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Amidation of amino ethylene-1,2-dicarboxylic acid diesters: a theoretical consideration

The amidation features of the Z- and E-isomers of amynoethylene-1,2-dicarboxylic acid diesters $MeO_2CCN=C(NRR^1)CO_2Me$, where R = H; R^1 = H, Me, *t*-Bu; R = R^1 = Me, have been considered based on the data of quantum chemical calculations in the PBE/def2-TZVPP approximation in the framework of Natural Bond Orbital (NBO). Amino-fumaric acid derivatives were chosen as objects for analysis since activated enamines containing conjugated enamine and carbonyl groups in their structure are one of the promising classes of regulators. It was shown by the calculations that for enamines I-IV, regardless of their configuration, conformers with α-s-trans, β-s-cis-arrangement of C=C and C=O bonds are most beneficial. These findings are consistent with experimental data on the relative configurational stability of the Z- and E-isomers of N-alkylaminoethylene-1,2-dicarboxylic acid diesters. The direction of the amidation reactions depends critically on the structure of the reactant and the reaction conditions. It was established that the amidation of amino acid-1,2-dicarboxylic acid diesters obeys to orbital control of the reaction. The observed regiospecificity of non-catalytic amidation on the α-ester group was explained by the joint influence of a decrease in the electrophilicity (increase in the energy of the loosening π-orbital) of the β-carbonyl group due to effective conjugation with the π-system of the C=C–NHR and an increase in the electrophilicity of the α-carbonyl group with an increase in its conjugation with the rest part of the molecule. The inertness of N,N-dimethylaminomaleate to reactions with amines is caused by the increased energy of $\pi^*_{C=O}$-orbitals of ester groups. Bis-amidation of amino-ethylene-1,2-dicarboxylic acid diesters is possible only in the presence of catalysts.

Keywords: amidation, quantum chemical calculations, activated enamines, regiospecificity, conformers, cisoid arrangement of bonds, transoidal arrangement of bonds, isomers, orbital control.

Introduction

In modern agricultural technologies must important attention is paid to use of plant promoters, because they, unlike other chemicals, usually require small doses for use, do not affect the environment and have contribution to the production of environmentally friendly agricultural products.

One of the promising classes of promoters are activated enamines, containing in their structure conjugated enamine and carbonyl groups, including derivatives of aminofumaric acid [1–3]. Thereby, the amidation of amino ethylene-1,2-dicarboxylic acid diesters has particular interest. It is known [4] that the direction of amidation reactions depends strictly on the structure of the reactant and the reaction conditions. The amino-fumaric acid diesters with unsubstituted nitrogen atom, at interaction with ammonia, primary and secondary aliphatic amines in absolute alcohols, produce monoamides of Z-2-amino-3-alkoxycarbonylacrylate acid, and in aqueous methanol — mostly or exclusively 1-alkyl-3-alkylaminopyrrole-2,5-diones (with the exception of reactions with ammonia and tert-butylamine, leading only to the corresponding monoamides).

The amino fumarates and monoamides of Z-2-amino-3-alkoxycarbonylacrylic acid in similar reactions under conditions of basic catalysis ($MeOH_{abc}$./MeONa) produce bisamides of aminofumaric acid. N-alkylaminofumarates and N-tert-butylaminomaleate at interaction with primary amines in any conditions produce 1-alkyl-3-alkylaminopyrrol-2,5-dione, and N,N-dialkylaminomaleates are inert in all cases.

Experimental

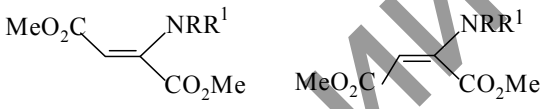
Quantum chemical calculations of the ground states of key compounds were carried out in the PBE/def2-TZVPP approximation [5, 6] in order to analyze and explain the observed experimental regularity. Quantum chemical calculations were carried out within the framework of the density functional theory [7, 8] using the PBE96 functional [9] and the basic set of atomic functions def2-TZVPP [10] using the Firefly 7.1 software complex [11], which fully satisfy to the decision of the tasks. Chemcraft 1.7 program was used to visualize the spatial structure and construct imine molecules [12].

