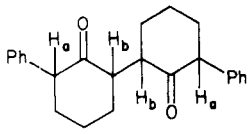
Table II. NMR Data



compd[a]	NMR (60 MHz, $CDCl_3$), δ
A	7.25 (br s, 10 H, C_6H_5), 3.9–3.5 (m, 2 H, H_a), 3.2–2.8 (m, 2 H, H_b), 2.5–2.1 and 2.1–1.7 (2 m, 12 H)
B	7.5 (s, 10 H, C_6H_5), 3.9–3.7 (m, 2 H, H_a), 3.2–2.7 (m, 2 H, H_b), 2.7–1.5 (m, 12 H)
C	7.5–7.0 (10 H, C_6H_5), 3.8–3.6 (m, 2 H, H_a), 3.2–2.8 (m, 2 H, H_b), 2.7–1.4 (m, 12 H)
D	7.5–7.0 (10 H, C_6H_5), 4.0–3.6 (m, 2 H, H_a), 3.3–2.8 (m, 2 H, H_b), 2.8–1.2 (m, 12 H)
E	7.5–7.0 (10 H, C_6H_5), 3.9–3.3 (m, 2 H, H_a), 3.1–2.6 (m, 2 H, H_b), 2.4–1.6 (m, 12 H)

[a] Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.2; H, 7.56; O, 9.24. Found (compound B): C, 82.89, 82.70; H, 7.59, 7.72. Found (compound C): C, 83.19, 18.42; H, 7.64, 7.64.

was carried out as usual except that the mixture was heated to ~50 °C for 1 day. The reaction was complete when the blue color turned cloudy green. The diastereomeric dimers **7** were isolated by chromatography and identified by NMR analysis. For isomer 1: ^1H NMR (60 MHz, $CDCl_3$) δ ~7.4–7.1 (m, ~6 H, meta and para aryl H), ~7.2–6.9 (br m, ~2 H, ortho aryl H), 6.7–6.3 (br m, ~2 H, ortho aryl H), 3.1–2.1 (m, 6 H, CH_2CO and $CH_2C(Ph)$), 2.1–1.0 (m, 10 H, $CH_2C(Ph)$ and methylenes); ^1H NMR (220 MHz, $CDCl_3$) δ 7.3–7.08 (m, 6 H), 6.99 (m, 2 H, ortho aryl H), 6.54 (d, 2 H, J = 7 Hz, ortho aryl H), 2.74 (dt, 2 H, J_t = 14 Hz, J_d = 4 Hz, $CH_2C{=}O$), 2.5–2.25 (m, 4 H, $CH_2C{=}O$ and CH_2CPh), 1.95–1.45 (m, 8 H, CH_2CH_2), 1.19 (qt, 2 H, J_q = 13 Hz, J_t = 4 Hz, $PhCCH_2\mathbf{CH_2}CH_2$). The NMR spectrum of the other isomer was similar except for a new broad resonance between δ 6.0 and 5.5 (ortho aryl proton). Variable-temperature NMR (100 MHz) showed that the ortho hydrogens of the aryl groups changed with temperature. This was because the rotation of the phenyl groups was hindered. The coalescence temperature was 69 °C, giving 17 kcal as the activation barrier for the exchange process. The yield of isolated dimers was 40%.

