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Interaction between charged groups. pK-values and conformations of the diastereomers of 3-amino-2,3-diphenylpropanoic acids and their ester and N-acetyl derivatives

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Dedicated to Acad. Dimiter Ivanov on the occasion of his 120th birth anniversary

The system of 1,2-disubstituted-1,2-diphenylethanes is characterized by the strong preference of the conformation with *antiperiplanar* phenyl groups in both diastereomers which positions the other substituents *ap* in the *erythro* and (+)-*sc* in the *threo* isomer. This proved true for the isomers of 3-amino-2,3-diphenylpropanoic acid and its N-acetyl and ester derivatives as evidenced by J_{2H3H}-couplings above 10 Hz found in formamide. Only the zwitterion of *erythro* amino acid **1a** showed a smaller value of 9 Hz indicating charge attraction overcoming partly the steric interactions. Molecular mechanics calculations by means of the Scheraga force field corroborated the interpretation. An IR-study of the equilibrium zwitterion – neutral amino acid showed the latter to be preferred in aprotic solvents ≈ 100% in pure DMSO for **1a** but decreased in the presence of water, until only the zwitterion was detected in 80% DMSO. The J_{2H3H}-couplings of **1a** (10.3 Hz in D_2O and 7.7.Hz in pure DMSO) indicated that solvation by water increases steric hindrance and suggested a strong hydrogen bond $CO_2H\ldots NH_2$ in aprotic media. The pK-values of all compounds were determined potentiometricly in 80% methylcellosolve and in 90% DMSO. The pK_1's of *threo* zwitterion **1a** for COOH were 0.8 pK units larger than those of the *erythro* isomer as predicted for *anti vs. gauche* charged groups. The pK_2-values of the isomers do not differ significantly, the electrostatic effects are apparently offset by steric hindrance from solvation of NH_3^+. The pK's of the ester and N-acetylated derivatives differ from those of the zwitterion by ca. 2 pK units evidencing strong effects of charge interaction. In organic solvents the acidities of COOH and NH_3^+ change strongly in opposite directions leading to appearance of neutral amino acid bands proven by the IR data.

Key words: intramolecular electrostatic interactions, vicinal charged groups in *sc* and *ap* conformations, *erythro- threo* isomers, pK-values in 80% methylcelosolve and 90% DMSO, zwitterion *vs.* free amino acid, conformations, molecular mechanics

INTRODUCTION

D. Ivanov and A. Spassov in 1931 [1,2] discovered the Ivanov reaction by reacting benzaldehyde with the dimagnesium salt of phenylacetic acid (known as the Ivanov reagent) opening the road to a wide range of 1,2-disubstituted-1,2-diphenyl compounds. The two chiral centres give rise to two diastereomers, the *threo* isomer being preferred. In general terms the Ivanov reaction is a base catalysed aldol reaction. Alternately, B. Kurtev and N. Mollov [3] discovered an acid catalysed version e.g. in the presence of $AlCl_3$ esters of phenylacetic acid add to hydrobenzamide yielding the esters of the title amino acids. The opposite *erythro* selectivity was observed [4]. Early studies on the conformations of 1,2-disubstituted-1,2-diphenyl compounds revealed from optical rotation studies [5] and from ^{1}H NMR vicinal coupling constants [6,7] an intriguing feature: the *threo* isomer existed mainly as the conformer with *gauche* Ph groups ((+)-*sc*, Scheme 1) contrary to qualitative conformational analysis. As shown on the conformational formulae below when X and Y are medium sized groups then the preferred conformers with both diastereomers should be with the large phenyl groups *anti*. Actually appreciation of "large" applied to a phenyl group stems from Eliel's A-values derived from *equatorial/axial* equilibria in cyclohexane systems; 3 kcal for Ph versus 1.8 kcal for Me. In open-chain systems there emerged from numerous studies reviewed in reference [8] that the *syn/anti* equilibrium in 1,2-diphenylethane is very similar of the methyl groups with a ΔG of *ca.* 0.8 kcal/mol. In 1,2-diphenylethane some attraction between *syn* phenyl groups is outweighed by the greater librational entropy

