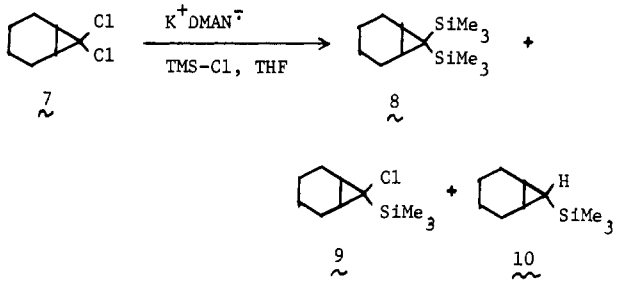
will undergo consecutive electron transfer before leaving the reduction sphere and being protonated as illustrated in Figure 1.

The phase effect observed here is also compatible with the carbene radical anion mechanism[1] which was proposed to explain the predominant formation of the parent hydrocarbon products in these reactions. Additional evidence for the intermediacy of carbene radical anions in these reaction systems is provided as follows. The reduction of 7,7-dichlorobicyclo[4.1.0]heptane (**7**) with potassium 1-



(dimethylamino)naphthalenide (K^+ $DMAN^{-}\cdot$) at −78 °C in the presence of an excess amount of chlorotrimethylsilane (Me_3SiCl) gave 7,7-bis(trimethylsilyl)- (**8**, 17%), 7-chloro-7-(trimethylsilyl)- (**9**, 41%), and 7-(trimethylsilyl)bicyclo[4.1.0]heptane (**10**, 34%).[9] When **9** was independently treated with $K^+DMAN^{-}\cdot$ in the presence of Me_3SiCl, it remained unreacted until the Me_3SiCl was consumed, and it slowly produced **10** instead of **8**. This means that compound **9**, once formed as the result of a stepwise silylation of **7**, must survive its further reduction to **8** in this reductant system which apparently is a pseudononhomogeneous solution reducing *gem*-dihalides. Therefore, **8** must be produced not via **9** but most likely via a cyclopropylidene radical anion. These results are comparable with the in situ quenching by 2-propanol-*d* in the reduction of **1** (X = Cl) with potassium naphthalenide,[1] where the intermediately formed monochlorocyclopropane compounds reacted with naphthalenide more slowly than the starting *gem*-dichloro compound.

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Registry No. **1** (X = Br), 36807-30-4; **3**, 54082-70-1; **4**, 50895-58-4; *meso*-**5**, 63183-84-6; (±)-**5**, 63152-30-7; **6**, 37520-11-9; **7**, 823-69-8; **8**, 56431-99-3; **9**, 84472-99-1; **10**, 67957-93-1; K^+-$DMAN^{-}\cdot$, 82136-09-2; Na, 7440-23-5; Li, 7439-93-2; ethanol, 64-17-5; 1-chloro-2-(2-cyclopropylethyl)cyclopropane, 84473-00-7; 1,2-bis(2-chlorocyclopropyl)ethane, 84473-01-8; 1,1-dichloro-2(2-cyclopropylethyl)cyclopropane, 84473-02-9; 1,1-dichloro-2-[(2-chlorocyclopropyl)ethyl]cyclopropane, 84473-03-0; 3-chlorotricyclo[5.1.0.$0^{2,4}$]octane, 84473-04-1; 3,8-dichlorotricyclo-[5.1.0.$0^{2,4}$]octane, 84473-05-2; 3,3-dichlorotricyclo[5.1.0.$0^{2,4}$]octane, 63098-57-7; 3,3,8-trichlorotricyclo[5.1.0.$0^{2,4}$]octane, 84519-58-4; 7,7-dibromobicyclo[4.1.0]heptane, 2415-79-4.

(9) The yield of **8** increased to 42% when the 7,7-dibromo derivative was treated under the same conditions.

(10) Structures of partially reduced intermediate products appearing in the product column of Tables I and II were determined on the basis of VPC–mass spectral analysis, separation, and further reduction to produce parent hydrocarbon **6** or **4**. Products bearing monochlorocyclopropane ring(s) were obtained as a mixture of stereoisomers with regard to the cis, trans geometry. *gem*-Dichloro products were independently synthesized via a stepwise CCl_2 addition–reduction–CCl_2 addition procedure.

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Relative Donor-Atom Effects on Rates of Isomerization of 3-Butenenitrile Catalyzed by Anions of the Same Basicity

Summary: For base-catalyzed isomerization of 3-butenenitrile in Me_2SO solution the order of rate constants for anions of the same basicity is $ArS^- > ArO^- > RSO_2NAr^- >$ 9-G-Fl^- (9-substituted fluorenyl carbanions). The relative rate constants vary somewhat with basicity since the Brønsted β values are 0.77, 1.0, 0.82, and ~0.8, respectively.