[4,4′-Bicyclohexenyl]-3,3′-dione (8). 2-Cyclohexen-1-one (0.96 g, 10 mmol) was converted to its enolate with LDA and oxidized with ferric chloride as described above. The diastereomeric dimers were isolated by high-performance LC (eluant 40% ether in hexane). For isomer 1: yield 0.080 g; white solid; mp 84–86 °C; IR (CCl_4) 3040, 1675 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.97 (dt, 2 H, J_d = 10 Hz, J_t = 3 Hz, $CH_2\mathbf{CH}{=}CHCO$), 6.0 (dt, 2 H, J_d = 10 Hz, J_t = 1.5 Hz, $CH_2CH{=}\mathbf{CH}CO$), 3.27 (dd, 2 H, J = 11 Hz, 7 Hz, $COC\mathbf{H}CH_2$), 2.45 (m, 4 H, $=CHC\mathbf{H_2}CH_2CH$), 1.92 (m, 4 H, $=CH_2CH_2C\mathbf{H_2}CH$). For isomer 2: yield 0.140 g; white solid; mp 90–100 °C; IR (CCl_4) 3040, 1675 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.93 (dt, 2 H, J_d = 10 Hz, J_t = 4 Hz, $CH_2\mathbf{CH}{=}CHCO$), 6.02 (dt, 2 H, J_d = 10 Hz, J_t = 3 Hz, $CH_2CH\mathbf{CH}CO$), 2.88 (t, 2 H, J = 7 Hz, $COC\mathbf{H}CH_2$), 2.42 (m, 4 H, $=CHC\mathbf{H_2}CH_2CH$), 2.0 (m, 4 H, $=CHCH_2C\mathbf{H_2}CH$). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; O, 16.82. Found: C, 75.20, 75.42; H, 7.46, 7.94.

1,4-Bis(*endo*-5-bicyclo[2.2.1]hept-2-enyl)butane-1,4-dione (9). Pure *endo*-5-acetylnorbornene was obtained from a commercial (Aldrich) sample of the isomer mixture by high-performance LC (eluant 10% ether in hexane). The endo isomer [bp 78–80 °C (20 mm)] shows a characteristic doublet of doublets at δ 6.0 for the olefinic protons in the NMR spectrum. The methine proton α to the carbonyl resonates at δ 3, overlapping with the bridgehead protons.

The enolate of *endo*-5-acetylnorbornene was prepared as usual with LDA and oxidized with ferric chloride as described. The crude product obtained was analyzed by GC (column A, 50–250 °C at 15 °C/min), and the yield of dimer was found to be 50%. Two recrystallizations of the product from ethanol–water gave the dimer as pale yellow needles: mp 69.5–72 °C; IR (CCl_4) 3050, 1710 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 6.15 (dd, 2 H, J = 5, 3 Hz, olefinic protons), 3.6–2.75 (m, 3 H, 2 bridgehead protons and CHCO), 2.68 (s, 4 H, $OCCH_2CH_2CO$), 2.0–1.1 (m, 4 H, ring protons).

Diethyl Succinate (10). LDA (12 mmol) was prepared as usual in 10 mL of dry THF and cooled to −78 °C. Ethyl acetate (0.97 mL, 0.88 g, 10 mmol; distilled from P_2O_5) was added dropwise via syringe. After 10 min, ferric chloride (1.78 g, 11 mmol) was added dropwise as a solution in 10 mL of dry DMF. The mixture was allowed to warm to room temperature. After being stirred overnight, the mixture was worked up as usual to give 0.67 g of crude product. The NMR spectrum of this material indicated it was diethyl succinate (~89% by weight) contaminated with small amounts of THF and hexane: yield 69%; NMR (60 MHz, $CDCl_3$) δ 4.15 (q, 4 H, J = 7 Hz, $CH_2\mathbf{CH_2}O$), 2.6 (s, 4 H, $COCH_2CH_2CO$), 1.25 (t, 6 H, J = 7 Hz, $C\mathbf{H_3}CH_2O$).

Acknowledgment. R.H.F. thanks F. J. Weigert for stimulating discussions, Donald Soring for technical assistance, and G. W. Parshall for encouragement during the final phases of this work. Analytical support from CR&DD's Analytical Division and especially from G. S. Reddy for the variable-temperature NMR analysis is gratefully acknowledged.