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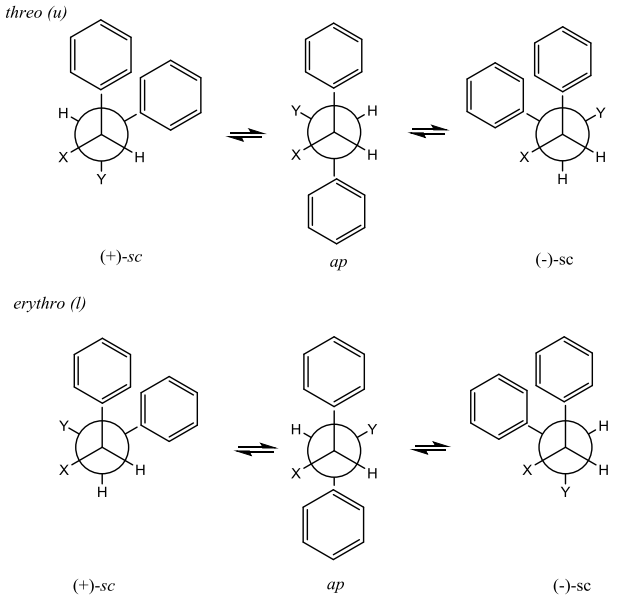
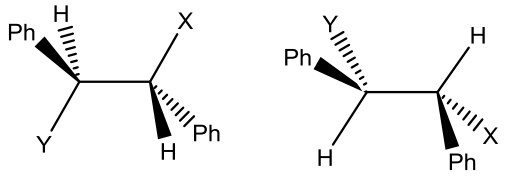
in the *anti* position. These preferences have been confirmed by advanced computational methods [9]. The case of 1,2-disubstituted-1,2-diphenyl compounds has also drawn a great amount of attention and has been also reviewed in [8] both with respect to experimental determination of preferred conformations and their theoretical interpretation. Molecular mechanics permitted conformational preferences to be discussed in terms of separate contributions: steric strain (torsional, angle and bond deformations), electrostatic interactions, hydrogen bonding. Among the huge mass of accumulated data on the diphenylethane system the absence of examples where X and Y are charged groups is conspicuous.



Scheme 1. Designation of conformations for rotation around the C-C bond bearing the neighbouring phenyl groups (the *like* or *unlike* from the R/S nomenclature coincide with *erythro/threo* designations when X and Y are more senior than the phenyl groups).

We now report the pK-values of the diastereomers of the 3-amino-2,3-diphenyl-propanoic acid and its N-acetyl and methyl and ethyl ester derivatives, their ^{1}H NMR vicinal coupling constants as a measure of the conformational preferences and the results of molecular mechanics study by means of the Sherraga force field. The dimethyl analogue, 3-amino-2-methylbutanoic acid, studied previously [10], exhibited evenly distributed populations of conformers and similar pK with both diastereomers. The general tendency observed in the case of compounds with vicinal phenyl groups shown on Scheme 1 for preferred *ap* conformation of the phenyl groups with the *erythro* isomer and (+)-*sc* conformation for the *threo* isomer meant that the expected disposition of the amino and carboxy groups in the amino acids will be *anti* in *erythro* but *syn* in *threo*. Thus the interactions of the two charged groups of the amino acid zwitterion in the two positions *anti* in *erythro* and *syn* in *threo* could hopefully be examined.