Sir: In previous communications we have shown that, in Me_2SO solution, rate constants for both S_N2 and E2 reactions of anions with alkyl halides correlate with the basicity of the anion as long as steric effects and the nature of the donor atom remain constant. Rate constants for anions of the same basicity, but with different kinds of donor atoms, may differ in either kind of reaction by factors greater than 10^4, however, and the relative order for S_N2 and E2 reactions is not the same. For example, toward $PhCH_2Cl$, S_N2 rate constants for anions of the same basicity are in the order $ArS^- \gg$ 9-G-Fl^- (9-substituted fluorenyl carbanions) > 2-NpO^- (2-naphthoxide oxanions) > Cb^- (carbazole nitranions),[1a] whereas toward cyclohexyl bromide (c-$C_6H_{11}Br$) the order of E2 rate constants is $ArS^- \gg$ 2-NpO^- > Cb^- > 9-G-Fl^-.[2] As a consequence of this difference in order 9-G-Fl^- carbanions react with c-$C_6H_{11}Br$ almost exclusively by an S_N2 pathway, whereas 2-NpO^- and Cb^- anions react with c-$C_6H_{11}Br$ almost exclusively by an E2 pathway.[2]

It seemed likely that the difference in reactivity order arose because of different inherent affinities of the various donor atoms in the anions for hydrogen in E2 reactions as compared to carbon in S_N2 reactions. We wondered, however, to what extent the difference was caused by the interaction of the donor atom with hydrogen, per se, i.e., deprotonation, as compared to the interaction of the donor atom with hydrogen in the context of the E2 transition state. As a first step in trying to answer this question we examined the effect of anions of the same basicity on the rate of isomerization of $CH_2{=}CHCH_2CN$ (**1**) to (*E*)- and (*Z*)-$CH_3CH{=}CHCN$ (**2**). Rate constants for the isomerization of **1** to **2** by 9-G-Fl^-, RSO_2NAr^-, ArS^-, and ArO^- ions are summarized in Table I and Brønsted plots are shown in Figure 1.

Examination of Figure 1 shows that the relative rate constants for catalysis of the isomerization of **1** to **2** by anions of the same basicity are as follows: $ArS^- > ArO^-$ (by 0.6 log unit at $pK_a = 10$);[3,4] $ArO^- > RSO_2NAr^-$ (by 0.6 log unit at $pK_a = 13$);[3] RSO_2NAr^- > 9-G-Fl^- (by 1.4 log units at $pK_a = 14$).[3] The order $S^- > O^- > N^- > C^-$ is the same as was observed for E2 rate constants with c-$C_6H_{11}Br$,[2] but the total spread of rate constants between S^- and C^- is only about 2.5 log units for the isomerizations compared to over 4 log units for the eliminations. These and earlier results[5,6] suggest that such donor-atom effects

(1) (a) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1982**, *47*, 169–170. (b) *Ibid.* **1982**, *47*, 3224–3232.

(2) Bordwell, F. G.; Mrozack, S. R. *J. Org. Chem.* **1982**, *47*, 4813–4815.

(3) Since the slopes of the lines differ slightly, the rate constants vary somewhat with the basicity at which the comparison is made.

(4) Thianions show a higher reactivity than oxanions of the same basicity at $pK_a = 10$ in Me_2SO, but the greater slope for the oxanion line suggests that the lines will cross at $pK_a = 13$ (see the dashed line in Figure 1).

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Table I. Rates of Isomerization of 3-Butenenitrile to (*E*)- and (*Z*)-2-Butenenitrile Catalyzed by Carbanion, Nitranion, Oxanion, and Thianion Bases in Me_2SO Solution at 25 °C

