



Tandem Michael addition of amines to maleic anhydride and 1,3-prototropic shift: experimental and theoretical results

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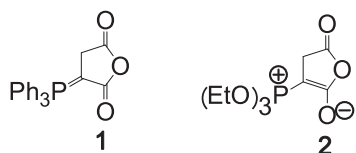
ABSTRACT

Amines, namely diethylamine, diphenylamine, benzylamine, and pyrrolidine react with maleic anhydride to form Michael adducts. The Michael adducts formed with the first three amines undergo tandem 1,3-prototropic shift to give the final products. Computational calculations at the DFT (B3LYP/6-31+G*) level reveal that a reactant-complex formed between the initially formed Michael adduct and the respective amine plays a crucial role in the 1,3-prototropic shift. In the reaction of pyrrolidine with maleic anhydride, Michael addition is not followed by 1,3-prototropic shift. The theoretical studies of the latter reaction show that a reactant-complex is not formed in this case. Dimethyl maleate and dimethyl fumarate react with pyrrolidine to give the same Michael addition product.

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1. Introduction

The Michael addition reaction over the years has developed as a powerful and versatile methodology for making C–C and C–X (X=N, O, P, S) bonds in organic synthesis.^{1–5} The aza-Michael reaction using amines and related nitrogen compounds as Michael donors assumes much importance, as it makes a variety of β -amino carbonyl synthons accessible.^{6,7} Dimethyl acetylenedicarboxylate⁸ and various electron deficient alkenes⁹ have been used as the Michael acceptors in a number of investigations. Although maleic anhydride¹⁰ is expected to be a good Michael acceptor, we could not find any report about its reaction with amines. However, diphenylphosphine was reported to react with maleic anhydride in Michael addition manner to give a tertiary phosphine.¹¹ On the other hand, reactions of maleic anhydride with triphenylphosphine^{12,13} and with triethyl phosphite¹⁴ have been shown to afford ylides **1** and **2**, respectively.



In these cases, it can be perceived that the final products are formed through nucleophilic addition followed by prototropic shift.

Likewise, a series of >P(O) -substituted succinimide and succinic anhydride derivatives were obtained from the Michael additions of dialkyl phosphites, ethyl phenyl-*H*-phosphinate, and diphenylphosphine oxide to *N*-phenyl/*N*-methylmaleimides and maleic anhydride, respectively.¹⁵

With this background, we were motivated to investigate the aza-Michael additions of primary and secondary amines with maleic anhydride. As expected, aza-Michael additions occur smoothly under mild conditions. The initially formed Michael adduct undergoes 1,3-prototropic shift, which is, however, amine-sensitive; the products resulting from the addition of diethylamine, diphenylamine, and benzylamine undergo 1,3-prototropic shift, whereas no 1,3-prototropic shift occurs in the case of the product formed from the addition of pyrrolidine. To look into the reason of this difference in the behavior of the initially formed aza-Michael adducts, we investigated the reactions theoretically and followed them on their potential energy surfaces (PES). The theoretical results reveal that for a 1,3-prototropic shift to occur, formation of the reactant-complex between the initially formed product and an amine molecule is essential. The experimental and theoretical results are presented here.

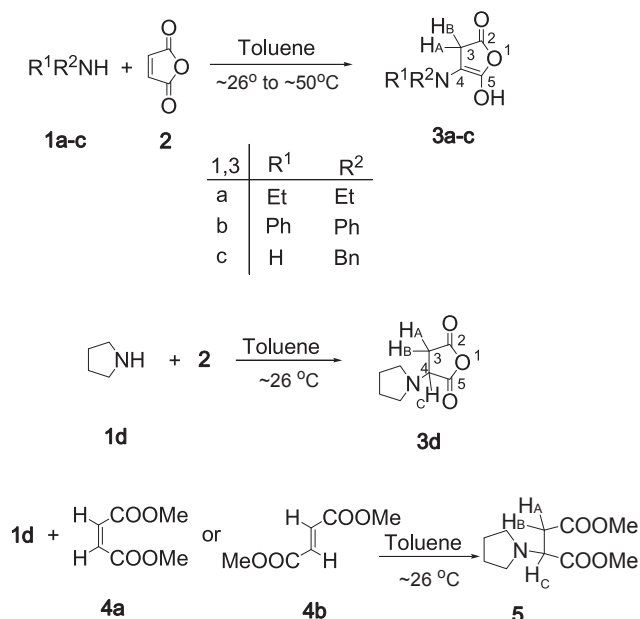
2. Results and discussion

2.1. Experimental results

Amines, **1a–c** on reacting with maleic anhydride in toluene afford the products, **3a–c**. On the other hand, pyrrolidine (**1d**) reacts

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with maleic anhydride under similar conditions to give the product, **3d**. The reaction of pyrrolidine with dimethyl maleate (**4a**) or dimethyl fumarate (**4b**) in toluene at ambient temp (ca. 26 °C) yields the product, **5** (Scheme 1).



Scheme 1. Reactions of amines with maleic anhydride and with dimethyl maleate or dimethyl fumarate.

The reactions with diethylamine and benzylamine are moderately exothermic and take ca. 30 min for completion at the ambient temp, while reaction with diphenylamine could be completed only after heating the reaction mixture at 50–60 °C for about 1 h. The reaction with pyrrolidine is mildly exothermic and is completed at ambient temp in ca. 2 h. The reactions of pyrrolidine with dimethyl maleate and with dimethyl fumarate are also moderately exothermic and take ca. 1 h for completion at ambient temp.