Table 1 Compounds studied.



l (erythro) *u (threo)*

Compound	Configuration	X	Y
1a[1]	*erythro*	CO_2^-	NH_3^+
1b[2]	*erythro*	CO_2H	NH_3^+
1c[3]	*erythro*	CO_2^-	NH_2
2a[1]	*threo*	CO_2^-	NH_3^+
2b[2]	*threo*	CO_2H	NH_3^+
2c[3]	*threo*	CO_2^-	NH_2
3a	*erythro*	CO_2Me	NH_2
3b[2]	*erythro*	CO_2Me	NH_3^+
4a	*threo*	CO_2Me	NH_2
4b[2]	*threo*	CO_2Me	NH_3^+
5a	*erythro*	CO_2Et	NH_2
5b[2]	*erythro*	CO_2Et	NH_3^+
6a	*threo*	CO_2Et	NH_2
6b[2]	*threo*	CO_2Et	NH_3^+
7a	*erythro*	CO_2H	NHCOMe
7c[3]	*erythro*	CO_2^-	NHCOMe
8a	*threo*	CO_2H	NHCOMe
8c[3]	*threo*	CO_2^-	NHCOMe

[1]The amino acids exist as zwitterions, see however text. [2]Hydrochloride. [3]Potassium salt.

EXPERIMENTAL

Uncorrected melting points were measured in capillaries. IR spectra on a Specord IR 75 or Bruker IFS 113v instrument in a 0.1 mm CaF_2 cell. ^{1}H NMR spectra in formamide on a Tesla 80 MHz or Jeol 100 MHz instruments. ^{1}H-NMR signals were referenced DMSO or DSS and coupling constants are given in Hz and without sign.

Materials

Inorganic materials and buffer components were of analytical grade and were used without further purification. Potassium hydroxide solutions were prepared with CO_2-free distilled water. Formamide used for NMR as solvent was purified by freezing and subsequent distillation. Dimethylsulfoxide for

pK determinations was dried over CaH_2 and then distilled *in vacuo*, Bp_{10} 73°C. Compounds **1a**, **1b**, **2a**, **2b**, **3a**, **3b**, **4a**, **4b**, **5a**, **5b**, **6a**, **6b** were obtained according to [4].

All potassium salts were obtained treating a weighed amount of the substrate with the exact equivalent volume of a KOH solution of known molarity. The solution obtained was evaporated to dryness on a rotatory evaporator.

3-acetylamino-2,3-diphenylpropanoic acids erythro **7a** *and threo* **8a**

3-Amino-2,3-diphenylpropanoic acids **1a** and **2a** (0.033 mmol) and NaOH (0.08 mmol) were dissolved in 10 ml of water. 0.1 mmol of $(CH_3CO)_2O$ were added under stirring. The precipitate formed is filtered and dissolved in aqueous KOH. The solution obtained is filtered and made acid with HCl. The precipitates obtained were recrystallized: **7a** from acetic acid**, 8a** from ethyl acetate-benzene. **7a** m.p. 244°C. Calcd for $C_{17}H_{17}NO_2$: C, 72.08; H, 6.01; N, 4.95. Found: C, 71.87; H, 6.26; N, 5.08. IR cm^{-1} γ_{COOH} 1718; γ_{CONH} 1638. **8a**, m.p. 184-185°C. γ_{COOH} 1705; γ_{CONH} 1640. Calcd for $C_{17}H_{17}NO_2$: C, 72.08; H, 6.01; N, 4.95. Found: C, 71.58; H, 6.08; N, 4.66.

Determination of pK-values in methylcellosolve(2-methoxyethanol)-water 80:20

The pK-values were determined by the procedure developed by Simon [11] adapted as follows:

Samples of a volume of 5 ml and a substrate concentration of 4.6 x 10^{-3} M were used. The galvanic cell comprised a vessel temperature controlled at 25.0 ± 0.1°C provided with a glass electrode Typ G 2222c, a calomel electrode, an electromagnetic stirrer and a flow of nitrogen. The titrating solution is added manually by means of an automatic burette (ABU13) with a total volume of 0.25 ml and accuracy of ± 0.001 at a rate of 40x in ten equal portions sufficient for the complete titration of the weighed sample. The pH was measured after each portion titrant on a Radiometer Typ PHM 26c pH-meter. The pK-values were obtained from the equation:

$$pK = pH - \log \frac{[A^-]}{[AH]}$$

The deviations from the average is maximally 0.05 pK units within a single titration. Two titrations were carried out for each compound and the average value was taken. The reability of the procedure was checked by determining the pK-value of benzoic acid. We obtained 6.63 which agrees well with the value of 6.57 given by Simon [11].

