BENZAMIDINIUM BENZOATES

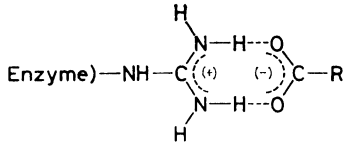
Jiří KRECHL, Svatava SMRČKOVÁ and Josef KUTHAN

Department of Organic Chemistry,
Prague Institute of Chemical Technology, 166 28 Prague 6

Received March 24, 1989
Accepted May 5, 1989

Various *p*-substituted benzamidinium benzoates (*III*), and benzamidinium *p*(*m*)-substituted benzoates (*IV*) were prepared and the nature of the amidinium – carboxylate interactions was examined by ^{1}H and ^{13}C NMR spectra. Based on the simple semiempirical quantum-chemical EHT method a presumption was made that the mutual influence between both counter-partners is substantially stronger compared to similar aliphatic compounds. The spectroscopic data are consistent with this presumption and exhibit good correlation between chemical shifts and Hammett's σ values.

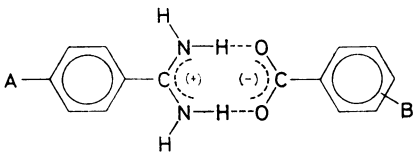
Arginine plays an important role in carboxylic substrates fixation in numerous enzymatic reactions as was demonstrated e.g. for lactate dehydrogenase[1,2], carboxypeptidase[3], malate dehydrogenase[4] and other enzymes[5]. The mentioned fixation consists in the formation of two parallel hydrogen bonds 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 and we also tried to find the mutual influence between the carboxylic and amidinium parts of more complex *p*-substituted benzamidinium carboxylates[7]. We did not succeed in finding any substitution effect at all in the case of simple counter pairs[6] and only slight mutual influence was found in more complicated structures[7] where one of the molecule components was aromatic. In our previous non-empirical calculations made on 4−31G level[6] for very simple compounds we

found that frontier molecular orbitals HOMO (Highest Occupied MO) and LUMO (Lowest Unoccupied MO) were exclusively located in one of the counter-partners. To realize whether searching for the substitution effect in more complicated compounds would be worth the effort we carried out the distribution comparison of the frontier orbitals in a series of three compounds with increasing complexity. Semiempirical quantum-chemical method EHT (ref.[8]) was chosen for this purpose and formamidinium formate (*I*), benzamidinium formate (*II*) and benzamidinium benzoate (*IIIa*) were investigated. As we reported earlier[6] at simple amidinium carboxylates the HOMO is not delocalized over the complete molecule at all, EHT calculation exhibit qualitatively the same result (Fig. 1) for formamidinium formate (*I*). When the amidinium part is aromatic (*II*) HOMO also slightly involves the carboxylic part and for benzamidinium benzoate (*IIIa*), both parts being aromatic, the localization of HOMO on the carboxylate is substantial. Therefore the presumption that a stronger substitution effect might be observed in benzamidinium benzoates seems to be reasonable. The results depicted on Fig. 1 encouraged us in the synthesis of two benzamidinium benzoate series: *IIIa–IIIh* and *IVa–IVg*, respectively (Scheme 2).



Compound	A	B
IIIa	H	H
IIIb	NH_2	H
IIIc	$t\text{-}C_4H_9$	H
IIId	CH_3	H
IIIe	C_6H_5	H
IIIf	Br	H
IIIg	CN	H
IIIh	NO_2	H
IVa	H	$p\text{-}NH_2$
IVb	H	$p\text{-}t\text{-}C_4H_9$
IVc	H	$m\text{-}NH_2$
IVd	H	$p\text{-}C_6H_5$
IVe	H	p-Cl
IVf	H	p-Br
IVg	H	$p\text{-}NO_2$

SCHEME 2

Compounds *IIIa–IIIe*, *IIIh* were prepared from the corresponding *p*-substituted benzamidinium chlorides and sodium benzoate; for *IIIg* preparation *p*-cyanobenzamidinium acetate was used. For the synthesis of compound *IIIf* the reaction of ethyl *p*-bromobenzenecarboximidate with ammonium benzoate was utilized. Compounds *IVa–IVg* resulted from the reaction of *p*-substituted sodium benzoate with benzamidinium chloride.

