Reaction of N,N′-Biisomaleimide with Butylamine. Amine-Catalyzed *cis–trans* Isomerization

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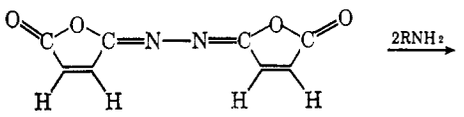
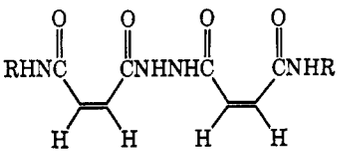
Reactions of N,N′-biisomaleimide with *n*-, *sec*-, and *t*-butylamine in dimethyl sulfoxide solution produce the anticipated ring-opened adducts, but different geometric isomers were obtained. An amine-catalyzed *cis–trans* isomerization is believed to have taken place. In the presence of a primary or a secondary amine, but not a tertiary amine, the N,N′-biisomaleimide–butylamine adducts were found to undergo simultaneous complexation and isomerization. Using a given butylamine as catalyst, the extent of isomerization decreases in the order N,N′-biisomaleimide–*n*-butylamine adduct > N,N′-biisomaleimide–*sec*-butylamine adduct > N,N′-biisomaleimide–*t*-butylamine adduct. When different butylamines were used as catalysts, the extent of isomerization for a given adduct decreases in the order *n*-butylamine > *t*-butylamine. Because of the small differences in basicity among these butylamines, our results suggest that steric interactions are responsible for the differences in the extent of isomerization. The occurrence of complexation during the isomerization provides a useful correlation for understanding the catalytic behavior of these amines. The mechanism proposed by Nozaki and Ogg for an acid- or salt-catalyzed isomerization of maleates to fumarates is extended to include amine-catalyzed isomerizations.

It was recently reported by Hedaya and his collaborators[1,2] that N,N′-biisomaleimide (I), similar to other isomaleimides,[3] reacts readily with nucleophiles to yield ring-opened adducts illustrated by II. These



I



II

IIa, R = *n*-Bu
b, R = *sec*-Bu
c, R = *t*-Bu

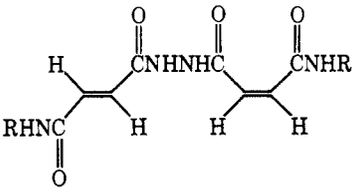
adducts were suggested to assume a *cis* configuration with respect to the carbon–carbon double bond. Reactions of I with aliphatic amines were shown in the present work to form in certain instances different geometric isomers. An amine-catalyzed *cis–trans* isomerization is believed to have taken place.

The base-catalyzed isomerization of maleic acid and its esters has received only limited attention. Meerwein and Weber[4] found that potassium in ether converted methyl maleate into methyl fumarate. Tanatar[5] and Pfeiffer[6] reported the isomerization of maleic acid to fumaric acid by means of ammonia and pyridine, respectively. Clemo and Graham[7] investigated systematically the catalytic action of various amines and found that only primary and secondary amines were effective; tertiary amines, even though they were stronger bases than many primary and secondary amines, did not lead to isomerization. It was concluded that organic bases are only effective as catalysts when they contain amino or imino hydrogen. A mechanism was proposed by these authors involving the formation of a coordinate link between the hydrogen atom of the base and the carbonyl oxygens of the maleic ester. Isomerization occurs as a result of rotation about the electron-deficient double bond.

We have examined the amine-catalyzed *cis–trans* isomerization of various N,N′-biisomaleimide–butylamine adducts. The catalytic activity of the three isomeric butylamines and the extent of isomerization of various adducts with a given amine were investigated. We have also studied the complexation of amine with these adducts and the correlation of the complex formation with the isomerization. A reconsideration of the mechanism for an amine-catalyzed isomerization is presented.

Results and Discussion

Reaction of N,N′-biisomaleimide (I) with *n*-butylamine in dimethyl sulfoxide (DMSO) solution at 25° was found to yield products consisting of both *cis–cis* adduct (IIa) and *cis–trans* adduct (IIIa). Under the same reaction conditions either *sec*-butylamine or *t*-butylamine produced only the corresponding *cis–cis* adduct IIb and IIc, respectively.



