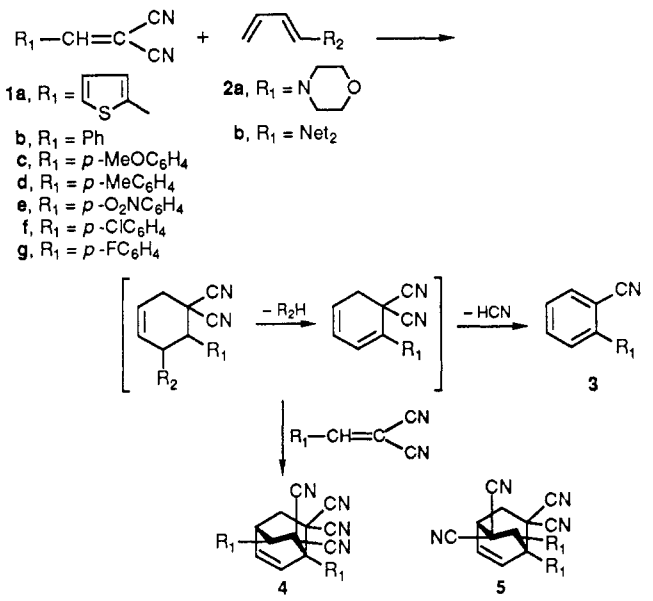
Scheme I



Experimental Section

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Bruker 300-MHz and Varian 60-MHz spectrometers, and chemical shift values are recorded in δ units (parts per million) relative to tetramethylsilane as internal standard. ^{13}C NMR spectra were obtained with proton-noise decoupling and proton-coupling on Bruker 300-MHz instrument, and chemical shifts are expressed relative to internal standard tetramethylsilane in $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer 237B IR spectrometer in potassium bromide disks. Mass spectra were recorded on a AEI MS30 instrument.

Ylidenemalononitriles **1** were prepared by condensing corresponding aldehyde with malononitrile.[6]

Dienamines **2** were prepared by condensing freshly distilled crotonaldehyde with freshly distilled corresponding secondary amine.

General Procedure for the Synthesis of Biaryl-2-carbonitriles. 2-(2-Thienyl)benzonitrile (3a). The solution of 2-thienylidenemalononitrile (**1a**) (1.60 g, 10 mmol) in dry benzene (20 mL) was added dropwise to the stirred solution of 4-(1,3-butadienyl)morpholine (**2a**) (1.39 g, 10 mmol) in dry benzene (10 mL) at room temperature under nitrogen blanket. Stirring was continued further for 24 h at room temperature. Benzene was then removed under reduced pressure, and the pasty material left was purified by column chromatography (silica gel, benzene) and recrystallized (hexane–benzene, 5:1) to afford 1.48 g (80%) of **3a** as bright red crystals, mp 160–161 °C. Reaction of **1a** with *N,N*-diethyl-1,3-butadienylamine (**2b**) under similar conditions yielded **3a** in 75% yield: IR (KBr) 2240 (C≡N), 1480, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.85–7.60 (m, 7 H); ^{13}C NMR ($CDCl_3$) δ 112.0, 118.7, 126.0, 126.2, 127.7, 127.9, 128.0, 132.5, 132.8, 137.8, 155.4; mass (M^+) 185. Anal. Calcd for $C_{11}H_7NS$: C, 71.32; H, 3.81; N, 7.56. Found: C, 71.40; H, 3.80; N, 7.50.

1,1′-Biphenyl-2-carbonitrile (3b). Benzylidenemalononitrile (**1b**) (1.54 g, 10 mmol) reacted with 4-(1,3-butadienyl)morpholine **2a** (1.39 g, 10 mmol) in benzene (as above). Chromatography (hexane) yielded 1,1′-biphenyl-2-carbonitrile (**3b**) (1.16 g, 65%) as light yellow oil, which crystallized on storing in cooling condition, mp 35–37 °C (lit.[2a] mp 26–36.5 °C).

