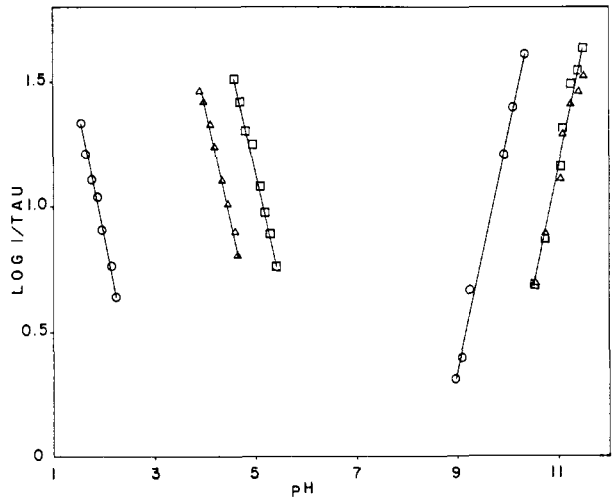

Figure 1. Log rate of proton exchange *vs.* pH: ○, 0.5 M $CH_3CH_2CO\mathit{NH}CH_3$ in 16 mol % *tert*-butyl alcohol in CO_2-free water; △, 0.5 M $C_6H_5CH_2\mathit{NH}CONHCH_3$ in 16 mol % *tert*-butyl alcohol in CO_2-free water; □, 0.5 M $C_6H_5CH_2NHCO\mathit{NH}CH_3$ in 16 mol % *tert*-butyl alcohol in CO_2-free water.

pH. pH measurements were determined with a Corning triple purpose Ag|AgCl electrode and a satured KCl reference electrode; the pH is assumed to be $-\log [H^+]$. NBS buffers were used as calibration standards. All pH measurements were obtained for solutions of the compounds studied in 16 mol % *tert*-butyl alcohol in CO_2-free water and are unbuffered. The pH of the solution was varied with HCl or KOH in the aforementioned solvent. Measurements were determined under argon in a water-jacketed vessel at 34 ± 0.5°, and at higher temperatures when E_a's were determined.

Solutions. The amide and disubstituted urea were studied as 0.5 M solutions in 16 mol % *tert*-butyl alcohol (Matheson Coleman and Bell analytical grade) in CO_2-free water. CO_2-free water was obtained by boiling triple-distilled water for 0.5 hr and cooling under argon previously passed through a soda–lime tower. All solutions were used within 3 hr of their making.

Calculations. Peak–valley ratios of collapsing doublets, or bandwidths at half intensity, were utilized to calculate τ values. Values of τ were computed from individual spectra using an IBM 360/65 computer programmed with the general equations of Arnold,[7] and are corrected for T_2; T_2's were obtained from the NCH_3 and NCH_2 line widths under slow proton exchange conditions and are limited by field inhomogeneity.

***N*-Benzyl-*N'*-methylurea.** To a solution of benzylamine in anhydrous ether at room temperature was added dropwise a 50% excess of methyl isocyanate. The resulting white precipitate was filtered and recrystallized from hot water until free of contaminants in the nmr; mp 97–98°.

***N*-Methylproplonamide.** The amide was obtained commercially (Eastman reagent grade), determined to be pure in the nmr, and used without further purification.

Results

Both *N*-benzyl-*N'*-methylurea and *N*-methylpropionamide were studied as 0.5 M solutions in 16 mol % *tert*-butyl alcohol in CO_2-free water. A least-squares plot of log $1/\tau$ *vs.* pH is shown in Figure 1 where the protolysis rate constants are equal to $[H^+]$ at the intercepts. The acid- and base-catalyzed rate constants are reported in Table I. The observed linear plots in Figure 1 indicate that exchange is pseudo-first-order with respect to $[H_3{}^+O]$ since water was in large excess.

The effect of concentration of the disubstituted urea on the protolysis constants could not be ascertained due to the insolubility of the compound at higher solute concentrations. However, bimolecular catalysis is not predicted with the title compound since Vold[8] and coworkers have shown that with concentrations of urea in water up to 2 M protolysis is independent of urea concentration. A similar finding has been observed with a structurally similar carbamate.[9] Catalysis by the alcohol could not be ascertained because of insolubility of the urea at lower alcohol concentrations and nonreproducibility of values at higher alcohol concentrations. The contribution of alcohol to the protolysis rate constants is probably not large since alcohol is present only to the extent of 16 mol % and exchange was observed to be slow in the absence of acid or base. The observed slow exchange in the absence of acid or base also effectively rules out intramolecular catalysis as being a significant contributor to the protolysis constants.