IIIa, R = *n*-Bu
b, R = *sec*-Bu
c, R = *t*-Bu

Amines are known to effect the isomerization of maleic acid and its esters to the fumaric forms.[4–7] This leaves unanswered, however, the question of why isomerization did not occur in the reactions involving either *sec*-butylamine or *t*-butylamine.

The isomerization of these adducts by various butylamines was investigated using the nmr method. Figure 1 shows the nmr spectra in the ethylenic proton regions of three N,N′-biisomaleimide–butylamine ad-

(1) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *J. Org. Chem.*, **31**, 1311 (1966).
(2) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *ibid.*, **31**, 1317 (1966).
(3) R. J. Cotter, C. K. Sauers, and J. M. Whelan, *J. Org. Chem.*, **26**, 10 (1961).
(4) H. Meerwein and J. Weber, *Ber.*, **58**, 1266 (1925).
(5) S. Tanatar, *J. Russ. Phys. Chem. Soc.*, **43**, 1742 (1911).
(6) P. Pfeiffer, *Ber.*, **47**, 1592 (1914).
(7) G. R. Clemo and S. B. Graham, *J. Chem. Soc.*, 213 (1930).

ducts after being heated at 60° for 10 min in the presence of 0.5 mol of *n*-butylamine/mol of adduct. The *cis*-ethylenic protons, which exhibit a singlet signal in DMSO solution, are observed as an AB quartet (J_{AB} = 13 Hz) in the presence of *n*-butylamine. This phenomenon is associated with a complexation of the hydrazide group of the adduct with the *n*-butylamine. Of specific interest, however, is the observation that all three of these adducts (IIa, b, and c) show absorption characteristic of *trans*-ethylenic protons (collapsed AB quartet, about 6.9 ppm) after being heated for 10 min with *n*-butylamine.

The results are summarized in Table I. It is seen that the extent of isomerization noticeably increased when the butyl group in the adduct was changed from *t*-butyl to *sec*-butyl to *n*-butyl.

TABLE I

ISOMERIZATION OF N,N'-BIISOMALEIMIDE–BUTYLAMINE ADDUCTS CATALYZED BY *n*-BUTYLAMINE IN DMSO SOLUTION

	Conditions			
Adduct	*T*, °C	*t*, min	%	%
IIa	60	10	75	25
IIb	60	10	83	17
IIc	60	10	86	14

The relative extents of isomerization of IIb by different butylamines were determined in a similar manner.

As seen in Table II, 85% isomerization was observed on treatment with 0.5 mol of *n*-butylamine for 10 min at 100° while only 8% isomerization occurred on treatment with *t*-butylamine under the same conditions.

TABLE II

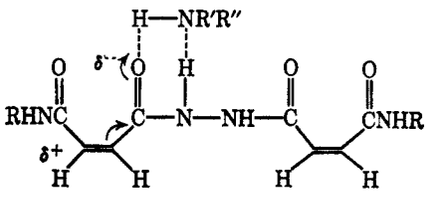
CATALYTIC ACTIVITIES OF SOME BUTYLAMINES IN THE ISOMERIZATION OF IIb

	Conditions			
Catalyst	*T*, °C	*t*, min	%	%
n-Butylamine	100	10	15	85
t-Butylamine	100	10	92	8

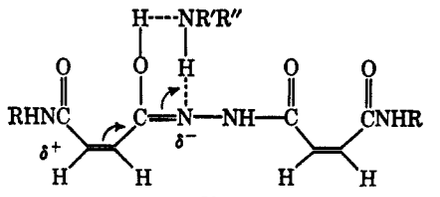
The ionic intermediate proposed by Clemo and Graham[7] seems not to be present in our system. Our data suggest that only the carbonyl of the hydrazide group participates during the isomerization.

In DMSO solution, the amide protons of IIb were observed as a doublet at 8.66 ppm. Addition of 0.5 mol of *t*-butylamine shifted the absorption due to the amide protons to 10.72 ppm, but did not change either the multiplicity (d, J = 8 Hz) or the relative intensity. In contrast, the addition of *t*-butylamine caused a disappearance of the 11.7-ppm hydrazide signal, and in its place was observed a singlet at 8.68 ppm having double the original intensity. This absorption is believed to result from a rapid exchange of the hydrazide protons with the protons of the added amine and indicates a complex of the type shown by IV or V.