Registry No. *meso*-**1**, 52690-71-8; *dl*-**1**, 52690-70-7; **2**, 75533-81-2; *meso*-**3**, 75533-82-3; *dl*-**3**, 75533-83-4; **4**, 51513-36-1; **5**, 27610-88-4; **6**, 75533-84-5; **7** (isomer 1), 75533-85-6; **7** (isomer 2), 75533-86-7; **8** (isomer 1), 75533-87-8; **8** (isomer 2), 75533-88-9; **9**, 75533-89-0; **10**, 123-25-1; *l*-carvone, 6485-40-1; cyclohexanone, 108-94-1; isophorone, 78-59-1; diisopropyl ketone, 565-80-0; pinocalone, 75-97-8; 2-phenylcyclohexanone, 1444-65-1; 2-cyclohexen-1-one, 930-68-7; *endo*-5-acetylnorbornene, 824-60-2; ethyl acetate, 141-78-6.

Supplementary Material Available: Table of atomic coordinates and thermal parameters (1 page). Ordering information is given on any current masthead page.

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Substituent Effects upon the Equilibration of 4-Cyano-1,4-dihydro-1-(substituted benzyl)nicotinamides with 1-(Substituted benzyl)nicotinamide Cations

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Received May 29, 1980

We have used the ring-substituted benzyl group ($XC_6H_4CH_2$) as a substituent on a nitrogen atom as a probe of charge generation (or charge neutralization) on that nitrogen atom in the transition states for a number of reactions of heterocyclic molecules.[1-3] This substituted benzyl group has a number of features which are attractive in its use as such a probe. (i) Substituents on the meta and para ring carbon atoms are relatively remote from the nitrogen atom, and so substituent effects are primarily electronic without any significant contribution from steric or solvation effects. (ii) The substituted phenyl ring is

(1) J. W. Bunting and D. J. Norris, *J. Am. Chem. Soc.*, **99**, 1189 (1977).
(2) J. W. Bunting, P. A. Lee-Young, and D. J. Norris, *J. Org. Chem.*, **43**, 1132 (1978).
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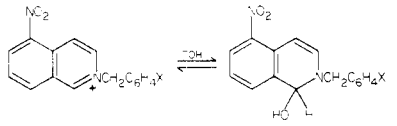
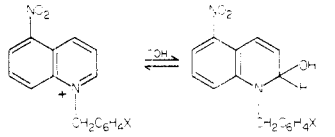
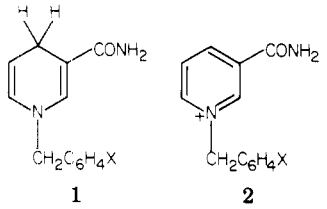
Table I. Hammett ρ Values for Charge Neutralization on Nitrogen Atoms

reaction	ρ	ref
$XC_6H_4CH_2\overset{+}{N}H_3 \overset{-H^+}{\rightleftharpoons} XC_6H_4CH_2NH_2$	−1.05	4
$XC_6H_4CH_2\overset{+}{N}H(CH_3)_2 \overset{-H^+}{\rightleftharpoons} XC_6H_4CH_2N(CH_3)_2$	−1.14	5
	−1.14	1
	−1.32	1

separated from the site of charge generation by the saturated carbon atom of the methylene group. Thus, resonance interactions of ring substituents with the nitrogen atom are unimportant, and normal Hammett σ constants can be used as quantitative measures of substituent effects. (iii) Equilibrium constants for reactions which formally generate (or neutralize) a full unit charge on the nitrogen atom are usually measurable. Substituent effects (X in $XC_6H_4CH_2$) on such equilibria allow the measurement of a ρ value which can be used as a reference point for the quantitative evaluation of partial charges (δ) in transition states in related reactions for which kinetic ρ values are obtainable; i.e., $\delta = \rho(\text{kinetic})/\rho(\text{reference equilibrium})$.