Determination of pK-values in DMSO(dimethylsulfoxide)-water 90:10

The procedure followed has been described previously [12]. The solvent mixture was prepared by weight from purified DMSO and bidistilled water free of carbonates. NMe_4Br (Schuchard, pure) was used without further purification. HCl solution was prepared from analytical grade reagent, NBu_4OH was from Fluka, a 40% water solution purified by passing through ion exchange resin Dowex 21K to remove CO_3^{2-}. DMSO was added to these water solutions as needed.

The potentiometric titrations were carried out in a temperature controlled cell (25 ± 0.2°C) with a diffusional potential comprising a glass electrode Radiometer Typ G 2222c and a reference electrode silver nitrate.

GE⁞⁞⁞ $HCl_{(M\ HCl)}$, $NBu_4OH_{(M\ NBu4OH)}$, 0.1M NMe_4Br
⎪⎪0.1M $AgNO_3$ in DMSO-H_2O 90:10, Ag

The contact between the sample and the reference electrode was J-shaped. The ionic strength of the samples was maintained constant at I = 0.1 M by means of NMe_4Br. The cell potential was measured with a Radiometer PHM-52 instrument (accuracy 0.2 mV). The galvanic cell was calibrated by determining the specific constant of the cell $E_a^{o'}$ in the acid region. $E_a^{o'}$ comprises the standard potential of the glass electrode, the potential of the reference electrode, the diffusion potential and the activity coefficients. The determination of $E_a^{o'}$ is based [12] on the full dissociation of HCl in 90% DMSO. With an available $E_a^{o'}$ pH in the cell can be found by the well known formula:

$$pH \equiv pC_H = \frac{Eao' - Emeas}{59.16}$$

where pC_H is the exponent of 10 of the proton concentration. Thus the pK-values are obtained from

$$pK = pC_H - \lg \frac{[A-]}{[AH]}$$

The equivalent volume, needed to perform the calculation, is determined by Gran's method [13].

The listed pK-values present the averages of two determinations.

pK-Value of benzoic acid in 90% DMSO was determined as 8.52.

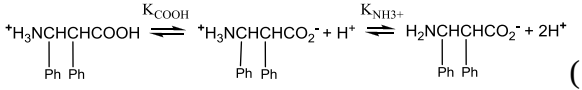
IR-spectra in DMSO

In order to assess the tautomeric forms of the amino acid: zwitterion – uncharged amino acid IR spectra were taken in 85-100% DMSO in CaF_2 0.1 mm cells.

RESULTS AND DISCUSSION

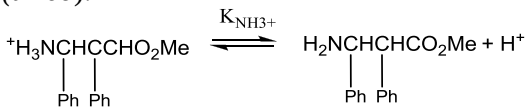
The pK-values obtained concern the following equilibria:

Amino acids, **1a** (erythro) and **2a** (*threo*):



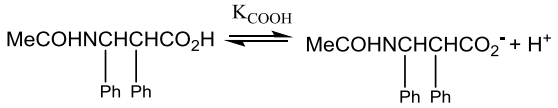
(1)

Esters of amino acids (only Me ester shown), Me **3a** (*erythro*), **4a** (*threo*); Et **5a** (*erythro*), **6a** *(threo*):



(2)

N-Acetylamino acids, **7a** (*erythro*) and **8a** (*threo*):



(3)

Table 2. pK-values of the diastereomeric amino acid and their N-acetyl and ester derivatives.