Figure 1.—Nmr spectra of (a) IIa, (b) IIb, and (c) IIc in DMSO solution containing *n*-butylamine measured after 10 min at 60°.



IV

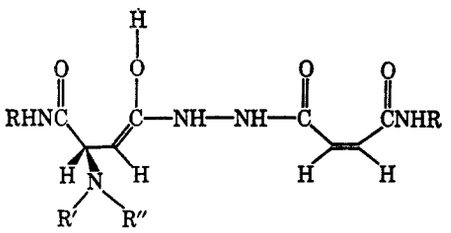


V

Infrared spectral changes were also consistent with these postulated complexes. The NH stretching absorption at 3170 cm^{-1} was converted into a very broad band extending from 3430 to 2520 cm^{-1} on addition of *t*-butylamine. This type of change has previously been

ascribed to the occurrence of a chelated hydroxy group through hydrogen bonding.[8]

Let us assume that the initial step of an amine-catalyzed isomerization involves a nucleophilic attack of amine at the *cis*-ethylenic double bond to generate an intermediate VI where R′ is alkyl and R″ is alkyl or hydrogen. This is analogous to the initial step in the Nozaki and Ogg mechanism for the acid- or salt-catalyzed isomerization of maleic acid and its esters.[9] We would then predict that the catalytic activities of the butylamines should parallel their nucleophilicities.



VI

A correspondence generally exists between the order of basicities and the order of nucleophilicities for a group of nucleophiles having the same attacking atom.[10] Thus the following order of catalytic activities would be expected for these amines (the pK_b values are in parentheses): *n*-butylamine (3.39) > *sec*-butylamine (3.44) > *t*-butylamine (3.55). Although the order is consistent with our observations, it is doubtful that the small differences in basicities between these three primary amines could account fully for our results. Additionally, the data shown in Table I cannot be satisfactorily explained in terms of nucleophilicity of the *n*-butylamine.

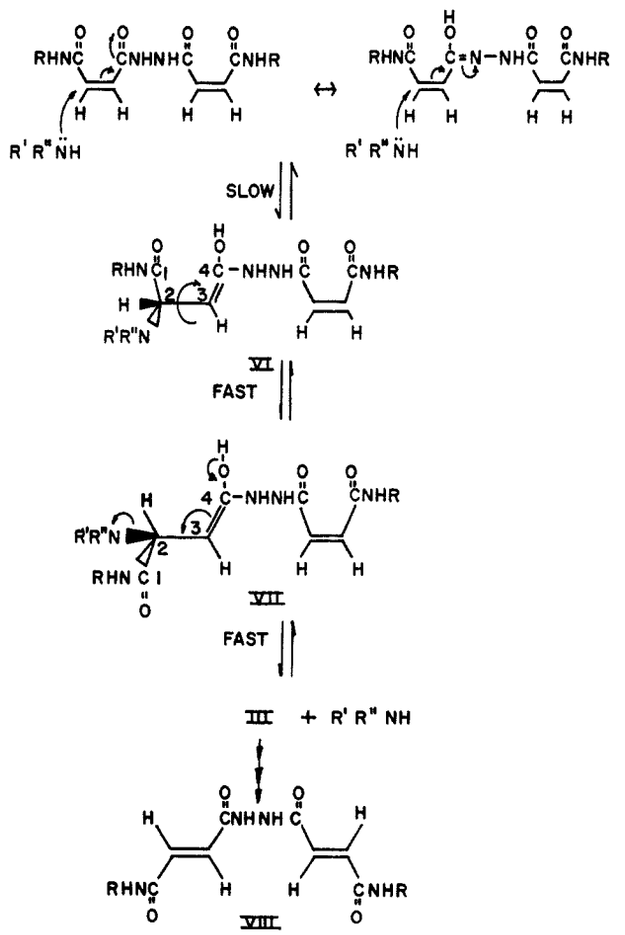
It is conceivable that the initial attack at the *cis*-ethylenic double bond could be hindered substantially when bulky species are involved. The dependence of rate of isomerization on the bulkiness of the neighboring butyl groups in a *cis–cis* adduct is consistent with the data shown in Table I. This result suggests that the incoming butylamine molecules encounter steric interactions of different degrees with the butyl groups present in the *cis–cis* adducts during the formation of the intermediate VI. Following this line of reasoning one would expect that the rates of isomerization of a given adduct should also be different when amines of different steric nature are employed as catalysts. This consideration is in agreement with the results shown in Table II. *n*-Butylamine was found to be a much more effective catalyst than *t*-butylamine in spite of their relatively close base strength. This observation is parallel to the result found in the reaction of amines with alkyl halides.[11] The effect of steric hindrance on the catalytic activity of a cyclic secondary amine was also observed by Janssen[12] in the isomerization of maleic acid based polyesters.

