p-SUBSTITUTED BENZAMIDINIUM CARBOXYLATES

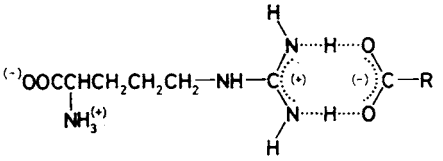
Jiří KRECHL[a], Svatava SMRČKOVÁ[a], Františka PAVLÍKOVÁ[b] and Josef KUTHAN[a]

[a] *Department of Organic Chemistry and*
[b] *Central Research Laboratories,*
Prague Institute of Chemical Technology, 166 28 Prague 6

Received October 14, 1988
Accepted February 27, 1989

Various *p*-substituted benzamidinium formates (*I*), acetates (*II*), trifluoroacetates (*III*) and pyruvates (*IV*) were prepared and the nature of the amidinium – carboxylate interactions were examined by ^1H and ^{13}C NMR spectra. The spectroscopic data are consistent with the presumtion that the carboxylic part is only slightly influenced by the diverse substitution of the aromatic benzamidinium ring.

In an effort to understand the elementary processes proceeding in the active centers of certain enzymes great attention is given to the question of substrate fixation. The crucial role of carboxylic substrates fixation is played by arginine as was demonstrated for lactate dehydrogenase[1,2], carboxypeptidase[3], malate dehydrogenase[4] and other enzymes[5]. The mentioned fixation consists in the formation of two parallel hydrogen bonds between two nitrogens of the arginine guanidinium group; and two oxygens of the carboxylate (Scheme 1).



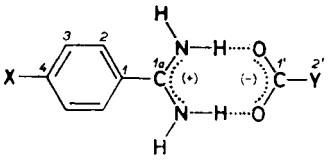
SCHEME 1

In our previous communication[6] we have applied an MO approach to understand the basic characteristics of this interaction between simple counter-ions of a different chemical nature. In this paper we wish to investigate some other aspects of the interaction between amidinium and carboxylate moieties.

Amidinium carboxylates are well defined, non-hygroscopic compounds with sharp melting points[7] as was originally demonstrated on some benzamidinium carboxylates in the pioneering work of Pinner[8]. Due to their suitable properties they had been frequently used for the carboxylic acids identification and characterization[9–11].

However, no detailed studies have yet been carried out in the field of amidinium carboxylates and the contemporary interest of organic chemists has been mainly focused to their use in heterocyclic synthesis[12]. Some compounds prepared in our Laboratory have been subjected to X-ray investigations[13-15].

We carried out the examination of 32 p-substituted benzamidinium carboxylates differing also in the substitution of the carboxylic part. Our aim was to establish a possible mutual influence between both counter partners in amidinium carboxylate molecules.



I, Y = H *III*, Y = CF_3
II, Y = CH_3 *IV*, Y = $COCH_3$

In formulae *I–IV*: *a*, X = H *b*, X = CH_3 *c*, X = $(CH_3)_3C$
d, X = C_6H_5 *e*, X = NH_2 *f*, X = NO_2 *g*, X = CH_3O *h*, X = CN

EXPERIMENTAL

Temperature data are not corrected. Melting points were determined on a Boetius apparatus The spectra were measured on Bruker AM 400 in $(CD_3)_2SO$ solutions related to tetramethylsilane. Experimental parameters were: for ^1H NMR 400·13 MHz, 64 K data points, digital resolution 0·2 Hz/point, pulse width 4 μs, temperature (owing to the solubility) 27—80°C; for ^{13}C NMR 100·61 MHz, 64 K data points, digital resolution 1 Hz/point, used APT (Attached Proton Test), pulse sequence, temperature 27—80°C. The solid state ^{13}C NMR spectra were measured on the Bruker MSL 200 apparatus, 50·32 MHz.

Preparation of 4-Substituted Benzamidinium Carboxylates *Ia–If*, *IIa–IIf*, *IIIa–IIIf*, *IVa–IVf*

Aqueous or aqueous-ethanolic solution (0·15 mol/l) containing 1 g of the corresponding *p*-substituted benzamidinium chloride (obtained from *p*-substituted benzonitrile[8]) was passed through a column (10 × 500 mm), packed with Dowex 1X8 (ref.[16]) or Amberlite IRA-401 (100—200 mesh) in the formate, acetate, tirfluoroacetate or pyruvate form, respectively. The resulting solution was evaporated in vacuo to dryness and the residue recrystallized from ethanol–water. The yields of carboxylates *Ia–If*, *IIa–IIf*, *IIIa–IIIf* and *IVa–IVf*, obtained in this way, were practically theoretical.

4-Methoxybenzamidinium Carboxylates *Ig–IVg*

A solution of 3 g (0·023 mol) 4-methoxybenzonitrile in 25 ml of dry dioxane was diluted with absolute ethanol (1·35 ml, 0·023 mol) and the resulting mixture was saturated with dry hydrogen

chloride for 1 h at 0°C. After cooling to −18°C the precipitated crystals were filtered off, treated with 10% aqueous potassium carbonate (80 ml) and extracted with ether. The collected etheral extracts, after drying over magnesium sulfate and evaporating, afforded a residue which was dissolved in hot saturated ammonium acetate solution in ethanol. After cooling to room temperature, 2·8 g (61%) colorless needles of *IIg*, m.p. 240–241°C, were isolated by filtration. The following ion exchange chromatography of the product using the formate, trifluoroacetate and pyruvate form of Amberlite IRA-401 gave the corresponding formate (*Ig*), trifluoroacetate (*IIIg*) and pyruvate (*IVg*), respectively (Table I).

4-Cyanobenzamidinium Carboxylates *Ih–IVh*

The general procedure[17] for the preparation of *p*-cyanobenzamidinium acetate (*IVh*) was applied. A sodium methanolate solution prepared from 106 mg (4·6 mmol) sodium and 60 ml methanol was added to 3 g (0·023 mol) 1,4-dicyanobenzene and the reaction mixture was kept at room temperature for 24 h. The resulting suspension was then mixed with 3·56 g (0·046 mol) ammonium acetate and 276 ml acetic acid and refluxed for 3 h. Crystals of 1,4-benzenedicarboxamidinium diacetate precipitated after cooling were filtered off and washed with hot ethanol. Yield was 3·0 g (45%), m.p. 272–273°C. For $C_{12}H_{18}N_4O_4$ (282·3) calculated: 51·06% C, 6·43% H, 19·85% N; found: 51·33% C, 6·26% H, 19·95% N. Crystalline acetate *IIh* (0·8 g, 17%) was obtained from the filtrate by evaporation. The corresponding formate *Ih*, trifluoroacetate *IIIh* and pyruvate *IVh* were prepared from acetate *IIh* using Amberlite IRA-401 in the formate, trifluoroacetate and pyruvate form, respectively (Table I).

RESULTS AND DISCUSSION

Melting points: We have not succeeded in finding any general structure – melting point relationships within the series of all benzamidinium carboxylates *Ia–Ih – IVa–IVh*, although the 4-amino derivatives *Ie–IVe* usually melt at lower temperatures (Table I). This is not surprising since phase transition temperatures are also influenced by the type of crystallographic symmetry[18] and may be different for various substituents X as well as Y. However, if two series of 4-substituted benzamidinium carboxylates have similar molecular topologies, certain structural effects on melting point temperatures may be expected. 4-Substituted benzamidinium acetates *IIa–IIh* and trifluoroacetates *IIIa–IIIh* are to be regarded as two such series of compounds in crystalline nets of which both the CH_3 and CF_3 groups may exhibit similar space requirements. As a matter of fact the plot of the corresponding melting point differences $\Delta T_{mp}(CF_3 - CH_3)$ versus Hammett σ_p-parameters for substituents X leads to an interesting correlation field. As follows from Fig. 1 the mutual relation of the considered magnitudes is to be interpreted as a correlation curve with a deviation of data for X = phenyl and tert. butyl, respectively. The different behaviour of both bulky 4-substituents may be explained by their special space requirements in the process of melting. However, it has to be noted that any Hammett type correlations with phase transition data are not justified in principle and their physical or chemical significance may therefore be questioned. We have concluded that the

TABLE I

Melting points and elementar analyses for compounds *I*—*IV*

Compound	Formula (M.w.)	M.p., °C	Calculated/Found		
			%C	%H	%N
Ia	$C_8H_{10}N_2O_2$ (166·2)	172—174[a]	57·82 57·92	6·07 6·11	16·86 16·77
Ib	$C_9H_{12}N_2O_2$ (180·2)	240—241	59·99 59·79	6·71 6·66	15·55 15·12
Ic	$C_{12}H_{18}N_2O_2$ (222·3)	258—259	64·84 65·09	8·16 8·07	12·60 12·25
Id	$C_{14}H_{14}N_2O_2$ (242·3)	226—228	69·41 69·61	5·82 5·98	11·56 11·35
Ie	$C_8H_{11}N_3O_2$ (181·2)	191—192	53·03 53·04	6·12 5·79	23·19 23·18
If	$C_8H_9N_3O_4$ (211·2)	230—231	45·50 45·16	4·30 4·47	19·90 19·38
Ig	$C_9H_{12}N_2O_3$ (196·2)	220—221	55·09 55·24	6·16 6·35	14·28 14·15
Ih	$C_9H_9N_3O_2$ (191·2)	237—239	56·54 56·50	4·74 5·32	21·98 21·93
IIa	$C_9H_{12}N_2O_2$ (180·2)	219—220[b]	59·99 59·52	6·71 6·71	15·55 14·97
IIb	$C_{10}H_{14}N_2O_2$ (194·2)	253—255	61·84 61·77	7·27 7·42	14·42 14·65
IIc	$C_{13}H_{20}N_2O_2$ (236·3)	233—234	66·07 66·23	8·53 8·47	11·85 11·67
IId	$C_{15}H_{16}N_2O_2$ (256·3)	250—251	70·29 70·52	6·29 6·32	10·93 10·49
IIe	$C_9H_{13}N_3O_2$ (195·2)	187—188	55·37 55·08	6·71 6·94	21·52 21·82
IIf	$C_9H_{11}N_3O_4$ (225·2)	220—222	48·00 48·12	4·92 4·90	18·66 18·14
IIg	$C_{10}H_{14}N_2O_3$ (210·2)	240—241	57·13 57·01	6·71 6·70	13·32 13·07
IIh	$C_{10}H_{11}N_3O_2$ (205·2)	196—198	58·53 58·34	5·40 5·84	20·48 19·95
IIIa	$C_9H_9N_2O_2F_3$ (234·2)	255—256	46·16 45·82	3·87 3·93	24·34[c] 24·20

TABLE I
(*Continued*)

Compound	Formula (M.w.)	M.p., °C	Calculated/Found		
			%C	%H	%N
IIIb	$C_{10}H_{11}N_2O_2F_3$ (248·2)	284—285	48·39 48·63	4·47 4·76	22·96[c] 22·81
IIIc	$C_{13}H_{17}N_2O_2F_3$ (290·3)	274—275	53·79 53·83	5·90 6·17	19·63[c] 19·51
IIId	$C_{15}H_{13}N_2O_2F_3$ (310·3)	296—298	58·07 58·11	4·22 4·27	18·37[c] 18·22
IIIe	$C_9H_{10}N_3O_2F_3$ (249·2)	189—190	43·38 42·92	4·05 3·85	22·87[c] 23·14
IIIf	$C_9H_8N_3O_4F_3$ (279·2)	277—278	38·72 38·61	2·89 2·98	20·42[c] 20·30
IIIg	$C_{10}H_{11}N_2O_3F_3$ (264·2)	262—264	45·46 45·44	4·20 4·29	21·57[c] 21·54
IIIh	$C_{10}H_8N_3O_2F_3$ (259·2)	252—253	46·34 46·08	3·11 3·10	21·99[c] 22·01
IVa	$C_{10}H_{12}N_2O_3$ (208·2)	189—191	57·69 56·80	5·81 5·81	13·45 13·31
IVb	$C_{11}H_{14}N_2O_3$ (222·2)	205—206	59·45 58·95	6·35 6·43	12·60 12·36
IVc	$C_{14}H_{20}N_2O_3$ (264·3)	170—171	63·32 63·23	7·63 7·53	10·60 10·32
IVd	$C_{16}H_{16}N_2O_3$ (284·3)	225—226	67·59 67·63	5·67 5·88	9·85 9·98
IVe	$C_{10}H_{13}N_3O_3$ (223·2)	170—171	53·81 54·45	5·87 6·06	18·82 19·58
IVf	$C_{10}H_{11}N_3O_5$ (253·2)	236—238	47·43 47·13	4·38 5·00	16·61 17·05
IVg	$C_{11}H_{14}N_2O_4$ (238·2)	211—212	55·46 55·41	5·92 5·91	11·76 11·61
IVh	$C_{11}H_{11}N_3O_3$ (233·2)	186—188	56·65 56·47	4·75 4·58	18·02 18·39

[a] Ref.[17] m.p. 176°C; [b] ref.[8] m.p. 229°C; [c] %F for compounds *IIIa*—*IIIh* given (imposible to determine nitrogen content).

phase transition accelerates the dissociation of a given amidinium carboxylate into its benzamidine and carboxylic acid component (Eq. (*A*)).

$$XC_6H_4C(NH_2)_2O_2CY \xrightarrow[\text{melting}]{\Delta T} XC_6H_4C(=NH)NH_2 + HO_2CY \qquad (A)$$

This assumption seems to be in agreement with the known similar lability of amidinium salts at elevated temperatures[8] and with our additional finding that mass spectra of amidinium carboxylates usually consist of the superposition of individual components measured under the same conditions. Considering the transformation (*A*), a deionization process, the correlation in Fig. 1 may be easily understood provided the melting points are in fact not purely physical properties but temperatures stimulating the chemical process (*A*). In accordance with the conclusion the apparent melting points of more strongly bound trifluoroacetates *IIIa–IIIh* are systematically higher than those of corresponding acetates *IIa–IIh*.

^{1}H NMR *spectra*: Because of the limited solubility only hexadeuteriodimethylsulfoxide solutions of compounds *Ia–IVa*, *IIa–IIh*, benzamidine *V*, benzamidinium chloride *VI* and benzamidinium perchlorate *VII* were investigated. In what form the amidinium carbocylates occur in the solute state was the question of main interest. As follows from Table II the interaction of benzamidine *V* with any protic acid results in the deshielding effects on all proton signals of the benzamidinium component. The N–H protons exhibit in all cases only one more or less broad signal. This may be explained by special solvation of substrate species with an excess of

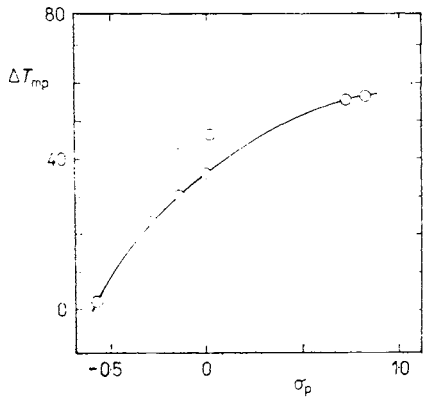


FIG. 1

Dependence of the $\Delta T_{mp}(CF_3-CH_3)$ on the Hammett σ_p-parameters

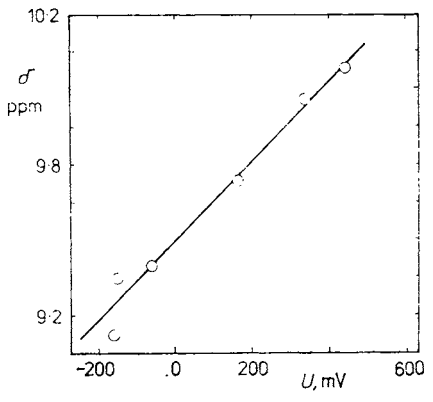
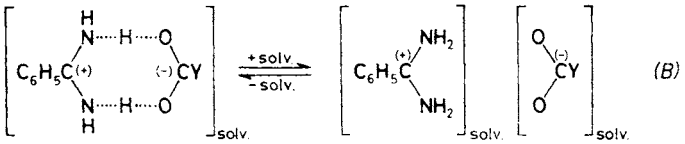


FIG. 2

Dependence of ^{1}H NMR chemical shifts of the amidinium group on the pK_a values of corresponding acids in DMSO

solvent molecules via hydrogen bonds. The observed signals are to be then assigned to heteroatomic protons not participating in the solvation in agreement with the variability of their integral intensities due to the substrate concentration. The plot of their chemical shifts versus pK_a values of the corresponding acids measured in dimethylsulfoxide[19] is given in Fig. 2. The mutual correlation of both magnitudes exhibit a certain relationship between the strength of a given acid and the deshielding effect. This interrelation excludes the occurrence of only isolated and solvated ions $[C_6H_5C(NH_2)_2]^{(+)}$ and $[YCO_2]^{(-)}$ in measured samples while linearity of the correlation may be interpreted by the assumption of the equilibrium (*B*) involving the "covalent" and counter-pair forms of benzamidinium salts.



(*B*)

The possible equilibration (*B*) evidently proceeds very rapidly under the conditions of measurement since only one set of time-averaged signals have been observed in all former discussed and following cases.

Three signals corresponding to the *ortho*-, *meta*- and *para*-protons of the aromatic ring have been found to be generally down field shifted in the benzamidinium compounds in comparison to the benzamidine signals (Table II). The deshielding

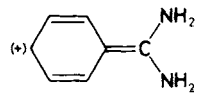
TABLE II

^{1}H NMR spectra of benzamidine and its salts (ppm)

Compounds	Aromatic protons			Protons of amidino group[a]	U^b mV	Protons of acid residue
	ortho	*meta*	*para*			
Ia	7·81	7·60	7·70	10·33	335	8·47
IIa	7·79	7·58	7·68	10·50	445	1·71
IIIa	7·84	7·62	7·74	9·45	−58	—
IVa	7·84	7·61	7·72	9·91	164	2·15
V	7·76	7·39	7·42	6·48	—	—
VI	7·86	7·62	7·74	9·40	−150	—
VII	7·81	7·63	7·75	9·09	−158	—

[a] Singlets in all cases; [b] the voltage of the glass electrode-SCE as the value linearly dependent[21] on pK_a is given, the calibration was not necessary.

effect decreases in the order *para* > *meta* > *ortho*. For example in the case of hydrochloride *VI*, values 0·32, 0·23 and 0·10 ppm were observed suggesting that the positive net charges in the corresponding counter pairs or ions are significantly delocalized mainly at the *para*-position in the sense of formula *VIII*. On the other



VIII

hand, mutual differences of the deshielding effects within the series of amidinium salts are substantially lower (0·04 to 0·07 ppm) but indisputably decreasing in the same order as the pK_a values of the partner acids, i.e. (HCl) < CF_3CO_2H < < CH_3COCO_2H < HCO_2H < CH_3CO_2H. This slight long-range interaction observed in the ^1H NMR measurements may also be regarded as a support for "covalent" carboxylate forms.