Compd	80% methylcellosolve		90% dimethylsulfoxide	
	K_{COOH}	K_{NH3+}	K_{COOH}	K_{NH3+}
1a	4.96	8.86	6.81	9.54
2a	4.18	8.98	6.08	9.25
3a		6.49		7.29
4a		6.57		7.28
5a		6.56		7.31
6a		≈6.6		7.28
7a	6.82		8.46	
8a	6.38		8.03	

In the zwitterion of the parent amino acids, **1a** and **2a**, Coulomb interactions are expected to increase K_{COOH} (decrease pK_{COOH}) because the attraction between the positively and negatively charged groups will shift the first equilibrium of Eqn. 1 to the right. Alternately the second equilibrium will be shifted to the left making the conjugated acid of the amino group a weaker acid i.e. increase pK_{NH3+}. This effect is nicely demonstrated by the roughly 2 pK units larger pK_{COOH}-values in the N-acetyl derivatives **7a** and **8a** compared to **1a** and **2a** in 80% methylcellosolve. The same difference persists with the data obtained in 90% DMSO only the ΔpK_{COOH}-values are slightly smaller (see below). Comparison of the p K_{NH3+}-values of the free acids with those of the esters in both solvents exhibits the expected effect which noteworthy is very similar to the one with pK_{COOH} in magnitude but opposite in sign. The similarity of the results obtainned on the pK in the two solvents systems suggests that the measurments are reliable.

The main reason for carrying out the present investigation is to establish the importance of the electrostatic interaction in the *syn* versus the *anti* position of the charged groups in zwitterions of β-amino acids making use of the unique conformational preferences in the system with neighbouring phenyl groups: the *erythro* isomer providing *anti* charged groups and the *threo* isomer – *syn* charged groups (Scheme 1). The closer distance in the *threo* isomer **2a** than in the *erythro* isomer **1a** predicts the former to be a stronger carboxylic acid which is confirmed by pK_{COOH} of **2a** found to be smaller by 0.8 pK units than that of **1a** in 80% methylcellosolve. In 90% DMSO ΔpK_{COOH} is slightly smalller 0.7 which fits the finding by means of IR-spectra that in 90% an appreciable amount of the neutral form of the amino acid is present (≈20%).

However, no significant difference was found for pK_{NH3+}-values of the two diastereomeric amino acids. We shall return to this point later.

The gap between pK_{COOH} and pK_{NH3+} in 90% DMSO is smaller *ca.* 2.5 - 3 pK units compared to 4-5 units in 80% methylcellosolve. This is readily explained by the well known phenomenon that aprotic dipolar solvents strongly destabilize anions and stabilize cations because the negative pole of the S=O bond is on the surface of the DMSO molecule. On the other hand, a disturbing fact concerning the assignment of the two pK-values, which one is due to COOH and which to NH_3, is that pK_{COOH} of the N-acetylamino acids and pK_{NH3+} of the amino esters become the same in values in 80% methylcellosolve, while in 90% DMSO the order is even reversed - the amino group becomes a weaker base that the carboxy anion: pK_{NH3+} of the esters in 90% DMSO are close in value to pK_{COOH} of the amino acids and similarly to pK_{COOH} of the N-acetylamino acids are close to pK_{NH3+} of the amino esters. This casts doubt on the assignment of first and second ionization constants of the amino acid. Another consequence is that if the order of the ionization constants of monocharged derivatives holds in amino acids then the neutral amino acid should be the prevailing tautomer.

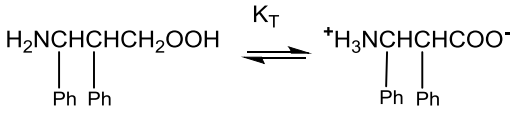
This problem was solved by measuring the tautomeric equilibria utilizing the fact that IR-bands

of COO^- and COOH appear at different frequencies. As reference, the bands in the N-acetylamino derivative **7a** and its potassium salt **7c** were taken. The intensities or absorbances, respectively, of these bands were utilised for a quantitative estimation of the concentration of the species in the tautomeric equilibria.

The data on the vicinal coupling constants summarised in Table 4 were collected in order to gain insight on the preferred conformations of the diastereoisomers **1a** and **2a** of the amino acids, their esters and N-acetyl derivatives as well as their salts.

