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Aminal-catalyzed isomerization of and addition to dimethyl maleate

A. Gilbert Cook,* Andrea B. Voges and Aster E. Kammrath

Department of Chemistry, Valparaiso University, Valparaiso, IN 46383, USA

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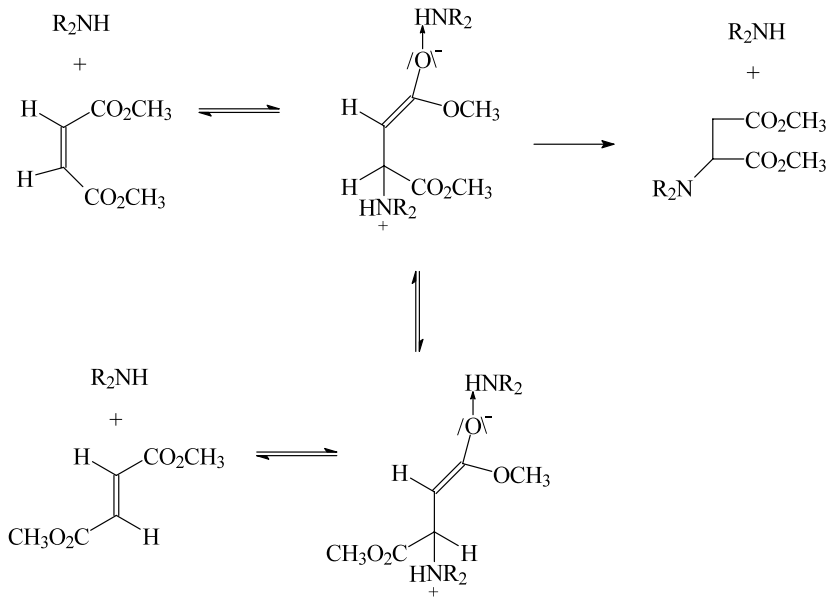
Abstract—The amine moiety of aminals adds to dimethyl maleate via azomethine ylid intermediates. The products of this reaction, in turn, cause dimethyl maleate to isomerize to dimethyl fumarate.

Dimethyl maleate and diethyl maleate are readily isomerized to the corresponding fumarate esters through the catalytic action of primary and secondary amines.[1–3] However, this isomerization is not catalyzed by tertiary amines.[1–3] Beside the inability of tertiary amines to cause this reaction, the mechanism for this isomerization must also take into account its overall third order (second order in amine), the correlation between amine base strength and reaction rate, and the change in order with change in solvent.[4,5] Various mechanisms have been proposed.[2,3,6,7] We favor the mechanism shown in Scheme 1.

In addition to the isomerization reaction, primary and secondary amines also add irreversibly across the activated carbon–carbon double bond of esters such as dimethyl maleate and fumarate as also shown in Scheme 1. We demonstrated that the hydrogen atom for this addition comes from the nitrogen-bonded-hydrogen of the amine by allowing morpholine-4-d^8 (**1**)



Scheme 1.

* Corresponding author. Tel.: 219-464-5389; e-mail: gil.cook@valpo.edu

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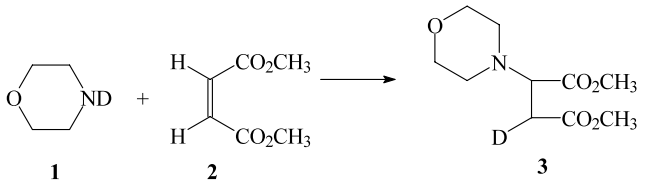
to react with dimethyl maleate (**2**) to give deuterated addition product **3**[†] (Eq. (1))



1 **2** **3**

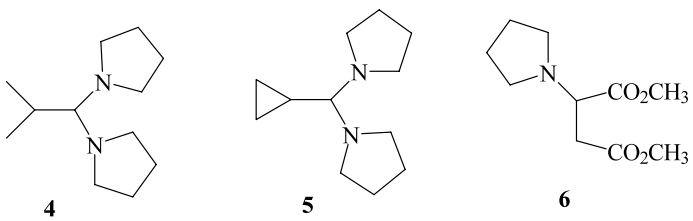
(1)

Enamines cause the maleate to fumarate isomerization to take place through a zwitterion intermediate.[9,10] These esters can also add reversibly across the carbon–carbon double bond of the enamine to give a cyclobutane derivative, or they can add irreversibly to the enamine's β-carbon to give substituted succinate esters.[9,10]