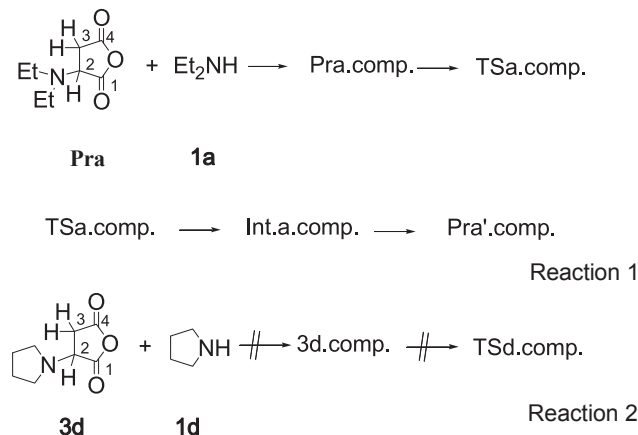
The products are syrupy mass (**3a,5**) or crystalline solid (**3b–d**), which have been characterized by IR and ¹H, and ¹³C NMR studies. An intense broadened absorption band at 3300 cm⁻¹ in the IR spectra and a broad signal at δ 9.26–14.70 ppm in the ¹H NMR spectra of **3a–c** confirmed the presence of an enolic hydroxy group. On the other hand, these two features are missing in the IR and ¹H NMR spectra of the product, **3d**. Furthermore, in the ¹H NMR spectra of **3a–c**, presence of two characteristic doublets (²J_{HH}=12.9 Hz) at δ 6.08–5.92 (H_A) and 6.30–5.67 (H_B) ppm resulting from an AB spin system confirms the diastereotopic nature of the methylene protons, H_A and H_B at C3 on the one hand, and absence of any proton at C4 on the other hand. However, in the ¹H NMR spectrum of the product, **3d**, presence of an ABC spin system can be detected distinctly, as a result of which, two double doublets at δ 3.10 ppm (dd, ²J_{HB,HA}=17.4 Hz, ³J_{HB,HC}=3.6 Hz) and δ 2.95 ppm (dd, ²J_{HA,HB}=17.4 Hz, ³J_{HA,HC}=7.5 Hz) and another double doublet at δ 4.14 ppm (³J_{HC,HA}=7.5 Hz, ³J_{HC,HB}=3.6 Hz) are observed. ¹H NMR signals of the other protons in the respective products are observed in the expected regions. The initial addition of pyrrolidine to dimethyl maleate and dimethyl fumarate leads to the respective enolic intermediates that have free rotation about the C2–C3 bond and hence on ketonization afford the same product.

In the case of **3a–c**, the resulting conjugation of the nitrogen lone pair can be conceived as the driving force for the 1,3-prototropic shift. Such tandem Michael addition/1,3-prototropic shift have been reported in the reaction of *tert*-butyl glycinate derivative with methyl propiolate in the presence of potassium *tert*-

butoxide.¹⁶ Although apparently, the possibility of the existence of a similar driving force appears in the case of the product, **3d** also, it does not undergo 1,3-prototropic shift. To look into the reason of this difference in the behaviors of the amines, we invoked computational chemistry.

2.2. Computational results

Yoshizawa and co-workers¹⁷ while studying the reaction pathway for direct benzene hydroxylation with FeO⁺ species theoretically reported the existence of the reactant-complex and the product-complex, which alter the energy profile of the reaction. On looking into the nature of the reactant-complex, it was found to be of π complex type involving dominant interactions due to electron donation from the Highest Occupied Molecular Orbital (HOMO) of benzene to the d-orbitals of the FeO⁺ fragment. No back-donation from the d-orbitals was observed. In some other cases also, involvement of these species has been detected.^{18–20} We have recently established theoretically that in the Michael addition of benzylamine with dimethyl acetylenedicarboxylate, 1,3-prototropic shift of the N–H proton to the carbanionic center of the zwitterionic intermediate in fact occurs through the intermediate-complex, formed between the intermediate molecule and a molecule of benzylamine; direct proton transfer is a high energy path.²¹ In the present case, we investigated theoretically formation of a reactant-complex between the initially formed Michael adduct (**Pra,3d**) and an amine molecule (**1a,d**) and computed the following two reactions at the DFT (B3LYP/6-31+G*) level²² (Scheme 2) using GAUSSIAN 03 package.²³



Scheme 2. Computed model reactions for the formation of reactant-complex and subsequent 1,3-prototropic shift.

As shown in Scheme 2, a reactant-complex could be located on the PES of the reaction 1, but our repeated attempts to locate a reactant-complex between the initially formed Michael adduct, **3d** and a molecule of pyrrolidine failed.

In accordance with the findings of Yoshizawa and co-workers,¹⁷ we expected the respective reactant-complexes involving interactions between the HOMO of the amine and LUMO of the initially formed product, i.e., **Pra** or **3d**. The HOMOs of diethylamine (**1a**) and pyrrolidine (**1d**) and the LUMOs of the initially formed products, **Pra** and **3d** along with their energies are shown in Fig. 1. The p orbital on nitrogen atom having lone pair constitutes the HOMO of the amine in both cases. The shapes of the LUMOs of the initially formed Michael products, **Pra** and **3d** are also similar. It may, however, be noted that the energy gap between the HOMO of pyrrolidine and LUMO of its initially formed Michael adduct, **3d** is greater than the corresponding gap between the HOMO of diethylamine and LUMO of its initially formed Michael adduct, **Pra**,

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