Geometry optimization was performed for all systems. There are several stable conformations for all studied compounds, so the search of the most stable geometry (having the least energy) was carried out by optimizing the structures of possible conformers.

The belonging of the found points to the minima and saddle points of the potential energy surfaces was confirmed by calculations of the second derivatives with respect to coordinates (Hessian calculation). The absence of imaginary frequency values in the vibrational spectrum testified that the optimized structures correspond to minimum.

The atomic populations, charges, and energies of intramolecular interactions were obtained using the natural orbitals of bonds (NBO) [13–15] with the help of NBO 5.G program [16] introduced in the Firefly 7.1 package. The NBO method allows to analyze nonempirical wave functions within one-and two-center localized orbitals, thus making it convenient to thoroughly analyze intra- and intermolecular interactions. The calculation was carried out for optimized geometries of the studied enamines. The NPA (Natural Population Analysis) scheme was used to obtain the values of atomic populations and charges. Earlier it was shown that of the charges that can be estimated by quantum chemical methods (Mulliken, AIM-, CHELPG -, MK-charges) the best correlation with the experimental and calculated values of chemical shifts ^{13}C NMR observed for NPA-charges [17]. By calculations it was established that obtained data will correspond to the location of the molecules in the gas phase or, at least, in solution of a non-polar aprotic solvent. In reality, almost all reactions were carried out in polar protic solvents — in absolute or aqueous methanol with specific solvating effect. Nevertheless, from our point of view, the use of calculated data to a sufficient degree is authentic and useful for analysis due to comparable impact of solvation on the properties of the considered related compounds — derivatives of aminoethylene-1,2-dicarboxylic acid.

N-derivatives of dimethyl ester amine-fumaric and amino-maleic acids I-IV were selected as objects for analysis:



Z E

R = H; R^1 = H (I), Me (II), *t*-Bu (III); R = R^1 = Me (IV)

Results and Discussion

Calculations identified that for enamines I-IV, despite their configuration, the conformers with α-s-trans,β-s-cis-arrangement of C=C and C=O bonds are the most favorable (Table 1). Wherein, for Z-II, Z-III N-alkyl derivatives of aminofumaric acid the transoidal arrangement of the substituent at the nitrogen atom and C=C bond is the most beneficial, while for aminomaleic acid — their cisoidal arrangement.

Table 1

Internal energies ($E_{int.}$) and dihedral angles ($\Theta_{NCC=O(\alpha),}$ °) of preferred conformers of Z-and E-isomers of enamines I-IV

Enamine	$E_{int.}$, a. u.[1]	$\Theta_{NC_2C_1=O(\alpha),}$ °	Enamine	$E_{int.}$, a. u.[1]	$\Theta_{NC_2C_1=O(\alpha),}$ °	ΔE_{int}[4], kJ/mol
Z-I	–589.3090	0	E-I	–589.2909	58.8	–47.5
Z-IIa	–628.5595[2]	0	E-IIa	–628.5555[2]	54.8	–10.5
Z-IIb	–628.5642[3]	21.7	E-IIb	–628.5512[3]	73.9	–34.1
Z-IIIa	–746. 3755[3]	0.5	E-IIIa	–746.3697[2]	59.1	–15.2
Z-IIIb	–746.3776[3]	42.0	E-IIIb	–746.3658[3]	74.9	–31.0
Z-IV	–667.8108	21.3	E-IV	–667.8148	71.5	10.5

Note. [1] — 1 a.u.= 1 Hartree = 2625,5 kJ/mol; [2] — cisoid arrangement of bonds R^1-N and C=C; [3] — transoid arrangement of bonds R^1-N and C=C; [4] — the difference between the total internal energies of the preferred conformers of the Z- and E-isomers. Conformer a — cisoid arrangement of bonds R1-N and C=C; Conformer b — transoid arrangement of bonds R1-N and C=C. All conformers have α-s-trans- β-s-cis-arrangement of bonds C=O and C=C.