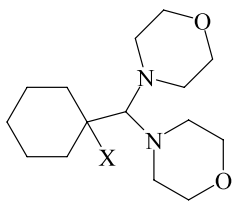
We have found that aminals also catalyze isomerization of dimethyl maleate to dimethyl fumarate. For example, at room temperature the pyrrolidine aminal of isobutyraldehyde (**4**) catalyzes the isomerization of dimethyl maleate (**2**) to dimethyl fumarate. However, since aminal **4** readily decomposes into an enamine and free pyrrolidine when it is heated for distillation, equilibrium between the aminal and the enamine plus pyrrolidine may exist at room temperature. In that case the pyrrolidine could cause this isomerization to take place. In order to determine whether this is the source of the aminal catalytic effect, the pyrrolidine aminal of cyclopropanecarboxaldehyde[11‡] (**5**) was allowed to react with dimethyl maleate. This aminal is stable to decomposition both upon distillation (bp 126–127°C/15 mm) and when a toluene solution of it is refluxed for 2 h. Cyclopropylcarbaminals typically do not decompose even upon distillation or prolonged heating.[12] These behave as if they have no hydrogen at the point of attachment to the cyclopropyl ring.[13] When a small amount of aminal **5** was placed in some dimethyl maleate at room temperature, isomerization took place within 15 seconds. Therefore, it must the aminal itself that is causing the isomerization to take place.

Irreversible addition of the aminal's amine moiety to the dimethyl maleate or dimethyl fumarate carbon–carbon double bond takes place with a wide variety of aminals including aminals **4**, **5**, **7a**, **7b**, **8a**,[14] **8b**,[15] and **9**. For example, the reaction of either aminal **4** or **5** with dimethyl maleate will produce significant amounts of addition compound **6**, a compound previously reported synthesized by another method.[16,17] In the case of aminal **5**, isomerization product dimethyl fumarate and addition product **6** are formed in equal amounts, that is a 1:1 ratio of isomerization product to addition product. Aminals **7a** and **7b** also give 1:1 ratios for these two products. For other aminals, the ratio of isomerization product to addition product will vary depending upon the aminal used. For example, aminal **8a** gives a 20:1 ratio of isomerization product to addition product.

The question that must be answered at this point is why aminals will catalyze the isomerization reaction whereas tertiary amines will not. There is also one aminal, hexamethylenetetramine, which will not catalyze this reaction.[18] We observed that the addition product formed from the addition of the aminal's amine moiety to the carbon–carbon double bond is formed *before* the first appearance of dimethyl fumarate crystals in the reaction mixture. This determination was made using GC–MS on the reaction mixture. We demonstrated that the appearance of the addition compound in the GC–MS spectrum was not due to a reaction on the GC column by performing an 'on-column pursuit' experiment.[19] Therefore, any products that are formed during



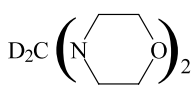
4 **5** **6**



7a X = H
7b X = D

H_2CNR_2

8a NR_2 = piperidine
8b NR_2 = morpholine



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[†] GC–MS, m/e: 232 (1), 173 (100), 158 (20).

[‡] ^{1}H NMR ($CDCl_3$), δ, ppm: 2.74–2.58 (m, 8H, pyrrolidine), 1.75–1.69 (m, 8H, pyrrolidine), 2.26 (d, 1H, J = 9.0 Hz), 0.97 (m, 1H), 0.57–0.47(m, 2H), 0.29–0.25 (m, 2H); ^{13}C NMR ($CDCl_3$), δ, ppm: 85.1 (N–C–N), 49.6 and 23.2 (pyrrolidine), 9.9 and 2.5 (cyclopropyl); GC–MS, m/e: 194 (0.2), 193 (0.7), 165 (4), 152 (13), 136 (28), 124 (100), 70 (23).

the addition reaction could cause the isomerization reaction to take place. So we will first consider the mechanism of this addition reaction. An important component for determining this mechanism is the origin of the hydrogen atom that is added to the carbon–carbon double bond of dimethyl maleate. The source of this hydrogen was determined by replacing the hydrogens in each of three positions in the aminal (see Fig. 1) with deuterium.

Deuterated aminal **7b** was synthesized by deuterium oxide hydrolysis of the pyrrolidine enamine of cyclohexanecarboxaldehyde[20] followed by production of the deuterated morpholine aminal **7b** in the usual manner.[21] Dimethyl maleate was isomerized to dimethyl fumarate with this aminal, but no deuterium was found in the addition product. So hydrogen 1 (see Fig. 1) was not the hydrogen source.

The deuterated morpholine aminal of formaldehyde (**9**)[§] was synthesized by allowing morpholine to react with deuterated paraformaldehyde. This aminal caused dimethyl maleate to isomerize, but no deuterium was found in the addition product. So hydrogen 2 (see Fig. 1) was not the hydrogen source.