4′-Methoxy-1,1′-biphenyl-2-carbonitrile (3c). (4′-Methoxybenzylidene)malononitrile (**1c**) (1.84 g, 10 mmol) reacted with 4-(1,3-butadienyl)morpholine (**2a**) (1.39 g, 10 mmol) in dry benzene (as above). Chromtographic purification (hexane) afforded biphenyl-2-carbonitrile (**3c**) (1.57 g, 75%) as crystalline solid: mp 156–157 °C; IR 2235, 1580, 1450, 755 cm^{-1}; ^1H NMR δ 3.82 (s, 3 H), 6.86–7.68 (m, 8 H); mass (M^+) 209. Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.29; N, 6.69. Found: C, 80.30; H, 5.31; N, 6.60.

4′-Methyl-1,1′-biphenyl-2-carbonitrile (3d). (4′-Methylbenzylidene)malononitrile (**1d**) (1.68 g, 10 mmol) reacted with 4-(1,3-butadienyl)morpholine (**2a**) (1.39 g, 10 mmol) in dry benzene (as above) to afford biphenyl-2-carbonitrile (**3d**) (1.43 g, 74%) as a crystalline solid, mp 120–121 °C, after chromatographic purification (hexane): IR 2240, 1590, 1465, 750 cm^{-1}; ^1H NMR δ 2.36 (s, 3 H), 6.85–7.70 (m, 8 H); mass (M^+) 193. Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.19; H, 5.70; N, 7.40.

4′-Nitro-1,1′-biphenyl-2-carbonitrile (3e). (4-Nitrobenzylidene)malononitrile (**1e**) (1.99 g, 10 mmol) reacted with 4-(1,3-butadienyl)morpholine (**2a**) (1.39 g, 10 mmol) in dry benzene (as above) to afford biphenyl-2-carbonitrile (**3e**) (1.45 g, 65%) as crystalline solid, mp 179–180 °C, after chromatographic purification (hexane–benzene, 10:1): IR 2240, 1600, 1520, 755 cm^{-1}; ^1H NMR δ 7.25–7.63 (m, 6 H), 8.22 (m, 2 H); mass (M^+) 224. Anal. Calcd for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.59; N, 12.49. Found: C, 69.80; H, 3.47; N, 12.53.

4′-Chloro-1,1′-biphenyl-2-carbonitrile (3f). Reaction of (4-chlorobenzylidene)malononitrile (**1f**) (1.88 g, 10 mmol) with 4-(1,3-butadienyl)morpholine (**2a**) (1.39 g, 10 mmol) in dry benzene (as above), after chromatographic purification, yielded biphenyl-2-carbonitrile (**3f**) (1.66 g, 78%) as crystalline solid, mp 115–116 °C (lit.[2a] mp 113–115 °C) and IR, NMR dcata same as reported.

4′-Fluoro-1,1′-biphenyl-2-carbonitrile (3g). Reaction of (4-fluorobenzylidene)malononitrile (**1g**) (1.72 g, 10 mmol) with 4-(1,3-butadienyl)morpholine **2a** (1.39 g, 10 mmol) in dry benzene (as above) after chromatographic purification yielded biphenyl-2-carbonitrile (**3g**) (1.38 g, 70%) as crystalline solid. The melting point and IR, NMR data are the same as reported.[2a]

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Registry No. **1a**, 28162-32-5; **1b**, 2700-22-3; **1c**, 2826-26-8; **1d**, 2826-25-7; **1e**, 2700-23-4; **1f**, 1867-38-5; **1g**, 2826-22-4; **2a**, 19352-93-3; **2b**, 14958-13-5; **3a**, 125610-77-7; **3b**, 24973-49-7; **3c**, 125610-78-8; **3d**, 114772-53-1; **3e**, 17254-19-2; **3f**, 89346-58-7; **3g**, 89346-55-4.