For enamines I-III, aminofumaric acid diesters (Z-isomers) are energetically preferable, thermodynamic preference of which are decreasing with increasing of volume of substituents at nitrogen atom. In the case of

enamine IV which has the most voluminous substituent, derivative of aminomaleic acid (E-isomer) is energetically most favorable. These conclusions approve experimental data on the relative configuration stability of Z- and E-isomers of diesters of N-alkylamino-ethylene-1,2-dicarboxylic acid [4].

The calculated data were used to explain the regiospecificity of the amidation reaction of amino ethylene-1,2-dicarboxylic acid derivatives. Theoretically, the amidation reaction can be carried out under conditions of charge control, in which the unshared electron pair of the amine nitrogen atom attacks the most electropositive carbon atom of the investigated molecule, or in the conditions of orbital control, in which the highest occupied molecular orbital (HOMO) of the nucleophile (the unshared electron pairs of amine) interacts with the lowest free molecular orbital (LFMO) of the electrophile.

Analysis of the data in Table 2 reveals that the maximum and almost identical partial positive charges ($q_{C1}(\alpha)$-$q_{C4}(\beta)$ = 0.022–0.038 ē are localized on the carbon atoms of the carbonyl groups, which should provide almost equally probable amidation with a small preference on α-ester groups. This contradicts the experimental data [4], according to which regio-specific amidation on α-alkoxycarbonyl group is observed for aminofumarates, and N,N-dimethylamino-maleate E-IV, for which the maximum q_C value is observed is generally inert in this reaction. Thus, the amidation of diesters of amine-ethylene-1,2-dicarboxylic acid does not obey the charge control of the reaction.

According to the perturbation theory of molecular orbitals (MO) [18], the orbital control of reaction is determined by the efficiency of the interaction between employed and vacant MOs, inversely proportional to the energy gap (ΔE) between them [19]. Respectively, regiospecificity of amidation of aminofumarates should depends on the ΔE value between interacting orbitals, that is MO $\pi^*_{C=O}$ of ester group and unshared pair of electrons of nitrogen atom of amine (nN). Then, independently on substituent at nitrogen atom, α-methoxylcarbonyl group in Z-isomers of enamines I-IV should be more reactive because of significantly less energy of π^*-MO of α-carbonyl group ($E\pi^*C_1$=O –135.5 ÷ –101.6 kJ/mol) in comparison with energy of π^*-MO of β-carbonyl group ($E\pi^*C_4$=O –83.5 ÷ –41.7 kJ/mol) and, correspondingly, lower value ΔE between interacting MOs. This fact correspond to observed regiospecificity of amidation of aminofumarates I, II in absolute methanol in the presence of basic catalysis. In the case of Z-III N-tert-butylaminofumarate two the most favorable conformers are observed that have practically equal enegries ($\Delta E_{BH.}$=5.5 kJ/mol), but far different dihedral angles $\Theta_{NC2C1=O(\alpha)}$ (Table 1) and energies of $\pi^*_{C1=O}$ MOs (Table 2). Obviously, amidation of Z-III enamine is only possible in the case of effective conjugation of α-ester group with C=C bond, leading to decrease of π^*C_1=O orbital energy and formation of an appropriate Z-IIIa conformer. Thereby, non-reactive with amines Z-IV N,N-dimethylaminofumarate deserves special attention, although dihedral angle $\Theta_{NC2C1=O(\alpha)}$ (Table 1), summary energy of conjugation of α-carbonyl group with double bond and energy of $\pi^*_{C1=O}$ MO are close to those for Z-II N-methylaminofumarate (Table 2), that enters in reaction of amidation. The explanation of this fact can't be connected with spatial difficulties for attack by nucleophile of ester group, because they are practically identical for considered enamines. The higher energy of $\pi^*_{C1=O}$ MO in Z-IV enamine could be exceptional reason.