Isomerization of these adducts could also be catalyzed by a secondary amine, but not by a tertiary amine regardless of the base strength. Such behavior is similar to that of maleic acid and its esters.[7]

(8) R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Amer. Chem. Soc.*, **71**, 1068 (1949).
(9) K. Nozaki and R. Ogg, Jr., *ibid.*, **63**, 2583 (1941).
(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 259.
(11) H. C. Brown and N. R. Eldred, *J. Amer. Chem. Soc.*, **71**, 445 (1949).
(12) B. Janssen, *Chimia*, **19**, 154 (1965).

In our view, the mechanism postulated by Nozaki and Ogg[9] can be extended to include an amine-catalyzed isomerization with some modifications. As illustrated by Scheme I, the initial step, which is believed to be

SCHEME I



the rate-determining step, involves a 1,4 addition of amine at the conjugated double bonds to generate the intermediate VI. In VI, bond 1–2 can rotate freely about the axis of bond 2–3 forming either a *trans* conformer, VII, or a *gauche* conformer (such as VI) with respect to bond 3–4. A *trans–cis* adduct, III, results when a rapid elimination of amine from the unstable intermediate VII occurs. An elimination of amine from a *gauche* conformer would regenerate the original *cis–cis* adduct, II. Further isomerization of III would form eventually the *trans–trans* adduct VIII.

Intermolecular hydrogen bonding to give complexes such as IV and V probably results in a polarization of the maleic carbon–carbon double bond, and thus would be expected to facilitate greatly nucleophilic addition to this unsaturated site. This consideration appears to explain the ease with which the isomerization can proceed under appropriate conditions. The actual rate of addition of amine to the double bond in this system, however, is strongly influenced by steric considerations.

Experimental Section

Instrumental.—A Varian Model A-60 instrument was used for the nmr measurements. Tetramethylsilane and DMSO (J. T. Baker, redistilled) were employed as the internal standard and solvent, respectively. For infrared spectra, a Perkin-Elmer

Model 221 was used with either potassium bromide pellets or DMSO solution in KBr cells. Melting points were taken with a Thomas–Hoover capillary apparatus and were corrected.

N,N'-Biisomaleimide (I) was prepared according the procedures previously described.[6] The crude product was recrystallized from dimethylformamide to yield a yellow solid (61%), mp 260° (lit.[1] mp 260°).

Anal. Calcd for $C_4H_2NO_2$: C, 50.00; H, 2.08; N, 14.58. Found: C, 50.19; H, 2.29; N, 14.41.

Reaction of N,N'-Biisomaleimide (I) with *n*-Butylamine.—Into a 50-ml three-necked flask, equipped with a condenser, thermometer, nitrogen inlet, rubber cap, and a magnetic stirrer was placed 1.92 g (0.01 mol) of I and 10 ml of redistilled DMSO. While under cooling with an outside water bath, 1.61 g (0.022 mol) of *n*-butylamine was introduced into the reaction vessel with a syringe. An exothermic reaction occurred immediately and an orange solution was obtained. The reaction was allowed to proceed at room temperature for 23 hr. The white solid formed in the flask was collected by filtration. It was washed successively with dimethoxyethane and ether and was dried under vacuum: white solid, mp >335°; yield 0.82 g (24.3%). This product was shown to be the *cis–trans* adduct IIIa: nmr (DMSO, 100°), δ 8.7 (s, 2, hydrazide), 8.18 (t, 2, J = 5 Hz, amide), 6.93 (s, 2, *trans*-ethylene), and 6.23 (s, 2, *cis*-ethylene); ir (KBr), 1625 cm^{-1} (medium, amide–amide I), 1591 (very strong, hydrazide–amide I), 1556 (strong, amide–amide II), 1473 (strong, hydrazide–amide II), and 996 (medium, *trans*-disubstituted ethylene).