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Reversal of the Order of Catalytic Efficiency of Primary and Secondary Amines in the Ionization of a Sterically Hindered Carbon Acid

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It is now generally recognized that base-catalyzed proton abstraction from carbon acids by primary and secondary amine bases follows the order of effectiveness, 2° amines > 1° amines, when comparing bases with the same pK_a value.[1,2] This differing catalytic effectiveness is easily observed in statistically corrected Brönsted plots for proton abstraction (or anion protonation) where these classes of amines normally fall on separate, though frequently parallel, linear plots. The observed trend has been attributed to a decrease in hydrogen-bonded solvation of the protonated amines with increasing N-substitution coupled with a lag in the development of this solvation in the

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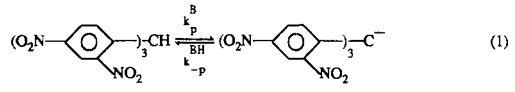
Table I. Rates of Amine-Catalyzed Proton Abstraction (k_p^B) from I and of Anion Protonation (k_{-p}^{BH}), Together with Acidity Constants for the Protonated Amines, in 50% H_2O–50% DMSO Solution at 25 °C (I = 0.5 M Me_4NCl)

no.	amine	pK_a^{BH}	k_p^B, $mol^{-1}\cdot L\cdot s^{-1}$	k_{-p}^{BH}, $mol^{-1}\cdot L\cdot s^{-1}$
1	aniline	3.73	1.43×10^{-5}	4.75×10^{-1}
2	aminoaceto-nitrile[a]	5.26	9.20×10^{-5}	9.30×10^{-2}
3	glycine ethyl ester[a]	7.24	8.40×10^{-4}	6.76×10^{-3}
4	glycinamide[a]	8.01	1.75×10^{-3}	3.21×10^{-3}
5	allylamine[a]	9.08	4.29×10^{-3}	5.90×10^{-4}, 6.3×10^{-4} [b]
6	2-methoxy-ethylamine	9.11	4.47×10^{-3}	6.30×10^{-4}
7	*n*-butylamine	9.99	1.21×10^{-2}	2.20×10^{-4}
8	morpholine	8.23	2.65×10^{-4}	2.85×10^{-4}
9	*N*-methyl-amino-ethanol[a]	9.39	5.70×10^{-4}	4.70×10^{-5}, 4×10^{-5} [b]
10	piperidine	10.38	5.28×10^{-3}	3.91×10^{-5}
11	pyrrolidine[a]	10.62	2.42×10^{-2}	1.03×10^{-4}

[a] pK_a^{BH} values measured in this work. [b] Calculated from k_p^B or k_{-p}^{BH} via eq 2.

transition state.[1b,3] While occasional anomalies within this general scheme have been reported,[2b,4,5] inversions of this reactivity order are rare.

In the course of our studies of proton abstraction from nitrophenyl-substituted methanes, we have recently measured some rates of amine-catalyzed ionization of tris(2,4-dinitrophenyl)methane (I) (eq 1) and have found that this system provides an unequivocal example in which primary amines are *more effective catalysts for proton abstraction* than the secondary amines morpholine, piperidine, and *N*-methylaminoethanol.



(1)

I II

Rate data for proton abstraction from I by various amines at 25 °C in 50% aqueous DMSO, together with rates of anion protonation by the corresponding conjugate acids, are shown in Table I, together with pK_a^{BH} values for the amines in this medium. The delocalized anion formed from I is extremely stable, enabling measurements to be made of either the ionization rate (k_p^B) and/or the protonation rate (k_{-p}^{BH}), depending upon pK_a^{BH}.

When only k_p^B or k_{-p}^{BH} was measurable, the rate in the opposite direction was calculated by means of eq 2. The value of pK_a^{CH} for I in 50% aqueous DMSO was determined spectrophotometrically to be 8.25.

$$k_p^B/k_{-p}^{BH} = K_a^{CH}/K_a^{BH} \quad (2)$$

In Figure 1, the statistically corrected values of k_p^B and pK_a^{BH} obtained from the data in Table I are plotted, from which it is evident that a good linear Brönsted plot (A) is obtained for deprotonation of I by primary amines, including aniline (β = 0.47). In contrast, no such homogeneity is apparent upon examination of the values obtained for the secondary amines studied. While the value for pyrrolidine falls approximately on the Brönsted line for the primary amines, the values for the other secondary amines are well below this line, indicating that they are significantly poorer catalysts than the primary amines used here.