The magnitudes of ρ values for equilibria, which involve substituted benzyl groups as substituents on nitrogen atoms, are somewhat sensitive to the molecular environment in the vicinity of the nitrogen atom (Table I). Because of the variability of these ρ values, it is clear than accurate transition-state studies require a reference equilibrium ρ value in a system that resembles as closely as possible the kinetic system under study.

We are currently engaged in a number of detailed kinetic and mechanistic studies of the reduction of various hydride acceptors by 1-(substituted benzyl)-1,4-dihydronicotinamides (1). Such reactions, in which 1 is oxidized to the



1 2

corresponding nicotinamide cation (2), are important model systems for reactions of the nicotinamide coenzymes and have attracted considerable interest[6] in attempts to elucidate the mechanisms of hydride transfer. We are attempting to use substituent effects in 1 to give an indication of the amount of charge generation on the ring nitrogen atom in the rate-determining transition states for such reactions. As indicated above, such studies require a reference ρ value from the equilibrium constants for a reaction in which formally a full positive charge is generated on the ring nitrogen atom. A suitable reference

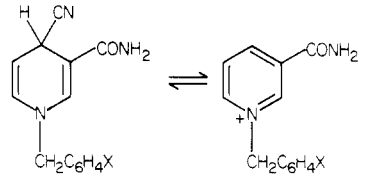
(6) (a) R. J. Kill and D. A. Widdowson in "Bioorganic Chemistry", E. E. van Tamelen, Ed., Academic Press, New York, 1978, Vol. IV, p 239; (b) D. S. Sigman, J. Hajdu, and D. J. Creighton, *Ibid.*, p 385; (c) T. Okamoto, A. Ohno, and S. Oka, *J. Chem. Soc., Chem. Commun.*, 181, 784 (1977); (d) S. Shinkai, Y. Kusano, T. Ide, T. Sone, and O. Manahe, *Bull. Chem. Soc. Jpn.*, 51, 3544 (1978); (e) R. Stewart and D. J. Norris, *J. Chem. Soc., Perkin Trans. 2*, 246 (1978); (f) P. van Eikeren and D. L. Grier, *J. Am. Chem. Soc.*, **99**, 8057 (1977).

Table II. Dissociation Constants for Reaction in Equation 1[a]

X	K, M (H_2O)	K, M (20% CH_3CN–80% H_2O)
4-CH_3	0.56 ± 0.03	0.090 ± 0.005
H	0.41 ± 0.02	0.071 ± 0.004
4-F	0.39 ± 0.02	0.056 ± 0.003
4-Br	0.26 ± 0.02	0.036 ± 0.002
3-F	0.21 ± 0.02	0.031 ± 0.002
3-CN	0.115 ± 0.005	0.0177 ± 0.0009
4-CN		0.0150 ± 0.0007

[a] At 25 °C, pH 11.3, ionic strength 1.0.

equilibrium is the dissociation of cyanide ion from 4-cyano-1,4-dihydronicotinamides (eq 1). Lindquist and



(1)

3 2

Cordes[7] have reported an equilibrium $\rho^* = -3.7$ for this reaction for a variety of substituents on N-1. However, there is reason to believe that there may be considerable uncertainty in this value (see later discussion).

We have now measured equilibrium constants for the reaction in eq 1 for a variety of substituents X in aqueous solution and also in 20% acetonitrile–80% water (in which most of our kinetic data have been obtained). Values of the dissociation constant, $K = [2][^-CN]/[3]$, were evaluated by the method of Lindquist and Cordes[7] in both water and 20% acetonitrile–80% water at 25° C, pH 11.3 and ionic strength 1.0 (KCl + KCN), and are listed in Table II. The value of $K = 0.41$ M for **3** (X = H) in water (ionic strength 1.0) is in reasonable agreement with $K = 0.33$ M (at ionic strength 0.5) reported for this derivative by Lindquist and Cordes.[7] Hammett correlations for each solvent system give the correlation eq 2 (for water) and 3 (for 20% acetonitrile–80% water).