The exchange of both NH groups of *N*-benzyl-*N'*-methylurea is specific acid and base catalyzed. In the presence of base, k_{-OH}'s for NH(methyl) and NH(benzyl) are not significantly different, while in the presence of H_3O^+ the k_{+H}'s differ with the $NH(CH_3)$ exchanging faster by nearly a factor of 10. Under acidic conditions exchange in *N*-methylpropionamide is considerably less (a factor of 10^2–10^3) than exchange observed with the title compound. Base-catalyzed exchange in the amide is larger than that observed in the urea (by a factor of 10).

A plot of log $1/\tau$ *vs.* temperature at a fixed pH yields the energies of activation (E_a) reported in Table I. Ac-

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tivation energies could not be obtained under acidic or basic conditions for the amide or acidic conditions for the urea due to decomposition at elevated temperatures.

Discussion

It can be reasoned that the difference in acid-catalyzed rate constants for $NH(CH_3)$ and $NH(CH_2)$ is due to differences in the inductive[10a] nature of methyl and benzyl substituents and to differences in their steric bulk.[10b] Under basic conditions the NH(benzyl) was expected to exhibit faster exchange than NH(methyl) due to the enhanced electronegativity of the benzyl group decreasing the availability of the lone-pair electrons on nitrogen by induction. The observed identical base-catalyzed protolysis rate constants for the two NH groups must therefore be due to factors other than polar influences. The greater steric bulk of the benzyl group compared to methyl can account for the observed base-catalyzed rate constants. The expected inductive enhancement of protolysis by the greater electronegativity of the benzyl group is offset by its larger bulk which sterically retards base removal of the proton from the adjacent urea nitrogen.

Under acid-catalyzed conditions, however, the greater electron-withdrawing and greater steric effects of the benzyl group will act in concert to reduce the proton exchange rate of the NH(benzyl) compared to the NH(methyl). The inductive electron-withdrawing effect of the benzyl compared to the methyl reduces availability of the lone-pair electrons, thus decreasing the proportion of protonated NH(benzyl) species (eq 1), a proposal

$$PhCH_2NHCNHCH_3 \overset{H_3O^+}{\rightleftharpoons} PhCH_2\overset{H}{\overset{|}{N}}CNHCH_3 \qquad (1)$$

similar to that postulated for exchange in amide[11] and carbamates.[9] A similar protonated species was proposed for urea.[8] In addition to inductive effects, greater steric hinderance to NH(benzyl) protonation also reduces the amount of protonated NH(benzyl) compared to $NH(CH_3)$.

From the acid-catalyzed rate constants (k_{H^+}) it is clear the two urea NH groups are more basic than the amide NH. Further evidence of this fact can be seen when under basic conditions the amide NH exchanges faster than either of the urea NH's when measured at the same pH.

A quantitative assessment of steric and polar influences on the NH proton exchange kinetics in the title compound cannot be made from this study. It is clear qualitatively, however, that steric and polar influences on NH proton exchange do occur and that they affect the kinetics in a predictable manner.

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Stereoselective Total Synthesis of (±)-Seychellene

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Abstract: An efficient, highly stereoselective total synthesis of the racemic form of the tricyclic sesquiterpene seychellene (**1**) is described. Conversion of the well-known Wieland–Miescher ketone **8** into the keto tosylate **6** was accomplished in 15 steps. Base-promoted intramolecular alkylation of **6** afforded, in high yield, the tricyclic ketone (±)-norseychellanone (**4**), which was readily converted into (±)-seychellene.

The structurally novel sesquiterpene (−)-seychellene (**1**) is a minor component of commercial patchouli oil, which is derived from *Pogostemon patchouli* Pallet *var. suavis* Hook. The isolation of this natural product was first reported in 1967 by Hirose, *et al.*,[2] while the structural and stereochemical elucidation was elegantly accomplished by Wolff and Ourisson.[3] Structurally and biogenetically, (−)-seychellene (**1**) is obviously closely related to the well-known sesquiterpenoid patchouli alcohol (**2**),[4] with which it cooccurs. We report in this paper[5] a total synthesis of (±)-**1** *via* a highly stereoselective route which fully corroborates the structural and stereochemical assignments.[3]

A careful analysis of the structure of seychellene (**1**) reveals a number of possible "key" reactions which might be employed in the construction of the required tricyclic carbon skeleton. One possibility which we considered, for example, was the intramolecular alkylation of an intermediate such as the bicyclic ketone **3**. This reaction, if successful, would produce (±)-norsey-

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