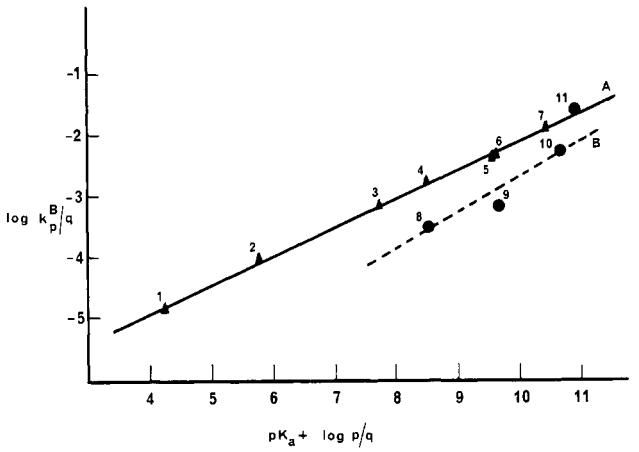


Figure 1. Statistically corrected Brönsted plots for proton abstraction from I in 50% aqueous DMSO at 25 °C. Line A: primary amines. Line B: morpholine and piperidine. Numbering is as in Table I.

On Brönsted plots derived from various studies of amine-catalyzed proton abstraction from carbon acids, the data for secondary amines normally lie *above* those for primary amines.[2,6–12] In a separate study of the deprotonation of 2,4,4′-trinitro- and 2,4,2′,4′-tetranitrodiphenylmethanes, we also observed such behavior, but the data for pyrrolidine lie above the Brönsted plots for the other secondary amines,[13,14] a situation that has sometimes been encountered in proton transfers at nitrogen atoms.[15] It is clear from Figure 1 that pyrrolidine (pK_a^{BH} = 10.62) exhibits in this work similarly enhanced reactivity, compared to secondary amines of comparable basicity, e.g., piperidine (pK_a = 10.38). That the point for pyrrolidine falls close to the line for the primary amines is therefore fortuitous and indicates that the reactivity of pyrrolidine toward I is reduced to a similar extent as is that of the other cyclic amines. We consider that the decreased reactivities of all secondary amines in proton abstraction from I result from the combined effects of the bulk of the approaching solvated base and of the substrate.

Other workers have also attributed abnormal ionization behavior to unfavorable steric interactions. For example, to account for his observation that tri-*o*-tolylmethane re-

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acted with bases at a CH_3 group rather than at the methine position, Barlett[16] assumed steric hindrance to base approach to be the overriding factor. Also steric hindrance to carbon protonation by protonated secondary amines has been reported for the reaction of benzylidene Meldrum's acid with morpholinium ion.[5,17]

Recently, morpholine and piperidine have been used as reference points to determine Brönsted $\beta^{RR'NH}$ values that were assumed to be typical for the behavior of secondary amines in various types of reaction.[9-12,18] Such $\beta^{RR'NH}$ values obtained for studies of the ionization of numerous carbon acids were generally identical with those (β^{RNH_2}) found for primary amine catalysts.[9-12] For example, β values of 0.65 and 0.69 have been reported for the deprotonation of phenylnitromethane by primary amines and the piperidine–morpholine pair, respectively, in 90% DMSO–10% H_2O.[10] Similar situations hold for the deprotonation of diphenylmethanes, e.g., 2,4,2',4'-tetranitrodiphenylmethane ($\beta^{RNH_2} = \beta^{RR'NH} = 0.45$), (α-cyanodiphenylmethane)bis(tricarbonylchromium(0)) ($\beta^{RNH_2} = 0.75$, $\beta^{RR'NH} = 0.72$), and of diketones, e.g., acetylacetone ($\beta^{RNH_2} = 0.45$, $\beta^{RR'NH} = 0.42$), 1,3-indanedione ($\beta^{RNH_2} = 0.42$, $\beta^{RR'NH} = 0.40$ in 50% DMSO–50% H_2O).[9,11b,12] These observations have implied that there is no major difference in the degree of proton transfer in the transition states for the corresponding reactions (with primary and secondary amines). However, the use of the piperidine–morpholine pair in the present work affords a $\beta^{RR'NH}$ value of 0.6 (line B of Figure 1). This value is markedly greater than that derived from line A for the primary amines (0.47), apparently indicating that proton transfer has made more progress in the transition states involving secondary amines that in those involving primary amines.