Table 2

Calculation of the quantum chemical analysis data for preferred conformers of Z- and E-isomers of enamines I-IV

No.	Bond length, *l*, Å				Partial charges, *e*					The energy of interactions, kJ/mol				Energy of π^*-orbital, kJ/mol		
	N-C_2	C_2=C_3	C_1-C_2	C_3-C_4	$q_{C1}(\alpha)$	q_{C2}	q_{C3}	$q_{C4}(\beta)$	q_N	Conjugation[1]	HB[2]	nN→π^3	C2=C3	C1=O	C4=O
Z-I	1.348	1.375	1.505	1.446	0.674	0.117	–0.395	0.652	0.709	81.6[a]	102.6[b]	30.6	205.6	–47.5	–135.5	–83.5
Z-II	1.351	1.385	1.505	1.440	0.673	0.122	–0.399	0.648	0.493	75.7[a]	107.2[b]	48.8	210.2	–43.3	–114.7	–81.1
Z-III	1.356	1.390	1.510	1.439	0.682	0.125	–0.393	0.645	0.514	56.3[a]	107.1[b]	61.2	209.7	–45.4	–126.7	–81.5
	1.351	1.386	1.508	1.440	0.683	0.135	–0.403	0.649	0.514	85.2[a]	108.3[b]	50.8	203.7	–33.1	–65.6	–75.9
Z-IV	1.365	1.377	1.515	1.455	0.671	0.114	–0.378	0.644	0.300	68.9[a]	89.8[b]	–	136.9	–33.1	–101.6	–41.7
E-I	1.371	1.360	1.514	1.458	0.690	0.142	–0.398	0.662	0.721	20.4[a]	90.6[b]	<2.1	126.5	–37.1	–67.5	–54.7
E-II	1.363	1.365	1.514	1.457	0.695	0.135	–0.419	0.662	0.500	25.0[a]	91.0[b]	<2.1	161.7	–28.4	–80.1	–44.1
E-III	1.363	1.367	1.520	1.455	0.698	0.151	–0.424	0.662	0.516	10.6[a]	94.3[b]	<2.1	179.9	–17.6	–71.2	–39.6
E-IV	1.367	1.370	1.520	1.453	0.701	0.143	–0.421	0.660	0.307	6.4[a]	95.8[b]	–	166.5	–21.0	–58.3	–42.0

Note. [1] — summary energy of interactions a) $\pi_{C2=C3}\rightarrow\pi^*_{C1=O}$, $\pi_{C1=O}\rightarrow\pi^*_{C2=C3}$; b) $\pi_{C2=C3}\rightarrow\pi^*_{C4=O}$, $\pi_{C4=O}\rightarrow\pi^*_{C2=C3}$; [2] — sum of energies interactions $nO\rightarrow\sigma^*_{H\text{-}N}$; [3] — Interaction energy $nN\rightarrow\pi^*_{C2=C3}$. HB-intramolecular hydrogen bond.

Taking into account that in the condition of amidation reaction the β-ester groups of I-IV aminofumarates and α-ester group of Z-IV enamine are inert, conditionally the energy of Z-IV enamine $\pi^*_{C1=O}$ MO can be taken as a high limit of $\pi^*_{C=O}$ energy, at which non-catalytic amidation of ester groups is impossible. In this case all considered aminomaleates in which the energy of α- and β-$\pi^*_{C=O}$ make up from –80.1 till –39.6 kJ/mol, should be inert in the reaction of amidation of any of ester groups. Unfortunately, this assumption impossible to check experimentally, first of all, on other aminomaleates. Respectively, formation of bis-amides of aminoethylene-1,2-dicarboxylic acid is possible only at decrease of energetic gaps between interacting orbitals, that possible to be reached by amidation in absolute alcohol in the presence of sodium methylate at intermediate formation of corresponding amide-aniones, that have more high energy of nitrogen atom's unshared pair of electrons. Really, fumarates and monoamides of Z-2-amino-3-alkoxylcarbonylacrylic acid in the condition of basic catalysis ($MeOH_{abs.}$/MeONa) form bisamides of aminofumaric acid [4].

Thus, although quantum-chemical calculations were carried out for molecules in gas phase, they let us explain experimental data on amidation of esters of N-derivatives of aminoethylene-1,2-dicarboxylic acid.