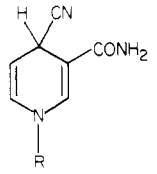
$$\log K = -0.88(\pm 0.04)\sigma - 0.38(\pm 0.01) \quad (\text{corr coeff} = 0.996) \quad (2)$$

$$\log K = -0.95(\pm 0.03)\sigma - 1.19(\pm 0.01) \quad (\text{corr coeff} = 0.998) \quad (3)$$

The data in Table II indicate that the presence of 20% acetonitrile in the aqueous solvent stabilizes the cyanide adducts relative to their nicotinamide cations by 6–7-fold (i.e., $\Delta\Delta G \approx 1.1$ kcal/mol) compared with strictly aqueous solutions. This increased stability is presumably a combination of an enhanced solvation of the neutral adducts in the less polar mixed solvent and reduced solvation stabilization of the nicotinamide cations and cyanide ions in this medium relative to water. The ρ values of eq 2 and 3 indicate that substituent effects on this equilibrium are only slightly medium dependent.

The important influence of the reaction medium on the magnitude of the dissociation constants for these cyanide adducts was also observed by Lindquist and Cordes,[7] who report that K increases 3.3-fold for the 1-methyl derivatives (4, R = CH_3) as the ionic strength of an aqueous reaction medium is increased from 0.5–3.0. These workers also report $\rho^* = -3.7$ (corr coeff = 0.98) for a series of six R substituents in 4. This ρ^* value can be converted to ρ =

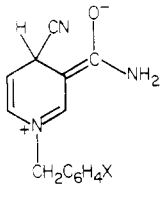
(7) R. N. Lindquist and E. H. Cordes, *J. Am. Chem. Soc.*, **90**, 1269 (1968).



4

$-3.7 \times 0.326 = -1.2$ for X substituents in **3** by making use of the relationship of Ritchie and Sager[8] ($\sigma^*(XC_6H_4CH_2) = 0.326\ \sigma^n(X) + \sigma^*(C_6H_5CH_2)$). We believe that this value for ρ, which is somewhat more negative than our result, is less reliable than the ρ values of eq 2 and 3 of the current work. The earlier work is based upon data for **4** (R = CH_3, $CH_3(CH_2)_2$, $C_6H_5CH_2$, 2,6-$Cl_2C_6H_3CH_2$, 4-$NO_2C_6H_4CH_2$, and 2-Cl-4-$NO_2C_6H_3CH_2$). For only three of these substituents (R = CH_3, $CH_3(CH_2)_2$, and $C_6H_5CH_2$) are both equilibrium constants and σ^* values known with certainty. For R = 4-$NO_2C_6H_4CH_2$ and 2-Cl-4-$NO_2C_6H_3CH_2$, the equilibrium constant is admitted to be uncertain due to relatively rapid secondary reactions with these substituents. For R = 2,6-$Cl_2C_6H_3CH_2$ and 2-Cl-4-$NO_2C_6H_3CH_2$, only rough estimates of appropriate σ^* values were available. Furthermore, for the above six R groups one cannot assume with certainty that variable solvation effects do not play a role in charge stabilization for the nicotinamide cations.

The values of $\rho = -0.88$ and -0.95 in eq 2 and 3 are somewhat smaller than the related ρ values in Table I. This suggests that the net change in charge on N-1 in the current reaction is somewhat less than that in the reactions of Table I. In making such comparisons, it is important to keep in mind that, although the reactions of Table I and eq 1 are written as formally involving a nitrogen atom bearing a unit positive charge, the true electron deficiency of such nitrogen atoms will actually be smaller than +1 because of intramolecular electron polarization and charge neutralization by the dipoles of solvating molecules. It is exactly these factors which require comparisons of kinetic and equilibrium ρ values to be made only for systems which resemble one another as closely as possible. For the reaction of eq 1, we note that **5** may be an important



5

resonance contributor to the electronic structure of the neutral cyanide adducts **3**. A significant contribution from **5** would reduce the magnitude of the net change in formal positive charge upon formation of the nicotinamide cations and so consequently reduce the magnitude of the ρ value for X substituents in the *N*-benzyl group.