The solubility of the parent amino acids is low in both water and organic solvents of low polarity, particularly of the *threo* isomer whose spectrum could only be recorded in 1:1 DMSO/H_2O. The spectra of all the remaining compounds were taken in formamide, a polar solvent with proton donor capacity. The protons of $HCONH_2$ resonate at low fields which permits spectra to be taken up to δ 5 ppm with the non deuterated solvent.

Table 3. Data on the tautomeric konstants K_T of *erythro* amino acid **1a** for equilibria in DMSO/ H2O solutions.



Solvent	K_T=[Zw]/[Neut]	Note
pure DMSO	≈0	Only the neutral form observed
95% DMSO	1.26	
90% DMSO	3.5	
80% DMSO	≈∞	Only the zwitterionic form observed

With the exception of **1a,** the *erythro* free amino acid, all vicinal couplings 2H:3H of the remaining compounds are greater than 10 Hz as expected because steric energy is known to determine the preference of *erythro anti* and *threo* (+)-*sc* conformations of Scheme 1. The lower J-constant of **1a** of

Table 4. Coupling constants, $J_{2H,3H}$ Hz, of amino acids, methyl and ethyl esters and N-acetylamino acids and their salts in $HCONH_2$.[1]

erythro			*threo*		
Compd	**Form**	**J_{2H3H} Hz**	**Compd**	**Form**	**J_{2H3H} Hz**
1a[2]	Free amino acid	9.0 (7.7[3a], 10.3[3b])	**2a**[6]	Free amino acid	10.9
1b[4]	HCl salt	10.0	**2b**[7]	HCl salt	10.9
1c[5]	Potassium salt	10.3	**2c**[8]	Potassium salt	10.5
3a[9]	Free methyl ester	10.1	**4a**[11]	Free methyl ester	10.8
3b[10]	HCl salt	11.0	**4b**[12]	HCl salt	11.2
5a[13]	Free ethyl ester	10.5	**6a**[15]	Free ethyl ester	10.5
5b[14]	HCl salt	11.2	**6b**[16]	HCl salt	≈11
7a[17]	Free acetylamino acid	11.8	**8a**[19]	Free acetylamino acid	10.3
7c[18]	Potassium salt	11.5	**8c**[20]	Potassium salt	9.6

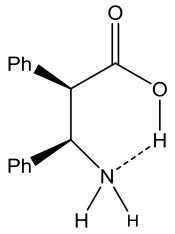
[1]Concentration of samples 0.04 g in 0.5 ml $HCONH_2$. Chemical shifts in δ (ppm) are listed in the corresponding footnotes; [2] 4.04 (d 1H), >5.25; [3a]In $DMSO_{d6}$; [3b]In D_2O 4.10 (d 1H), 4.95 (d 1H), 7.32 (s 10H); [4] 4.27 (d 1H), 4.98 (d 1H); [5]3.72 (d 1H), 4.45 (d 1H); [6]In $DMSO_{d6}$/ D_20 1:1; 3.80 (d 1H), 4.60 (d 1H), 7.04 (s 4H), 7.18 (s 6H); [7]4.24 (d 1H), 4.90 (d 1H); [8]3.62 (d 1H), 4.39 (d 1H); [9]3.20 (s 3H), 3.81 (d 1H), 4.40 (d 1H); [10]3.30 (s 3H), ≈4.37 (d 1H), 5.50 (d 1H); [11]3.57 (s 3H), ≈3.85 (d 1H), 4.40 (d 1H); [12]3.57 (s 3H), ≈4.35 (d 1H), 4.96 (d 1H); [13]0.70 (t 3H), 3.3 (q 2H), 3.67 (d 1H), 4.39 (d 1H); [14]0.71 (t 3H), 3.72 (q 2H), 4.34 (d 1H), 4.96 (d 1H); [15]1.01 (t 3H), 3.8 (d 1 H), ≈ 4 (4H, CH_2 + NH_2), 4.32 (d 1H); [16]1.02 (t 3H), 4.2 (q 2H), ≈4.0 (d 1H), 4.92 (d 1H); [17]1.57 (s 3H), 3.96 (d 1H), >5.25; [18]1.46 (s 3H), 3.93 (d 1H), >5.25; [20]1.83 (s 3H), 3.84 (d 1H), >5.25.