anion	pK_a[a]	β	k_2,[b] M^{-1} s^{-1}
9-(*m*-ClC_6H_4)-fluorenyl	16.85		0.92
9-PhS-fluorenyl	15.4		5.2×10^{-2}
2-$PhSO_2$-9-Ph-fluorenyl	13.8	~0.8	3.1×10^{-3}
(*p*-$CH_3OC_6H_4$)NSO_2CH_3	13.85		0.12
$C_6H_5NSO_2CH_3$	13.05		2.2×10^{-2}
$C_6H_5NSO_2Ph$	11.95		3.8×10^{-3}
(*m*-BrC_6H_4)NSO_2Ph	10.5	0.82 ± 0.03	2.15×10^{-4}
p-$CH_3OC_6H_4S^-$	11.2		5.0×10^{-3}
$C_6H_5S^-$	10.3		1.1×10^{-3}
p-$BrC_6H_4S^-$	9.0	0.77 ± 0.03	1.0×10^{-4}
3,5-$Cl_2C_6H_3O^-$	13.55		0.42
3,4,5-$Cl_3C_6H_2O^-$	12.75		7.1×10^{-2}
2,4,5-$Cl_3C_6H_2O^-$	11.45		4.65×10^{-3}
2,3,4,5-$Cl_4C_6HO^-$	10.05	1.0 ± 0.04	1.1×10^{-4}

[a] The pK_a value of the conjugate acid of the anion in Me_2SO solution. [b] The rates were measured in Me_2SO at 25 °C by monitoring the appearance of (*E*)- and (*Z*)-2-butenenitrile (GLC analysis) with varying concentrations of anion catalyst. Averages of the calculated second-order rate constants for 2–5 runs, each with four or five aliquots, agreed to better than ±10% for thianions, oxanions, and nitranions. The data for carbanions are less precise, perhaps because the solutions are more basic and therefore more sensitive to reaction with oxygen.

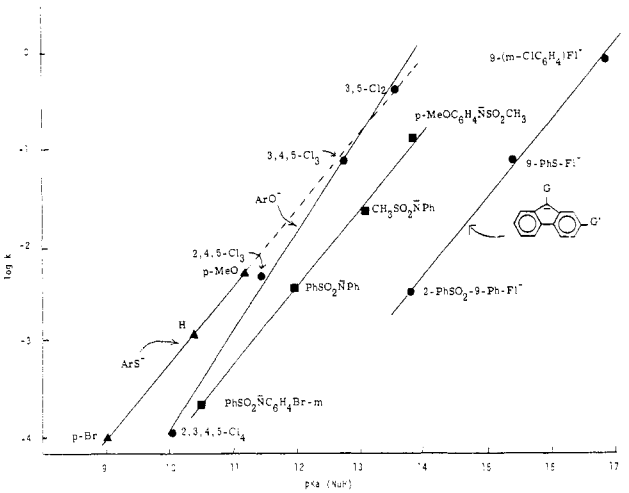
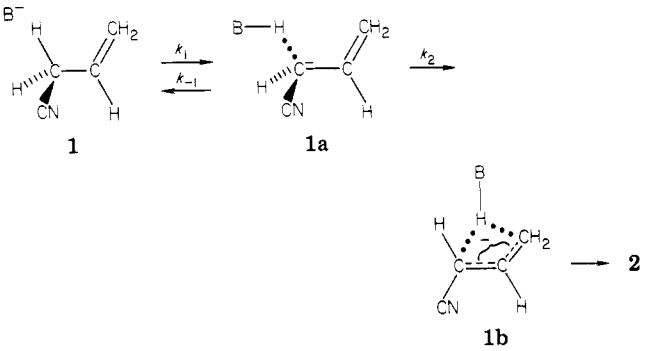


Figure 1. Brønsted plots for the isomerization of 3-butenenitrile to (*Z*)- and (*E*)-2-butenonitriles in Me_2SO solution at 25 °C catalyzed by thianions (▲), oxanions (●), nitranions (■), and carbanions (●).

are characteristic of reactions where proton transfer is rate limiting. These donor-atom effects for anions of the same basicity explain the appreciable scatter commonly observed in Brønsted plots in hydroxylic solvents where it is always necessary to use different families of bases to construct extended plots.[1b] They also explain the difficulty in deciding whether or not apparent curvature in such plots is caused by donor-atom effects or is inherent in the Brønsted plot.[1b]

The smaller variation in donor-atom effects and the higher β values for base-catalyzed isomerizations (β = 0.8–1.0; Table I) than for E2 eliminations (β = 0.35–0.5)[2,7] indicate that the transition states and reaction profiles for these two types of reactions are substantially different. The β value of 1.0 for reaction of ArO^- ions in Me_2SO with **1** is in close accord with β values for isotopic exchanges catalyzed by oxanions in H_2O with similar cyano carbon acids (β = 0.94 for ArO^- with $CNCH_2CH{=}CHCH_2CN$[10] and β = 0.98 for RCO_2^- with *t*-BuCH$(CN)_2$).[11] All of these reactions can be represented by a general two-step mechanism proposed by Cram,[12] for example