It should be noted that according calculation data (Table 2) energy of $\pi^*_{C1=O}$ MO is directly connected with efficiency of its conjugation with π-system of other part of molecule — removal of α-carbonyl group from molecule plane leads to increase of its MO. For example, change of digedral angle $\Theta_{NC2C1=O(\alpha)}$ in Z-III enamine from 0.5 to 42° increases energy of $\pi^*_{C1=O}$ MO for 61 kJ/mol, in energetically preferable Z- or E-isomers of I-IV enamines energy of $\pi^*_{C1=O}$ MO is increased generally symbatically to increasing of $\Theta_{NC2C1=O(\alpha)}$ values. Energy of conjugation of unshared electron pair (UEP) of nitrogen with π-bond of C=C (interaction of $nN\rightarrow\pi^*_{C2=C3}$) in I-IV E-isomersis increased with increasing of energy of UEP (–729.6, –651.9, –618.9 and –627.1 kJ/mol, respectively); in the case of Z-isomers the corresponding pattern is not observed (–598.5, –577.5, –559.9, –566.9 and –581.8 kJ/mol, respectively), possibly because of concomitant impact of intramolecular hydrogen bond N-H…O=C_4 (interaction $nO\rightarrow\sigma^*_{H\text{-}N}$). Summary energy of conjugation (sum of interaction energies, Table 2) in Z-isomers of I-IV enamines significantly high than in E-isomers, which explains the increased thermodynamical stability of Z-I-Z-III isomers; decreasing of relative stability of Z-isomer of IV enamine is caused by steric interaction between voluminous ester and dimethylamine groups. On other hand, observed change in bond length (elongation of C_2=C_3 and shortening of N-C_2, C_1-C_2, C_3-C_4 in Z-isomers relatively to E-isomers) is also stipulated by more high energies of conjugation in Z-isomers.

Conclusions

Thus, the amidation of amino ethylene-1,2-dicarboxylic acidsdiesters is obey to orbital control of the reaction. The observed regiospecificity of non-catalytic amidation on the α-complex ester group is due to the combined effect of decreasing electrophilicity (increasing the energy of loosening π-orbitals) of the β-carbonyl group due to effective conjugation with the π-system C=C–NHR and increasing the electrophilic α-carbonyl group with increasing its conjugation with the rest molecules. The inertness of N,N-dimethylamino maleate to reactions with amines is caused by the increased energy of the π * C=O-orbitals of the complex ester groups. Bis-amidation of amino-ethylene-1,2-dicarboxylic aciddiesters is possible only in the presence of catalysts.

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Аминоэтилен-1,2-дикарбон қышқылының диэфирлерін амидирлеу: теориялық тұрғыдан қарастыру