Table 5. Local minima of the conformational energy of the zwitterions of the 3-amino-2,3-diphenylpropanoic acid in kcal/mol and statistical weight at 300°K.

	$\Delta E = E_o - (E_o)g$	**Nonbonded**	**Electrostatical**	**Hydrogen bonding**	**Normalized stat. weight**
		threo global minimum $(E_o)g$ = -15.7			
(+)-sc	0.0	-3.6	-11.3	-1.0	1.0
ap	11.0	5.0	-11.9	-1.1	0.0
(-)-sc	8.5	1.0	-6.6	0.0	0.0
		erythro global minimum $(E_o)g$ = -10.7			
(+)-sc	5.3	6.9	-11.9	-1.0	0.0
ap	0.0	-4.5	-6.5	0.0	1.0
(-)-sc	2.2	3.8	-11.8	-1.1	0.0

9 Hz in formamide is also not surprising because *gauche* charged groups of opposite sign will lower the energy of the *sc* conformations in the *erythro* isomer and thus decrease the population of *erythro anti*. The same interaction of course stabilizes the (+)-*sc*-conformation in the *threo* isomer **2b.**

The still lower value of J_{2H3H} of 7.7 Hz observed with **1a** in pure $DMSO_{d6}$ shows that an attractive interaction arises in the neutral amino acid stronger than that in the zwitterion, where according to the IR data the neutral form of the amino acid entirely prevails in practice. This apparently is due to a hydrogen bond.



In D_2O on the contrary a larger J_{2H3H} of 10.3 Hz is observed. Although the obvious reason appears the higher dielectric coefficient of water, this is hardly the whole reason because intramolecular Coulomb interactions take place mainly through the hydrocarbon skeleton of low dielectric coefficient. Actually ε = 2.0 is most commonly used in molecular mechanics. More likely of importance is the solvation of the groups: water solvates both cations and anions thus increasing their steric demands and thus overriding the attraction of the charged groups. The better solvation of $–NH_3^+$ than of $-NH_2$ explains the systematically higher J_{2H3H}-couplings found in the hydrochlorides of the amino esters compared to the free amino esters (Table 4).

MM deals with empirical force fields which agree quantitatively with experiments when they are well calibrated for a class of compounds. The preferred conformations are properly predicted. The closer local minima over the global one in the *erythro* case correspond to the greater mobility of the conformational equilibrium. The computed difference in the electrostatic interactions between the *sc* and *ap* positions of the charged groups amounts to ca. 4.5 kcal/mol. Only a small part of it is expressed to change pK_1 by 0.8 pK units indicating the complexity of factors determining experimental pK-values. Noteworthy is that in the case of the amino acid studied the *threo* isomer is more stable which is not common. On Table 5 are listed the local minima for the conformational energy of the conformations of the zwitterions of the *threo* and *erythro* isomers of 3-amino-2,3-diphenylpropanoic acid (Scheme 1), calculated by means of the Sheraga force field [14].