In this mechanism deprotonation leads in the first step to a strongly H-bonded, "localized" carbanion (**1a**). In the second step **1a** is converted to a weakly H-bonded, "delocalized" carbanion (**1b**). The order of rates, $O^- > N^- > C^-$, revealed in Figure 1, corresponds to the relative H-bonding abilities of B–H in **1a** and **1b**. Isomerization, exchange, etc. may occur in step 2 or subsequent steps. Such deprotonations are usually endoenergetic with a higher barrier for step 1 than for step 2. Nevertheless, k_2 is often rate limiting since $k_{-1} > k_2$ is not uncommon.[13]

Our studies in Me_2SO solution indicate that the Brønsted relationship is generally applicable to reactions of carbanions with electrophiles. β has been observed to increase from about 0.3 to 1.0 along the series for the six reaction types studied to date, S_N2,[1] S_N2',[17] E2,[2] S_NAr,[18] base-catalyzed isomerization, and electron transfer.[19] For S_N2 reactions β varies but little for anions with different donor atoms.[1a] In all of these reactions β measures the sensitivity of the reaction rates to changes in carbanion basicity. As a working hypothesis we suggest that the size of β may be associated with the activation barrier for a

(5) J. F. Bunnett and L. A. Retallick (*J. Am. Chem. Soc.* **1967**, *89*, 423–428) obtained similar results for S^- and O^- in MeOH. They estimated that EtS^- ions were about 1 or 2 log units better than MeO^- ions of the same basicity at catalyzing (a) the isomerization of cholest-5-en-3-one and (b) the epimerization of menthone. In a related study PhS^- ion has been shown to be much better than MeO^- ion at effecting elimination reactions in MeOH, despite its much lower basicity.[6]

(6) Bunnett, J. F.; Davis, G. T.; Tanida, H. *J. Am. Chem. Soc.* **1962**, *84*, 1606–1614. Bunnett, J. F.; Baciocchi, E. *J. Org. Chem.* **1967**, *32*, 11–16.

(7) Brønsted β values of 0.36 have been reported for E2 reactions of ArS^- ions with c-$C_6H_{11}Br$ in EtOH[8] and 0.39 for reactions of ArO^- ions with 4-bromoheptane in EtOH.[9]

(8) McLennan, D. L. *J. Chem. Soc. B* **1966**, 705–708.

(9) Hudson, R. F.; Klopman, G. *J. Chem. Soc.* **1964**, 5–15.

(10) Walters, E. A.; Long, F. A. *J. Am. Chem. Soc.* **1969**, *91*, 3733–3739.

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(13) The low k_H/k_D isotope effects and high β values observed in the isotopic exchange reactions[10,11] suggest that $k_{-1} > k_2$ in these reactions. Other examples where low k_H/k_D isotope effects and/or high β values suggest that this mechanism is operative include the deprotonation of $HCCl_2F$ by HO^- in H_2O,[14] deprotonation of $HCCl_3$ in H_2O ($\beta \simeq 1$),[15,16] and detritiation of PhC≡CH in water ($\beta \simeq 1$).[16]

(14) Hine, J.; Burske, N. W. *J. Am. Chem. Soc.* **1965**, *78*, 3337–3339.

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(16) Kresge, A. J. *Acc. Chem. Res.* **1975**, *10*, 354–360.

(17) Clemens, A. H., unpublished results.

(18) Hughes, D. L., unpublished results.

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given reaction type as predicted by the principle of least motion.[20] Thus, β is large for reactions requiring relatively little molecular reorganization in changing from ground to transition state, such as proton transfers from cyano carbon acids and single-electron transfers, and decreases in size for reactions requiring more molecular reorganization, such as E2 reactions.

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Registry No. 9-(*m*-ClC_6H_4)-fluorenyl, 73872-45-4; 9-PhS-fluorenyl, 71805-72-6; 2-$PhSO_2$-9-Ph-fluorenyl, 73872-40-9; (*p*-$CH_3OC_6H_4$)NSO_2CH_3, 84498-90-8; $C_6H_5NSO_2CH_3$, 61057-11-2; $C_6H_5NSO_2Ph$, 28627-70-5; (*m*-BrC_6H_4)NSO_2Ph, 84498-91-9; *p*-$CH_3OC_6H_4S^-$, 26971-83-5; $C_6H_5S^-$, 13133-62-5; *p*-$BrC_6H_4S^-$, 26972-20-3; 3,5-$Cl_2C_6H_3O^-$, 65800-69-3; 3,4,5-$Cl_3C_6H_2O^-$, 60154-34-9; 2,4,5-$Cl_3C_6H_2O^-$, 45773-92-0; 2,3,4,5-$Cl_4C_6HO^-$, 84498-92-0; 3-butenenitrile, 109-75-1.