Experimental Section

Materials. The bromide salts of 1-(substituted benzyl)-nicotinamide cations were synthesized by refluxing nicotinamide with the appropriate substituted benzyl bromide in acetone. The products were recrystallized several times from ethanol and characterized by ^1H NMR spectroscopy and molecular-weight determination by Volhard titration of bromide ion as X, mp dec, exptl mol wt (calcd mol wt): 4-CH_3, 238–239 °C, 309.1 (307.2); H, 206–208 °C (lit.[9] 205 °C), 291.6 (293.0); 4-F, 246–247 °C (lit.[10] 247–249 °C), 313.6 (311.2); 4-Br, 263–264 °C; 3-F, 240–241 °C, 312.3 (311.2); 3-CN, 256–258 °C, 321.1 (318.2); 4-CN, 275–276 °C, 319.3 (318.2).

Spectroscopic-grade acetonitrile was used for the preparation of acetonitrile–water mixtures. Potassium hydroxide, potassium cyanide, and potassium chloride were the best commercially available grades.

Dissociation constants, $K = [2][^-CN]/[3]$, were measured by the general method of Lindquist and Cordes[7] at pH 11.3 (KOH), 25 °C, and ionic strength 1.0 (KCl + KCN) in both water and 20% acetonitrile–80% water. The absorbances of solutions containing mixtures of nicotinamide cation (8×10^{-5} M) and cyanide ion were recorded as a function of time at 340 nm on a Varian Cary 210 spectrophotometer. At this wavelength, the absorbance initially increases due to formation of the cyanide adducts **3**, becomes constant after 2–7 min, depending upon the X substituent and the cyanide concentration, and then undergoes subsequent slower changes due to various base-catalyzed decomposition reactions. Detailed spectroscopic studies have shown[7] that the initial adsorbance increase is due to the formation of **3**. For each nicotinamide cation, the constant absorbance (A) at 340 nm was recorded at about eight cyanide ion concentrations in the range $[^-CN] = 0.04$–0.5 M for aqueous solutions and $[^-CN] = 0.004$–0.1 M for 20% acetonitrile–80% water. Values of K were then evaluated[7] from the reciprocals of the slopes of plots of $-A/[^-CN]$ vs. A. The absorbance at 340 nm of each nicotinamide cation is negligible at the concentrations used in the present study.

Registry No. **3** (X = 4-CH_3), 75420-69-8; **3** (X = H), 19432-61-2; **3** (X = 4-F), 75420-70-1; **3** (X = 4-Br), 75420-71-2; **3** (X = 3-F), 75420-72-3; **3** (X = 3-CN), 75420-73-4; **3** (X = 4-CN), 75420-74-5.

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Unusual Long-Range Cyclopropyl Participation in 1-Substituted *exo*-Tricyclo[3.2.1.$0^{2,4}$]octanes

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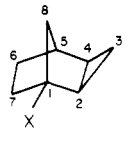
Received June 30, 1980

Our recent interest in inductive withdrawal by cyclopropanes[1] and continuing studies by a number of groups[2] on long-range effects of cyclopropane rings have prompted us to study 1-substituted *exo*- and *endo*-tricyclo[3.2.1.$0^{2,4}$]octanes **1** and **2**. Our earlier work on 4-substituted nortricyclenes[1] has convinced us that, especially in bridged bicyclic compounds, there is appreciable electron withdrawal by a cyclopropane when placed at a position which is γ or δ from a reaction center. An increase in the acidity of carboxylic acids and a decrease in acetolysis rates of tosylates were the experimental proofs used. Since isolated inductive withdrawal with no apparent homoallylic or homobenzylic participation of double bonds



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