CONCLUSION

The ^1H NMR J_{2H3H}-couplings above 10 Hz found in formamide for the diastereomers of 3-amino-2,3-diphenylpropanoic acid, its salts and ester and N-acetyl derivatives confirmed the expectation of *anti* amino and carboxy groups in the *erythro* isomers and *syn* in the *threo* ones according to general preferences found in 1,2-disubstituted-1,2-diphenylethane systems. Coulomb attraction in the zwitterion only slightly enhances the *gauche* conformation in the *erythro* isomer (J = 9.0 Hz). This conformation is disfavored in water (10.3 Hz) apparently because of increasing steric demands due to solvation. An entirely different phenomenon was observed in DMSO – the low J = 7.7 Hz is actually the result of a strong hydrogen bond between the NH_2 and COOH groups in the neutral form of amino acid with an abundance of ca. 100% in pure DMSO according to IR spectral data. The presence of water rapidly decreases the percentage of the neutral form: around 20% in 90% DMSO and ca 0% in 80% DMSO. The traditional measure of electrostatic effects is $\Delta pK = pK_2 – pK_1$ for ionizations of the two charged groups. When the groups are different, as in the case of amino acid, the effect of charge is exhibited by ΔpK between the pK's in the zwitterion and the N-acetyl or ester derivatives where one of the charges is removed. These ΔpK-values amounted to ca. 2 pK units according to our pK-measurements in two solvents: 80% methyl cellosolve and 90% DMSO. The effect of proximity of the charged groups, *syn* versus *anti* disposition in the zwitterion, is measured by ΔΔpK between ΔpK of the diastereomers. An early study of Gentschew and Toleva [15] showed a small ΔΔpK of 0.3 between **1a** and **2a** in water (0.1M KCl). This was interpreted by means of Tanford's model [16] that closer proximity in *threo* (*syn*) is compensated by a lower effective dielectric constant, D, in *erythro* (*anti*) because less interaction is realized through the solvent of large D [10]. As expected, in solvents with smaller D, 80% methyl cellosolve and 90% DMSO, larger ΔΔpK of 0.9 and 0.5 were found, respectively. Molecular mechanics calculations gave an electrostatic energy difference of 4.5 kcal/mol between the diastereomeric zwitterions corresponding to 3.2 ΔΔpK at 300 K.

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ВЗАИМОДЕЙСТВИЕ НА ЗАРЕДЕНИ ГРУПИ. РК И КОНФОРМАЦИИ НА ДИАСТЕРЕОМЕРИТЕ НА 3-АМИНО-2,3-ДИФЕНИЛПРОПАНОВАТА КИСЕЛИНА, МЕТИЛОВИТЕ И ЕТИЛОВИТЕ Й ЕСТЕРИ И N-АЦЕТИЛНИ ПРОИЗВОДНИ

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(Резюме)

Характерно за системата на 1,2-дизаместени-1,2-дифенилетани е силното предпочитание на конформацията с *антиперипланарни* фенилни групи, поради което другите заместители застават *ар* в *еритро* и (+)-*sc* в *трео* изомера. Същото явление бе установено за изомерите на 3-амино-2,3-дифенилпропановата киселина и нейните N-ацетилни и естерни производни съгласно J_{2H3H}-константите > 10 Хц, измерени в формамид. Само цвитерионът на *еритро* амино киселината **1a** даде по-ниска стойност 9.0 Хц, указание, че привличането на зарядите е преодоляло частично стеричните взаимодействия. Пресмятания с молекулна механика със силовото поле на Шерага подкрепиха тази интерпретация. ИЧ-спектроскопски изследвания на равновесието цвитерион - неутрална амино киселина показаха, че неутралната форма е предпочетена в апротни разтворители, при **1a** ≈ 100% в чист DMSO, но намалява при добавяне на вода като при 80% DMSO вече се наблюдава само цвитерионът. pK-константите бяха определени потенциометрично в 80% метилцелосолв и в 90% DMSO. pK_1-константите за *трео* цвитерйона **1a** са с 0.8 pK единици по-големи от тези на *еритро* изомера, очаквано съотношение между *анти* и *гош* заредени групи. pK_2-константите на изомерите не се различават съществено; видимо електростатичното взаимодействие частично се компенсира поради стерично пречене породено от солватиране на NH_3^+. pK на естерите и на N-ацетилираните производни се различават с около 2 pK единици от тези на цвитерйона, отразяващо силното влияние на взаимодействието на заредените групи. В органичните разтворители силно се променят киселиностите на COOH и NH_3^+ в обратни посоки, което води до поява на неутралната форма, доказана с ИЧ изследванията.