Табиғи байланыс орбитальдарының (Natural Bond Orbital, NBO) формализмі шеңберінде PBE/def2-TZVPP жуықтауында кванттық-химиялық есептеулер деректерінің негізінде Z- және E-изомерлердің аминоэтилен-1,2-дикарбон қышқылы диэфирлерінің $MeO_2CCH{=}C(NRR^1)CO_2Me$ амидирлеу ерекшеліктері қарастырылды, мұнда R = H; R^1 = H, Me, t-Bu; R = R^1 = Me. Реттеушілердің перспективалы класстарының бірі белсенді түрдегі құрылысында байланысқан енамин және карбонил топтары бар эмальдар болып табылады, талдау жасау нысандар ретінде аминофумар қышқылы туындылары таңдалады, сондықтан, амино-этилен-1,2-дикарбон қышқылының диэфирін амидирлеу реакциялары жүргізілді. Есептеулер көрсеткендей, I-IV енаминдер үшін олардың конфигурациясына қарамастан, C=C және C=O байланыстарының орналасуында α-s-trans, β-s-циске ие конформерлер тиімді болып табылады. Бұл қорытындылар N-алкиламиноэтилен-1,2-дикарбондық қышқылдар диэфирлерінің Z- және E-изомерлерінің салыстырмалы конфигурациялық тұрақтылығы туралы тәжірибелік деректерге сәйкес келеді. Амидирлеу реакцияларының бағыты реактант құрылымына және реакция жағдайына критикалық жағынан байланысты болады. $MeO_2CCH{=}C(NRR^1)CO_2Me$, мұнда R = H; R^1 = H, Me, *t*-Bu; R = R^1 = Me амино-этилен-1,2-дикарбон қышқылы диэфирлерінің Z- және E-изомерлерінің амидирлеу ерекшеліктері қарастырылған. Анықталғандай, амино-этилен-1,2-дикарбон қышқылы диэфирлерін амидирлеу реакциясының орбиталдық бақылауына бағынады. α-күрделі эфирлер топтары бойынша каталитикалық емес амидирлеудің байқалған аймаққа тән болуының байқалуы π-жүйесімен C=C–NHR-мен тиімді байланысына β-карбонил тобын төмендететін электрофильділіктің (π-орбиталдың көпсіту энергиясын жоғарылату) және қалған молекула бөлігімен байланысу артумен α-карбонил тобының электрофильділігін жоғарылатумен байланысты. Аминдермен N,N-диметиламиномалеаттың реакцияларға инерттілігі $\pi^*_{C=O}$-күрделі эфирлер топтарының орбиталдары энергиясының артуымен байланысты болып келеді. Амино-этилен-1,2-дикарбон қышқылының диэфирлерін бис-амидирлеу тек ғана катализаторлардың қатысуымен мүмкін болады.

Кілт сөздер: амидирлеу, квантты-химиялық есептеулер, белсенді енаминдер, аймаққа тән, конформерлер, байланыстардың цисоидты орналасуы, трансоиды байланыстың орналасуы, изомерлер, орбиталық бақылау.

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Амидирование диэфиров аминоэтилен-1,2-дикарбоновой кислоты: теоретическое рассмотрение

На основании данных квантово-химических расчетов в приближении PBE/def2-TZVPP в рамках формализма натуральных связевых орбиталей (Natural Bond Orbital, NBO) рассмотрены особенности амидирования Z- и E-изомеров диэфиров аминоэтилен-1,2-дикарбоновой кислоты $MeO_2CCH=C(NRR^1)CO_2Me$, где R = H; R^1 = H, Me, *t*-Bu; R = R^1 = Me. Так как одним из перспективных классов регуляторов являются активированные енамины, содержащие в своей структуре сопряженные енаминную и карбонильную группы, в качестве объектов для анализа выбраны производные аминофумаровой кислоты. Расчёты показали, что для енаминов I-IV, независимо от их конфигурации, наиболее выгодными являются конформеры, обладающие α-s-*транс*, β-s-*цис*-расположением связей C=C и C=O. Эти выводы согласуются с экспериментальными данными по относительной конфигурационной устойчивости Z- и E-изомеров диэфиров N-алкиламиноэтилен-1,2-дикарбоновой кислоты. Направление реакций амидирования критическим образом зависит от строения реактанта и реакционных условий. Установлено, что амидирование диэфиров аминоэтилен-1,2-дикарбоновой кислоты подчиняется орбитальному контролю реакции. Наблюдающаяся региоспецифичность некаталитического амидирования по α-сложноэфирной группе обусловлена совместным влиянием снижения электрофильности (повышением энергии разрыхляющей π-орбитали) β-карбонильной группы вследствие эффективного сопряжения с π-системой C=C–NHR и повышением электрофильности α-карбонильной группы с ростом ее сопряжения с остальной частью молекулы. Инертность N,N-диметиламиномалеата к реакциям с аминами вызвана повышенной энергией $\pi^*_{C=O}$-орбиталей сложноэфирных групп. Бисамидирование диэфиров аминоэтилен-1,2-дикарбоновой кислоты возможно лишь в присутствии катализаторов.

Ключевые слова: амидирование, квантово-химические расчеты, активированные енамины, региоспецифичность, конформеры, цисоидное расположение связей, трансоидное расположение связей, изомеры, орбитальный контроль.

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