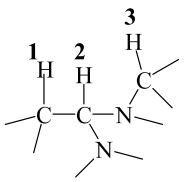
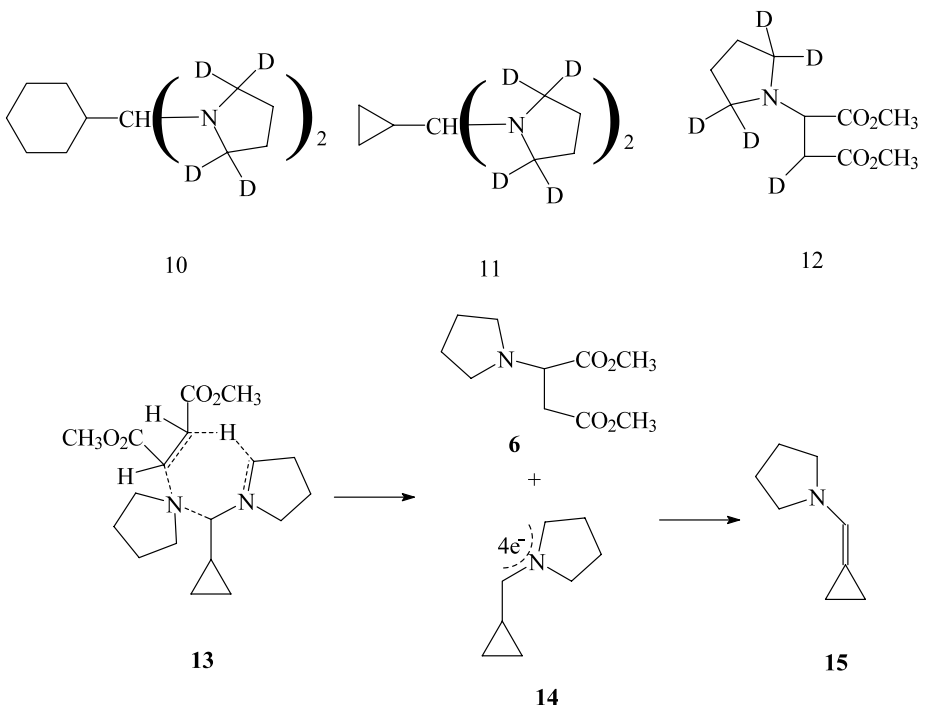


Figure 1.

Pyrrolidine-2,2,5,5-d_8[22] was synthesized by $LiAlD_4$ reduction of succinimide. This amine was then allowed to react with cyclohexanecarboxaldehyde and cyclopropanecarboxaldehyde to produce deuterated aminals **10** and **11**, respectively. Both these aminals caused dimethyl maleate to isomerize and produced addition product **12**. Addition product **12**[¶] had a deuterium atom adding to the carbon–carbon double bond in each of these two cases. So hydrogen 3 (see Fig. 1) is a hydrogen source for the addition reaction. A proposed transition state for this addition reaction is **13** (see Scheme 2) which then leads to azomethine ylid[23,24] **14** and addition product **6** (see Scheme 2). There is a yellow–orange color that develops during these reactions, which indicates a strong possibility of an azomethine ylid intermediate. A hydride transfer would then lead to enamine **15**. This hydride transfer is very favorable energetically as shown by ab initio calculated energies (HF/6-31G*) of enamine **15** (−364.880326 hartrees) as compared to that of azomethine ylid **14** (−364.825304 hartrees), a large difference in stabilities of 0.0594 hartrees or 34.5 kcal/mol. So the azomethine ylid intermediate rapidly converts to the more stable enamine. This enamine then in turn causes the isomerization reaction to take place. The different rates of isomerization for dimethyl maleate with different aminals are due to the relative stabilities of the azomethine ylid intermediates produced with different aminals. The reason that hexamethylenetetramine aminal does not catalyze this reaction is because it cannot achieve the planar geometry necessary for an azomethine ylid intermediate.[25] The addition product which has had protium added instead of deuterium may have come about from trace amounts of water which would hydrolyze the



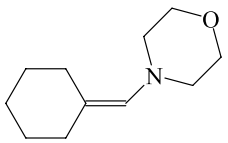
Scheme 2.

[§] GC–MS, m/e: 188 (1), 102 (100), 58 (9).

[¶] ^{13}C NMR ($CDCl_3$), δ, ppm: 171.3, 171.1, 60.2, 51.7, 51.2, 35.0, 22.9. GC–MS, m/e: 220(1.5), 161(100), 146(26), 128(17).

enamine to the aldehyde and secondary amine, the latter then adding to the maleate ester.

There are two lines of evidence that show that enamines are produced in these reactions as proposed in the mechanism shown above. The first is the appearance of enamine signals in the NMR spectra of the products. For example the reaction mixture produced by use of aminal **7a** shows ^{13}C NMR signals at 131.7 and 130.0 ppm (C=C–N) corresponding to the signals of known enamine **16**.[26] The second line of evidence is the production of cycloaddition product **17** when aminal **5** is allowed to react with dimethyl maleate. It is identified by the GC–MS spectrum of the product mixture. This compound is produced by the cycloaddition of enamine product **15** with dimethyl maleate through a known reaction[9,10] in a ratio of 3:1 addition product to trapped enamine product **17**. The balance of the enamine appears as the hydrolyzed product due to trace amounts of water. The ratio of enamine product to addition product as determined by a combination of GC–MS and NMR is about one to one in all these reactions. This is the expected ratio for the postulated mechanism. In summary, for this reaction there is a ratio of isomerization to addition product of 1:1, and a ratio of addition product to enamine product of 1:1.



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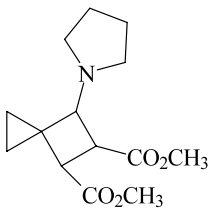

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