(20) Hine, J. *J. Org. Chem.* **1966**, *31*, 1236-1244. Tee, O. S.; Altmann, J. A.; Yates, K. *J. Am. Chem. Soc.* **1974**, *96*, 3141-3146. Altmann, J. A.; Tee, O. S.; Yates, K. *Ibid.* **1976**, *98*, 7132-7138.

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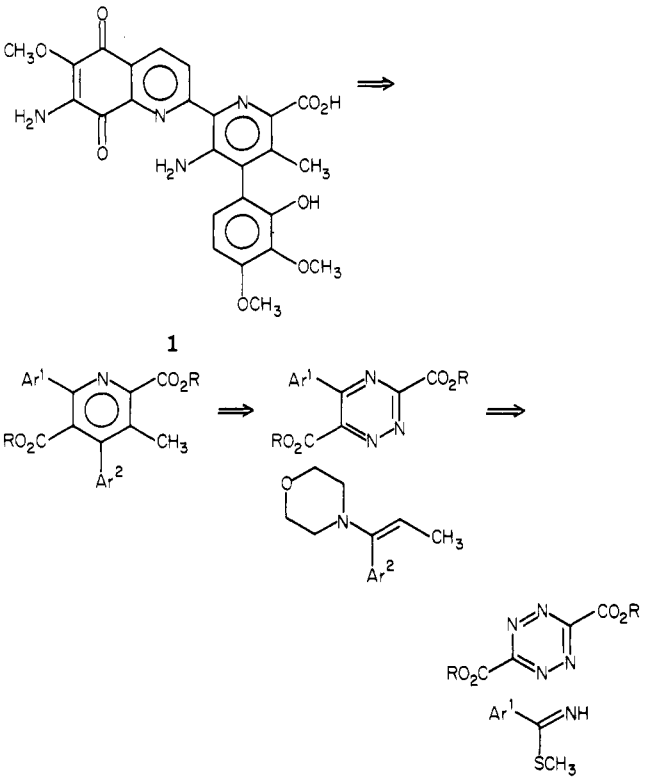
Formal Total Synthesis of Streptonigrin[1]

Summary: An efficient, formal total synthesis of streptonigrin (1) is detailed and is based on the implementation of two consecutive inverse electron demand Diels–Alder reactions: 1,2,4,5-tetrazine + *S*-methyl thioimidate (streptonigrin ABC ring construction) and 1,2,4-triazine + morpholino enamine (streptonigrin CD ring construction).

Sir: Streptonigrin (1) was first isolated from the broth of *Streptomyces flocculus* by Rao and Cullen,[2a] and through the chemical degradative and spectral studies of Woodward, Biemann, and Rao,[2b] the correct structure was proposed in 1963 and later confirmed in an X-ray crystal study.[2c] Since that time streptonigrin has been the subject of extensive biological and chemical studies.[3] It has been found to be active against Gram-positive and Gram-negative bacteria as well as a number of tumors including herpes simplex I/III and mouse mammary tumors. Although the toxicity associated with the administration of streptonigrin has decreased the potential clinical use of this agent, reports of its use in combination therapy with vincristine, prednisone, and bleomycin have been described.[3] Moreover, recent studies on the chemical mechanism by which streptonigrin exerts its biological effects, efforts to define the essential structural requirements for activity, and investigations on the biosynthesis of streptonigrin have renewed interest in this and related antitumor antibiotics.[4]

Scheme I



1

The complex structural features of streptonigrin (1), a substituted quinone quinoline possessing a pentasubstituted pyridine, the chemical and biological interest in streptonigrin, and the potential application of structurally related analogues have provided the incentive for much synthetic work[5] which has resulted in two reported total syntheses.[5a,b]

The synthetic utility of the inverse electron demand Diels–Alder reactions of heterocyclic azadienes has gone largely unrecognized due to the ambiguities concerning the mode of cycloaddition, the lack of useful, electron-rich dienophiles, and the lack of demonstrated or dependable synthetic procedures and applications. Herein, we disclose a short, convergent formal total synthesis of streptonigrin (1) based on the implementation of two consecutive inverse electron demand Diels–Alder reactions: the first for construction of the ABC ring system (1,2,4,5-tetrazine + *S*-

(1) Presented in part at the 184th National Meeting of the American Chemical Society, Kansas City, MO, Sept 1982.

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