These results suggest that β values derived from data for secondary amines may not always reflect those for other classes of amines, especially in reactions involving highly sterically hindered substrates.

From the plots of Figure 1, values for the intrinsic rate constants for deprotonation of I (k_0) may be obtained.[3,19] These intrinsic rate constants are the values of k when

$$pK_a^{BH} + \log p/q = pK_a^{CH} = 8.25$$

and are found to be $\log k_0 = -2.95$ from plot A and $\log k_0 = -3.75$ from plot B, placing them among the lowest reported values.[3,11b,20] Low intrinsic rate constants are normally observed in those carbon acid ionizations that either occur with extensive solvent reorganization and/or give rise to highly delocalized carbanions.[3,21] The anion II is extremely stable in 50% aqueous DMSO and has $\lambda_{max} = 720$ nm ($\epsilon = 29\,300$), indicating extensive charge delocalization. Formation of this anion will involve considerable structural–electronic–solvational reorganization, and this will contribute significantly to the extremely low k_0 values found for I. In addition, the twist angle of each ring of II is presumably greater than that found for the triphenylmethyl anion (31–2° av) or, possibly, at any given instant one ring is orthogonal to the other two and these could then be coplanar, c.f. the 9-phenylfluorenyl anion.[22-24] In either situation there will be a considerable barrier to protonation of II and therefore a low intrinsic reactivity for I, as is observed.

Experimental Section

Materials. Tris(2,4-dinitrophenyl)methane was parepared according to the procedure of Margerum et al.[25] mp 260 °C (lit.[25] mp 256–8 °C). Solvents were purified and solutions made up as previously described.[12] Buffers were purified commercial products.

Measurements. Kinetic studies were made at 720 nm on a Durrum-Gibson 135 stopped-flow spectrophotometer with a thermostatted cell compartment (±0.5 °C). pH determinations were carried out as in other studies, on a Tacussel Isis 20000 pH meter. pK_a^{BH} values for the buffers in 50% aqueous DMSO were taken from previous studies,[12] except where otherwise indicated in Table I.

Registry No. I, 3626-18-4; aniline, 62-53-3; aminoacetonitrile, 540-61-4; glycine ethyl ester, 459-73-4; glycinamide, 598-41-4; allylamine, 107-11-9; 2-methoxyethylamine, 109-85-3; *n*-butylamine, 109-73-9; morpholine, 110-91-8; *N*-methylaminoethanol, 109-83-1; piperidine, 110-89-4; pyrrolidine, 123-75-1.

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Stereoselective Synthesis of (24*S*)- and (24*R*)-24-(Hydroxymethyl)cholesta-5,22(*E*)-dien-3β-ol: Model Compounds for Stereochemical Assignments of Polyhydroxylated Marine Steroids

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During our continuing work on polyhydroxysteroids and steroidal glycosides from echinoderms[1] we isolated a series of steroids with unusual oxygenation of the side chain. The latest additions are glycosides of polyhydroxysteroids isolated from the starfish *Coscinasterias tenuispina*[2] [coscinasteroside C; i.e. 28-*O*-β-D-glucopyranosyl-24-methyl-5α-cholest-22(*E*)-ene-3β,6α,8,15β,16β,28-hexol 4'-sulfate], *Pisaster brevispinus*,[3] and a steroid isolated from the ophiuroid *Ophiolepis superba*,[4] all possessing a Δ^{22}-24-hydroxymethyl side chain. The structures of these compounds were determined by means of spectral data and some chemical transformations, but the stereochemistry at C-24 remained to be defined. The growing number of naturally occurring steroids with such a structural feature, and the limited amount of natural compound usually available, made it desirable to develop a technique using

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