Finally we tried to find a possible long range substituent effect in the series of *p*-sbustituted benzamidinium trifluoroacetates *IIIa*–*IIIh* and acetates *IIa*–*IIh*. No defined substituent chemical shifts have been observed in the ^{19}F NMR spectra of compounds *IIIa*–*IIIh* (Table III). This finding may be associated with the above-mentioned circumstance that benzamidinium trifluoroacetates mainly exist as counter-pairs under the conditions of measurements. Nevertheless small but quite definite long range substitution chemical shifts of acetate protons have really been observed in the series of acetates *IIa*–*IIh* (Table IV) and confirmed by several two component measurements. If a mixture of two X-substituted benzamidinium acetates in hexadeuteriodimethylsulfoxide was investigated by ^1H NMR only one averaged signal has been recorded in agreement with the rapid equilibria (*B*).

^{13}C NMR methyl chemical shifts were measured only for a limited number of amidinium carboxylates because of their low solubilities. No decisive long-range substituent effect has been observed for X-substituted benzamidinium acetates *IVa*, *IVb*, *IVg* (Table V).

TABLE III

^{19}F NMR spectra (ppm) of *p*-substituted benzamidinium trifloroacetes *IIIa*–*IIIh*

IIIa	*IIIb*	*IIIc*	*IIId*	*IIIe*	*IIIf*	*IIIg*	*IIIh*
−75·492	−75·564	−75·539	−75·489	−75·514	−75·589	−75·539	−75·538

The high resolution solid state NMR spectrum was measured for the compound *IIa* (Table V). The comparison of the *IIa* spectra measured in $(CD_3)_2SO$, $D_2O$and solid phase, respectively, shows that compound *IIa* is solvated in water and dissociated to the benzamidinium cation and acetate anion. Chemical shifts of the latter fit to those tabulated[20] for sodium acetate in water, while in spectrum measured in $(CD_3)_2SO$ the acetate counter-part corresponds to solid state measurements.

In conclusion the influence of the aromatic ring substitution on the carboxylic part behavior depends mainly on the covalent forms of the examined salts in solution. The lower the pK_a of a given acid the more pronounced is the counter pair form. Only salts with a substantial occurrence of the "covalent" form exhibit a slight mutual influence between both parts.

TABLE IV

^1H NMR spectra (ppm) of *p*-substituted benzamidinium acetates *IIb*—*IIh* in $(CD_3)_2SO$ at 25°C

Compound	Protons of substituent[a]	Aromatic protons	Protons of amidino group	Protons of acetate part
IIb	2·39	7·37, 7·69	10·25	1·70
IIc	1·31	7·74, 7·60	10·20	1·71
IId	7·67 m	7·67 m	10·20	1·70
IIe	6·10	6·62, 7·55	10·25	1·68
IIf	—	8·03, 8·31	9·01	1·82
IIg	8·85	7·11, 7·80	10·25	1·70
IIh	—	7·95, 8·10	9·70	1·78

[a] In all cases except *p*-phenyl derivative singlets.

TABLE V

^{13}C NMR spectra (ppm) of some benzamidinium acetates

Compound	2′	1′	1a	1	2	3	4	X
IIa[a]	24·401	182·400	167·909	128·807	130·389	128·680	135·270	—
IIa[b]	24·990	177·670	162·520	132·230	126—131 (5 peaks)			—
IIa	24·730	176·510	166·020	129·830	128·750	127·400	132·810	—
IIb	24·430	175·760	165·380	127·370	129·200	127·250	142·900	20·900

[a] In D_2O; [b] solid state measurement.

The authors thank Dr M. Ludwig, Institute of Chemical Technology, Pardubice, for the pK_a *measurements and Dr B. Schneider, Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, for the solid state* NMR *experiments.*

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Translated by the author (J. Krechl).