EXPERIMENTAL

Temperature data are not corrected. Melting points were determined on a Boetius apparatus. NMR spectra were measured on Bruker AM 400 in $(CD_3)_2SO$ or D_2O solutions related to tetramethylsilane or sodium 4,4-dimethyl-4-silapentasulfonate, respectively. Experimental parameters were: for ^1H NMR 400·13 MHz, 64 K data points, digital resolution 0·2 Hz/point, pulse width 4 μs, temperature (depending on 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), two-dimensional spectroscopic technique HETCOR, pulse sequence, temperature 27–80°C.

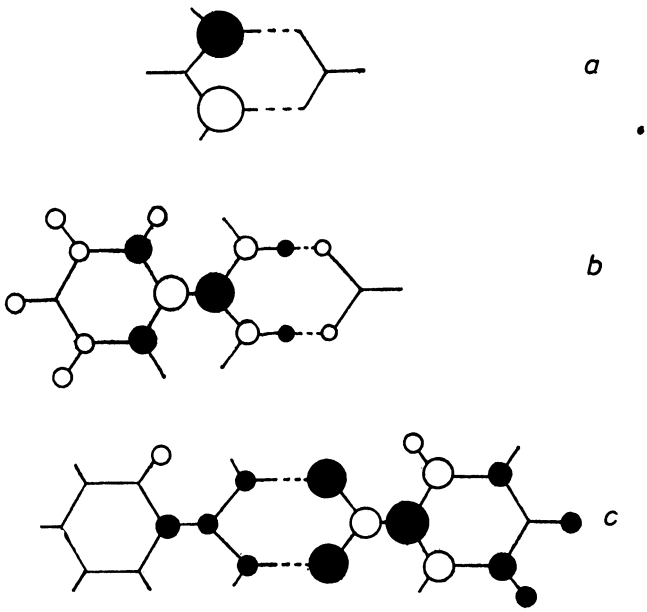


FIG. 1

HOMO distribution in the molecules of formamidinium formate *I* (*a*), benzamidinium formate *II* (*b*) and benzamidinium benzoate *IIIa* (*c*) calculated by the EHT method. HOMO is slightly unsymmetrical because of compound *IIIa* geometry[9]

TABLE I

Melting points and elemental analyses for compounds *III* and *IV*

Compound	Formula (M.w.)	M.p., °C	Calculated/Found		
			%C	%H	%N
IIIa	$C_{14}H_{14}N_2O_2$ (242·3)	250—252[a,b]	69·42 69·72	5·83 5·92	11·56 11·53
IIIb	$C_{14}H_{15}N_3O_2$ (257·3)	238—240[a]	65·35 65·18	5·87 5·77	16·33 16·14
IIIc	$C_{18}H_{22}N_2O_2$ (298·4)	245—248[a]	72·46 72·03	7·43 7·41	9·39 9·33
IIId	$C_{15}H_{16}N_2O_2$ (256·3)	233—236	70·29 70·21	6·29 6·42	10·93 10·91
IIIe	$C_{20}H_{18}N_2O_2$ (318·4)	253—255[a]	75·45 74·91	5·70 5·81	8·80 8·88
IIIf	$C_{14}H_{13}N_2O_2Br$[c] (321·2)	263—265[a]	52·36 51·84	4·08 4·13	8·72 8·44
IIIg	$C_{15}H_{13}N_3O_2$ (267·3)	267—269[a]	67·40 67·42	4·90 4·80	15·72 15·58
IIIh	$C_{14}H_{13}N_3O_4$ (287·3)	268—270[a]	58·53 58·51	4·56 4·69	14·63 14·64
IVa	$C_{14}H_{15}N_3O_2$ (257·3)	192—193	65·35 65·50	5·87 5·87	16·33 15·90
IVb	$C_{18}H_{22}N_2O_2$ (298·4)	253—255[a]	72·46 71·89	7·43 7·19	9·39 9·43
IVc	$C_{14}H_{15}N_3O_2$ (257·3)	206—209[a]	65·35 64·97	5·87 5·49	16·33 15·87
IVd	$C_{20}H_{18}N_2O_2$ (318·4)	198—199[a]	75·45 75·39	5·70 5·75	8·80 8·63
IVe	$C_{14}H_{13}N_2O_2Cl$[d] (276·7)	244—245[a]	60·77 60·25	4·74 4·52	10·12 10·16
IVf	$C_{14}H_{13}N_2O_2Br$[e] (321·2)	247—249[a]	52·36 52·68	4·08 4·12	8·72 8·77
IVg	$C_{14}H_{13}N_3O_4$ (287·3)	282—284[a]	58·53 58·62	4·56 4·60	14·63 14·53

[a] Exhibits sublimation before melting; [b] ref.[11] m.p. 230°C. [c] calculated 24·88%Br, found 25·02%Br; [d] calculated 12·81%Cl, found 12·91%Cl; [e] calculated 24·88%Br, found 24·65% Br.

General Procedure for the Preparation of Compounds *IIIa—IIIe, IIIh, IVa—IVg*

The mixture of equimolar amounts of (substituted) benzamidinium chloride and corresponding sodium (substituted) benzoate in water was heated to 60°C. The precipitate obtained after cooling was recrystallized from ethanol – water or ethanol–chloroform solution. Melting points and elemental analyses are given in Table I.

TABLE II

NMR spectra (δ, ppm) of compounds *IIIa—IIIh* (amidinium parts)

Compd.	^{1}H				^{13}C					
	A	*o*	*m*	NH_2	A	C-1	C-2	C-3	C-4	C_{amidin}
IIIa	7·71	7·85	7·61	10·65	—	129·39	128·83	127·54	133·07	166·31
IIIb	6·17	6·65	7·60	8·49 11·20	—	113·45	129·28	112·70	153·86	164·85
IIIc	1·29	7·79	7·63	10·40	30·69	126·44	127·44	125·69	156·33	166·03
IIId	2·41	7·75	7·43	10·48	20·95	126·34	127·49	129·35	143·59	165·92
IIIe	[a]	7·95	7·95	10·53	[b]	128·12	129·04	128·25	144·66	165·79
IIIf	—	7·85	7·78	10·67	—	128·69	131·86	129·66	126·83	165·44
IIIg	—	8·12	8·01	10·81	117·83	134·03	128·61	132·67	115·15	165·13
IIIh	—	8·09	8·43	10·90	—	135·53	129·43	123·71	149·94	164·98

[a] 7·53 (*o* + *m* protons), 7·46 (*p* protons); [b] 138·52 (C-1), 126·95 (C-2 + C-3), 128·44 (C-4).

TABLE III

NMR spectra (δ, ppm) of compounds *IIIa—IIIh* (carboxylate parts)

Compd.	^{1}H		^{13}C				
	o	(*m* + *p*)	C_{carbox}	C-1	C-2	C-3	C-4
IIIa	7·93	7·36	171·59	138·50	128·88	127·31	129·45
IIIb	7·90	7·33	171·09	138·86	128·85	127·22	129·28
IIIc	7·92	7·35	171·51	138·50	128·89	127·31	129·46
IIId	7·91	7·36	171·43	138·60	128·87	127·28	129·39
IIIe	7·95	7·37	171·54	138·59	128·91	127·31	129·45
IIIf	7·91	7·35	171·57	138·35	128·89	127·34	129·53
IIIg	7·93	7·37	171·71	138·25	128·92	127·38	129·61
IIIh	7·92	7·36	171·68	138·05	128·91	127·40	129·69

p-Bromobenzamidinium Benzoate *IIIf*

To the solution of 1 g (5 mmol) *p*-bromobenzonitrile was dissolved in 25 ml of dry dioxane, 0·5 ml (0·4 g, 8 mmol) of absolute ethanol was added and the mixture was saturated with dry hydrogen chloride. After 12 h the solvent was evaporated under reduced pressure and crystalline

TABLE IV

NMR spectra (δ, ppm) of compounds *IVa*—*IVg* (amidinium parts)

Compd.	^{1}H				^{13}C				
	o	*m*	*p*	NH_2	C-1	C-2	C-3	C-4	C_{amidin}
IVa	7·83	7·59	7·69	10·70	129·81	128·76	127·43	132·83	166·09
IVb	7·85	7·60	7·70	10·63	129·51	128·81	127·54	133·01	166·28
IVc	7·86	7·60	7·70	10·58	129·42	128·78	127·55	133·00	166·11
IVd	7·87	7·62	7·72	9·06 12·24	129·33	128·86	127·59	133·14	166·39
IVe	7·86	7·62	7·72	10·56	129·28	128·84	127·60	133·14	166·31
IVf	7·86	7·62	7·72	9·08 11·99	129·21	128·85	127·60	133·17	166·35
IVg	7·86	7·63	7·73	10·40	129·15	128·87	127·63	133·24	166·31

TABLE V

NMR spectra (δ, ppm) of compounds *IVa*—*IVg* (carboxylate parts)

Compd.	^{1}H			^{13}C					
	B	*o*	*m*	B	C_{carbox}	C-1	C-2	C-3	C-4
IVa	5·30	7·61	6·47	—	172·36	125·66	130·43	112·23	150·21
IVb	1·29	7·85	7·35	34·28 31·08	171·72	135·87	128·77	124·01	151·99
IVc	4·96	7·21 7·09	6·97 6·58[b]	—	172·29	139·36	115·16	147·73	115·08[a]
IVd	[c]	8·02	7·67	[d]	170·75	136·48	129·62	128·85	141·60
IVe	—	7·91	7·39	—	170·27	134·21	130·75	127·34	137·62
IVf	—	7·84	7·54	—	170·33	137·58	131·06	130·36	123·32
IVg	—	8·21	8·12	—	169·27	145·03	129·96	122·73	148·14

[a] C-5 127·55, C-6 117·04; [b] protons *p*-; [c] protons *o*- 7·71, *m*- 7·48, *p*- 7·38; [d] C-1 139·82, C-2 125·87, C-3 126·69, C-4 127·52.

residue made alkaline with sodium hydroxide with cooling in ice bath. Ethyl *p*-bromobenzenecarboximidate was then extracted with ether and immediately mixed with the saturated ethanolic solution of 0·7 g (5 mmol) ammonium benzoate. The precipitated crystals were crystallized from the ethanol–chloroform mixture (1 : 1).

For quantum chemical calculations the EHT method[8] was used. Coordinates for the fragment $-C(NH_2)_2O_2C-$ were selected from X-ray data[9], geometry for the rest of molecule was standard[10].

RESULTS AND DISCUSSION

Elemental analyses and melting points of compounds *IIIa*–*IIIh* and *IVa*–*IVg* are summarized in Table I. Melting points of all 15 prepared compounds fall into a relatively narrow interval of about 90°C. Both aminoderivatives *IIIb* and *IVa* and benzamidinium *p*-phenylbenzoate *IVd* melt below 200°C, high melting points are exhibited by both nitroderivatives *IIIh* and *IVg*. The majority of the prepared compounds sublime.

The substitution effect was followed by ^1H and ^{13}C NMR spectroscopy. Spectra of the compounds *IIIa*–*IIIh* and *IVa*–*IVg*, measured in hexadeuteriodimethylsulfoxide, are summarized in Tables II–V. As follows from the Tables chemical shifts changes of the acidic part of *III* and of the benzamidinium part of *IV*, respectively, are relatively small (0·04 to 0·06 ppm for ^1H NMR and 0·4 to 1·8 ppm for ^{13}C NMR, respectively) but well attributable and comparable among each other for different compounds. With the change of substituents all traced signals are shifted with a quite defined mode The generalized scheme of the shifts is depicted on Fig. 2 and may be compared with the sense of HOMO distribution change (cf. Fig. 1).

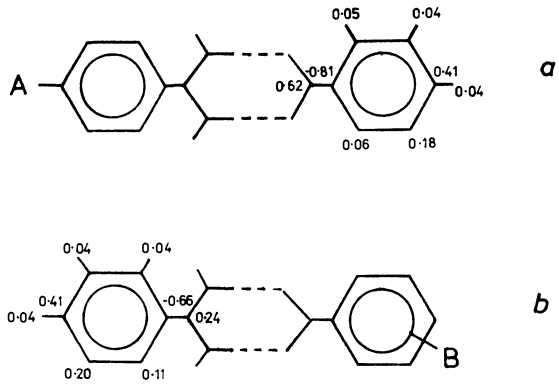


FIG. 2

NMR shift differencies of unsubstituted parts of compounds *IIIa*–*IIIh* (*a*) and *IVa*–*IVg* (*b*) (extreme differencies given). The negative values are given for decreasing chemical shift in the dependence on Hammett σ_p constants

For two different dependencies of chemical shifts on the Hammett σ constants the respective plots are shown in Fig. 3.

^{1}H NMR experiments helped us to go deeper into the problems of solvation and dissociation of amidinium carboxylates in dimethylsulfoxide and aqueous solutions,

TABLE VI

^{1}H NMR spectra (δ, ppm) of compounds *IIIa*, *IIIb* and *IIIh* (carboxylate part) in D_2O

Compd.	*o*	*m*	*p*
IIIa	7·858	7·462	7·536
IIIb	7·860	7·464	7·530
IIIh	7·862	7·468	7·539

TABLE VII

^{1}H NMR spectra (δ, ppm) of compounds *IIIa* and *IVe* (amidinium part) in D_2O

Compd.	*o*	*m*	*p*
IIIa	7·758	7·603	7·749
IVe	7·760	7·603	7·750

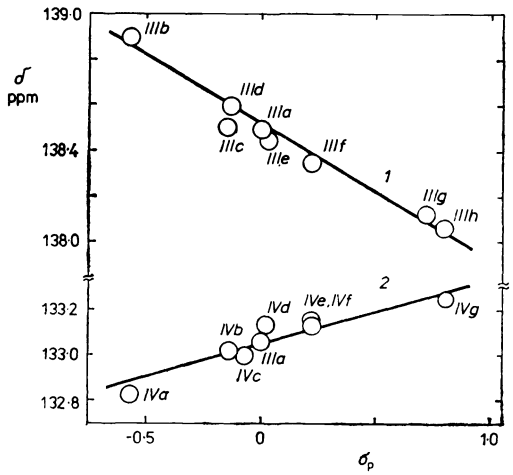


FIG. 3

Dependence of ^{13}C NMR chemical shifts (δ, ppm) on Hammett σ_p (or σ_m for *IVc*) constants for: *1* benzoate C-1 in compounds *IIIa*—*IIIh* (ϱ −0·5); *2* benzamidinium C-4 in compounds *IIIa* and *IVa*—*IVg* (ϱ 0·3)

respectively. In Table VI there are ^{1}H NMR signals of the carboxylic parts of compounds *IIIa*, *IIIb* and *IIIh*, measured in D_2O and in Table VII similar information for the amidinium component of compounds *IIIa* and *IVe* is given. As follows from the Tables VI and VII maximal deviation of the signals is 0·009 ppm, in most cases only 0·002 ppm, this value being behind the accuracy of the ^{1}H NMR measurement. This observation could be interpreted as if in all D_2O measurements the spectra of dissociated and probably solvated counter-parts of the molecules are recorded. The substitution on one counter-partner has no influence on the proton chemical shifts of the other. Thus the conclusion that non-dissociated amidinium carboxylates remain in dimethylsulfoxide solutions but not in the aqueous ones seems to be justified. Dimethylsulfoxide appears as a suitable solvent for amidinium-carboxylates properties investigation.

The authors thank Dr F. Pavlíková, Central Research Laboratories, Prague Institute of Chemical Technology, for the ^{1}H *and* ^{13}C NMR *measurements.*

REFERENCES

1. Adams J. M., