Notes

Relationship between the Solid-State and Solution Conformations of β-(Benzylamino)crotonate

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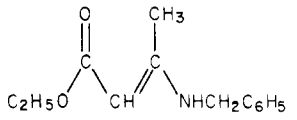
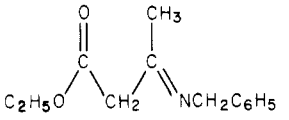
Schiff bases are important intermediates in several enzyme-catalyzed reactions[1,2] and the Schiff bases of dicarbonyl compounds and monoamines (i.e., β-(benzylamino)crotonate) are of interest as systems for study of the effects of solvents on hydrogen bonding.[3,4] In addition, the enamine tautomer of these Schiff bases is conformationally mobile and appears to provide an example of conformational/configurational polymorphism involving cis–trans isomerism about a double bond.[5,6] Finally, these Schiff bases provide another example of the use of the solid state to isolate one isomer from an equilibrium mixture of isomers in solution.[7] Other examples of the use of crystallization to isolate a particular isomer include crystallizations of histamine and choline,[8] chlorocyclohexane,[9] 1,1-bis(isopropoxycarbonyl)-9,1′-bis[fluorenylidene],[10] *p*-nitrobenzophenone methylimine,[11] *N*-(1,2,3-trimethylbutenylidene)-1-benzenesulfonamide[12], (*tert*-butoxycarbonyl)phenylalanine,[13] and several *meso*-dihalobutanes such as meso-β,β′-dibromoadiponitrile[14].

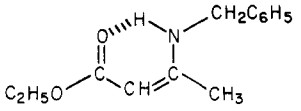


enamine tautomer

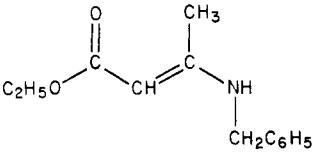


ketimine tautomer

Infrared studies by Dabrowski and Schad[15-17] and NMR studies by Dudek and Volpp[18] show that ethyl β-(benzylamino)crotonate exists in a low melting (mp 23 °C) and a high-melting (mp 75–80 °C) crystalline isomer which were suggested to have structures Ia and Ib. Also, isomerization takes place between these isomers in solution.[3,18,19]



Ia, mp 23 °C
cis (*Z*) isomer



Ib, mp 75–80 °C
trans (*E*) isomer

This paper reports the crystal structure of isomer Ib and uses this structure as a basis for investigation of the isomers of I in solution. This paper also illustrates the knowledge that can be gained by using an approach which involves crystal structure determination and solution conformational analysis.

Experimental Section

Preparation of Ethyl β-(Benzylamino)crotonate. Ethyl β-(benzylamino)crotonate was prepared by the method of Mohlau[20] and the high-melting isomer was obtained from acetone by cooling in the refrigerator. The crystals of the isomer had a melting point of 75–80 °C (lit. mp 79 °C).

NMR Studies. NMR spectra were obtained in 5-mm tubes with Me_4Si as an internal reference on a Varian FT-80 or EM-360 spectrometer. The variable-temperature study was carried out on a 0.15 M dimethyld_6 sulfoxide (Merck Sharp and Dohme, Ltd.) solution by using a Perkin-Elmer R32 spectrometer. The temperature-dependent chemical shifts of methanol and glycol were used to calibrate the temperature. The isomerization of Ib ⇄ Ia was studied in the range from 25 to 50 °C. The data were plotted according to first-order kinetics, and the plots were treated by using least-squares analysis. The correlation coefficients for these analyses were greater than 0.99.

The conformation of both Ia and Ib about the N18–C20 and C13–N18 bonds was studied in Me_2SO-d_6 solution by using the Karplus equation. For both Ia and Ib, the H19–N18–C20–H coupling constant was 5.7 Hz.

Crystal Data Collection and Structure Solution for the High-Melting Isomer of Ethyl β-(Benzylamino)crotonate (Ib).[25] Least-squares analysis of the position of 13 independent hand centered reflections gave a = 19.655 (8) Å, b = 5.778 (3) Å, c = 10.632 (3) Å, V = 1207.44 Å^3, Z = 4, ρ_{calcd} = 1.21 g/cm^3, mol wt for $C_{13}H_{17}NO_2$ 219.29 $F(000)$ = 472, μ = 0.66 (Cu Kα, λ = 1.5418), and space group $P2_12_12_1$. Data were collected on a Picker four-circle diffractometer (card driven) using Ni-filtered Cu Kα radiation and a scintillation detector. A θ–2θ scan of 2.2° was appplied with a scan speed of 60 s/deg. Backgrounds were counted for 10 s at each end of the scan range. The reciprocal region *hkl* was explored to a 2θ maximum of 133°. Two standards were measured after each group of 60 reflections. The intensity of the reflections was corrected for decay of these standards. There were 1174 reflections out of with 1094 satisfied the condition that $F_o > 3\sigma(F_o)$ and were considered observed.

The structure was determined by direct methods by using the MULTAN program.[21] An *E* map based on the solution having the

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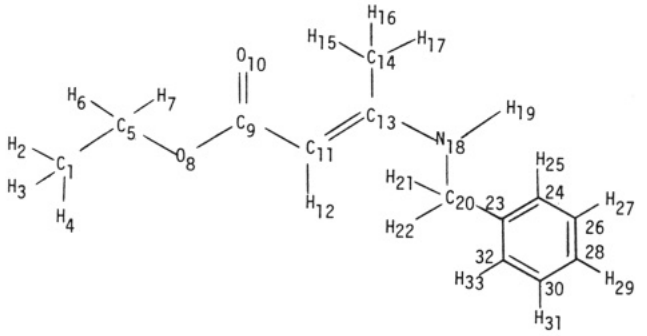

Figure 1. Numbering scheme for the Schiff's base ethyl β-(benzylamino)crotonate (Ib). Atom numbers are given.

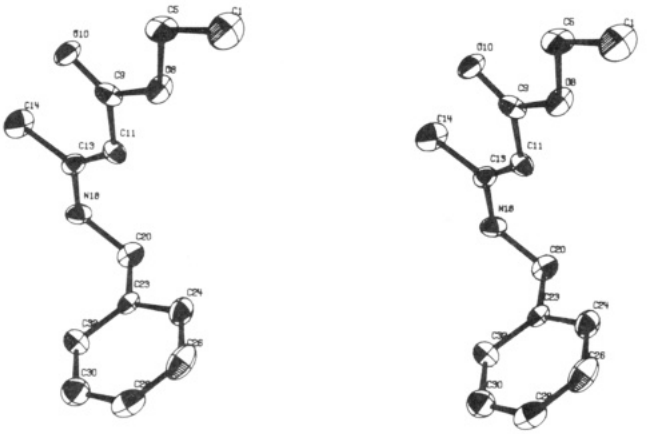

Figure 2. ORTEP drawing of the structure of the high-melting isomer of ethyl β-(benzylamino)crotonate (Ib).

highest figure of merit revealed the positions of all but one of the nonhydrogen atoms. The remaining nonhydrogen atom was located on a difference Fourier map. Refinement of these positions first with isotropic and then with anisotropic temperature factors proceeded smoothly to an R factor 0f 0.12. A difference map allowed the location of 5 of the 17 hydrogen atoms. The rest of the hydrogen atoms were placed in calculated positions. Further refinement of the nonhydrogen atoms only gave a final R factor of 0.080 after eight reflections were omitted because they apparently suffered from extinction. A final difference map contained no recognizable molecular fragments. The highest peak on this map had a height of 0.33 e/A^3. Final positional parameters are listed in Table I. The final temperature factors are listed in Table II of the supplemental material. Tables III–V of supplement material list the bond lengths, bond angles, and intermolecular contacts.

Results and Discussion

Figure 1 shows the numbering scheme used in the crystallographic and conformational studies.

An ORTEP drawing of the high-melting isomer of ethyl β-(benzylamino)crotonate (Ib) is shown in Figure 2. The crystal packing is dominated by an NH···O hydrogen bond. The distance for this intermolecular interaction is 3.03 Å which is well within the expected range for NH···O hydrogen bonds. The intermolecular contacts listed in Table V reflect this N18···O10 interaction and the interaction of groups adjacent to N18 and O10. The intermolecular contact C28···C24 reflects a phenyl–phenyl interaction.

NMR spectroscopy gives the ratios of *cis*-Ia/*trans*-Ib at equilibrium. The ratios are solvent dependent and range from 95:5 in $CDCl_3$ to 86:14 in acetone-d_6 to 55:45 in Me_2SO-d_6. The rate of isomerization was solvent dependent with a half-life of 6.7 min in $CDCl_3$, 6.6 h in Me_2SO-d_6, and 18.4 h in acetone-d_6.

The rate of isomerization of Ib to Ia has been studied in Me_2SO-d_6 at temperatures of 28, 35, 42, and 50 °C. The rate constants at these temperatures are 0.119, 0.158, 0.347, and 0.512, respectively. These data give an activation energy of 13.6 kcal/mol.

Table I. Final Positional Parameters (Fractional) with esd's in Parentheses

	x/a	y/b	z/c
C1	0.0815 (5)	−0.1936 (18)	0.2790 (8)
C5	0.1189 (4)	0.0209 (16)	0.2428 (6)
O8	0.1282 (2)	0.0162 (9)	0.1065 (4)
C9	0.1640 (3)	0.1975 (13)	0.563 (6)
O10	0.1855 (3)	0.3505 (9)	0.1237 (4)
C11	0.1706 (3)	0.1683 (12)	−0.0776 (6)
C13	0.2074 (3)	0.3171 (13)	−0.1497
C14	0.2440 (4)	0.5287 (15)	−0.0988 (7)
N18	0.2152 (3)	0.2865 (10)	−0.2754 (5)
C20	0.1902 (3)	0.0863 (13)	−0.3439 (6)
C23	0.1149 (3)	0.0934 (12)	−0.3737 (6)
C24	0.0728 (4)	−0.0946 (13)	−0.3432 (6)
C26	0.0051 (4)	−0.0930 (15)	−0.3752 (8)
C28	−0.0232 (3)	0.0963 (15)	−0.4399 (8)
C30	0.0180 (4)	0.2828 (14)	−0.4688 (7)
C32	0.0862 (3)	0.2846 (13)	−0.4358 (7)
H2	0.038	−0.211	0.236
H3	0.114	−0.337	0.256
H4	0.077	−0.194	0.375
H5	0.089	0.161	0.268
H7	0.165	0.036	0.288
H12	0.147	0.029	−0.120
H15	0.280	0.450	−0.033
H16	0.794	1.111	0.550
H17	0.256	0.618	−0.178
H19	0.240	0.412	−0.324
H21	0.200	−0.057	−0.294
H22	0.216	0.080	−0.428
H25	0.095	−0.235	−0.296
H27	−0.026	−0.235	−0.351
H29	0.925	0.088	0.541
H31	0.000	0.422	−0.531
H33	0.116	0.425	−0.457

Me_2SO-d_6 solutions of I were studied in order to get an approximation of the conformation of both Ia and Ib about the C13–N18 and C20–N18 bonds. Both Ia and Ib had an H19–N18–C20–H21,22 coupling constant of 5.7 Hz. Application of the Karplus equation[22] gave an H–N18–C20–H dihedral angle of 35° which corresponds to an H–N18–C20–H dihedral angle of approximately 85°. The corresponding angle in the crystal is 79°. However, the close agreement between the calculated dihedral angle in solution and the solid state angle may be fortuitious since the applicability of the Karplus equation to enamines is not established. For Ia, both IR and NMR studies show that there is a strong NH···O hydrogen bond, indicating the C13–N18 dihedral angle is approximately 360°. The corresponding angle in the crystal is −5°.

The crystal structure and the results of the solution NMR and IR studies reported herein are consistent with published reports.[15-19] In the high-melting isomer, ethyl β-(benzylamino)crotonate exists as the trans enamine (Ib) in the solid. NMR and IR studies of melts of the low-melting isomer strongly suggest that this isomer exists as this cis enamine isomer (Ia). Thus this Schiff base appears to provide a example of conformational/configurational polymorphism involving cis–trans isomerization.

As was found in an earlier study of OH···O hydrogen bonds,[23] dimethyl sulfoxide is unusually effective in breaking hydrogen bonds to carbonyl groups. When the solvent is changed from chloroform-d to acetone-d_6 to dimethyl-d_6 sulfoxide, the percent of cis isomer at equi-

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librium and the ΔG (at 25 °C) decreased from 95% (ΔG = 1.745 kcal/mol) to 86% (ΔG = 1.028 kcal/mol) to 55% (ΔG = 0.119 kcal/mol). This result is due to the ability of dimethyl sulfoxide to compete with a carbonyl group for the NH hydrogen bond. In addition, dimethyl sulfoxide may associate with the carbonyl group.[23] Acetone shows less ability to break the NH···O hydrogen bond in the cis isomer because the carbonyl group in acetone is not as polarized as the sulfoxide group in dimethyl sulfoxide. The results of these studies are consistent with the effect of solvents on the proportions of cis and trans isomers of the Schiff bases of monoalkylamines and ethyl acetoacetate where the cis/trans ratio varies from 15:1 in CCl_4 to 10:1 in $CDCl_3$ to 7:5 in Me_2SO.[19]

The activation energy for isomerization (13.6 kcal/mol) in Me_2SO is consistent with either a mechanism involving isomerization about the double bond or a mechanism involving a ketimine intermediate. Rotation barriers as low as 9.1 kcal/mol have been observed for dialkenylamino ketones.[24] This low rotation barrier is apparently due to the fact that the transition state for isomerization resembles one of the possible charge-separated resonance structures. In order to test whether a ketimine was present, we measured the exchange of the olefin hydrogen atom of I in Me_2SO/D_2O. This hydrogen atom did exchange but at a much slower rate than isomerization, ruling out a mechanism involving only isomerization via the ketimine.

In conclusion, this paper illustrates another example of a useful approach to the analysis of conformationally (configurationally) mobile systems. This approach involves initial crystallographic analysis and subsequent solution studies. When information from these studies (crystallographic and solution) is combined, a complete picture of conformationally mobile systems is obtained.

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Registry No. **Ia**, 21759-74-0; **Ib**, 21731-13-5.

Supplementary Material Available: Table II, final temperature factors; Table III, bond lengths; Table IV, bond angles; Table V, intermolecular contacts (3 pages). Ordering information is given on any current masthead page.

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4-Alkoxybenzonitriles from *O*-Alkyl-4-nitrobenzaldoximes: An Elimination–Aromatic Substitution Reaction

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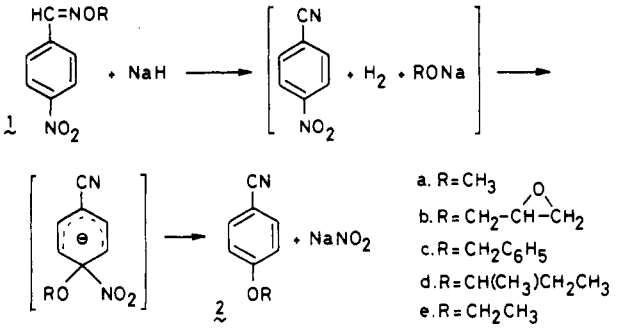
It has been reported that, in dipolar aprotic solvents, an aromatic nitro group activated by a single ortho or para carbonyl-type function can be replaced by nucleophiles ranging from hydroxyl or alkoxyl anions[1] to mercaptides[2,3] and oximate anions.[4] The latter nucleophile reacts with 4-nitrobenzonitrile to give an *O*-aryl aldoxime that undergoes elimination to the corresponding nitrile: these transformations constitute a "one pot" method for the conversion of aldoximes into nitriles.[4] In an extension of this work,[5] (*E*)-4-nitrobenzaldoxime was found to give 4-hydroxybenzonitrile upon alkaline treatment in Me_2SO solution containing a small amount of 4-nitrobenzonitrile. The proposed reaction pathway[5] involves a nitro displacement to afford *O*-(4-cyanophenyl)-4-nitrobenzaldoxime, followed by a base-promoted elimination leading to 4-hydroxybenzonitrile (the leaving group) and the chain carrier, 4-nitrobenzonitrile.

Scheme I



In relation to the above results, we now report that in dipolar aprotic solvents (dimethylformamide or dimethyl sulfoxide), the *O*-alkyl ethers of 4-nitrobenzaldoxime react with bases to give the corresponding 4-alkoxybenzonitriles in good yields.

The starting oxime ethers **1a–d** were obtained in excellent yields by alkylation of 4-nitrobenzaldoxime sodium salt with the appropriate alkyl halide in DMF solution.[6] Treatment of a DMF solution of the above oxime ethers with an excess of sodium hydride at room temperature afforded the 4-alkoxybenzonitriles **2a–d**, which were identified by their melting points and spectroscopic characteristics. Thus, the IR spectra of **2a–d** showed a strong absorption at 2235 cm^{-1}, due to the cyano group stretching. Comparison of the NMR spectra of **2a–d** with those of the oxime ethers **1a–d** showed the disappearance of the aldoxime proton signal near δ 8.0 and an upfield shift of 0.6–0.8 ppm for the aromatic signals. Mass spectrometry was used to confirm the structure of **2b**.

The above elimination–aromatic substitution reactions were also carried out in an NMR tube with hexadeuterated Me_2SO as a solvent; similar results were then obtained. **2a–c** were formed very fast (less than 1 min after the addition of NaH) whereas in the case of **2d** the reaction was completed after 3 h. Unfortunately, the reaction kinetics could not be established, since the hydrogen evolved during the process caused a loss of resolution of the NMR signals.

We propose a reaction pathway for the formation of 4-alkoxybenzonitriles **2a–d** involving an intial elimination of the alkoxide moiety from the oxime ethers **1a–d**, followed by a displacement of the nitro group (as nitrite anion) by the nucleophilic attack of the alkoxide anion (Scheme I).

The second step takes place readily because of the activating effect of the dipolar aprotic solvent. The replacement of the nitro group on 4-nitrobenzophenone by

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