Anal. Calcd for $C_8H_{12}O_2N_2$: C, 56.80; H, 7.69; N, 16.57. Found: C, 56.56; H, 7.75; N, 16.75.

The above filtrate was poured into 50 ml of water and the pinkish solid which precipitated was collected, washed with an acetone–ether mixture, and dried under vacuum: pale yellow solid; mp 150°; yield 3.02 g (65.1%). This product was assigned to be the *cis–cis* adduct IIa: nmr (DMSO, 70°), δ 11.4 (s, 2, hydrazide), 8.81 (t, 2, J = 5 Hz, amide), 6.17 (s, 4, *cis*-ethylene); ir (KBr), identical with that of IIIa except no 996-cm^{-1} absorption was observed.

Anal. Calcd for $C_8H_{12}O_2N_2$: C, 56.80; H, 7.69; N, 16.57. Found: C, 56.55; H, 7.57; N, 16.47.

The aqueous solution was combined with the acetone–ether washings and concentrated to less than 5 ml with a rotating evaporator. The solution was diluted with a small amount of acetone and was poured into 50 ml of ether. A reddish brown, resinous material was obtained: yield 0.061 g (1.8%). This resinous material exhibits in the nmr weak ethylenic proton signals but a broad signal at about 8 ppm which is presumably due to the presence of various amido and amino protons.

Reaction of N,N'-Biisomaleimide (I) with *sec*-Butylamine.—The reaction was carried out in the same manner as described above. There was no insoluble product formed by the end of the reaction. Two fractions of product were obtained. The DMSO-soluble, water-insoluble fraction was a greenish yellow solid, mp 204°, yield 3.16 g (93.3%). This product was shown to be the *cis–cis* adduct IIb: nmr (DMSO, 70°), δ 11.4 (s, 2, hydrazide), 8.66 (d, J = 8 Hz, 2, amide), and 6.19 (s, 4, *cis*-ethylene); ir (KBr), 1625 cm^{-1} (medium, amide–amide I), 1596 (very strong, hydrazide–amide I), 1555 (strong, amide–amide II), and 1493 (strong, hydrazide–amide II).

Anal. Calcd for $C_8H_{12}O_2N_2$: C, 56.80; H, 7.69; N, 16.57. Found: C, 56.13; H, 7.78; N, 16.53.

The water-soluble, ether–acetone-insoluble fraction was a reddish brown, resinous substance, yield 0.041 g (1.2%).

Reaction of N,N'-Biisomaleimide (I) with *t*-Butylamine.—The reaction was carried out in the same manner as described above. There was no insoluble product formed by the end of reaction. Two fractions of products were isolated. The DMSO-soluble, water-insoluble fraction was a greenish yellow solid, mp 222°, yield 3.08 g (91.1%). This product was shown to be the *cis–cis* adduct IIc: nmr (DMSO, 100°), δ 8.6 (broad s, 4, hydrazide and amide), and 6.20 (s, 4, *cis*-ethylene); ir (KBr), 1625 cm^{-1} (medium, amide–amide I), 1590 (very strong, hydrazide–amide I), 1556 (strong, amide–amide II), and 1490 (strong, hydrazide–amide II).

Anal. Calcd for $C_8H_{12}O_2N_2$: C, 56.80; H, 7.69; N, 16.57. Found: C, 56.00; H, 7.80; N, 16.18.

The water-soluble, ether–acetone-insoluble fraction was a reddish brown, resinous material, yield 0.034 g (1%).

Isomerization Measurement.—Appropriate amounts of a *cis,cis*-N,N'-biisomaleimide–butylamine adduct and an amine were dissolved in dimethyl sulfoxide and transferred into a thin-walled nmr tube which was sealed under an argon atmosphere. The tube was then placed in the nmr cavity which was preheated to the desired temperature, and held for 10 min. The spectra of the ethylenic proton regions were immediately recorded. Amounts of the *cis*- and *trans*-ethylenic protons were determined by both area integration and weighing.

Registry No.—I, 6990-21-2; IIa, 17954-86-8; IIb 17954-87-9; IIc, 17954-88-0; IIIa, 17954-89-1.

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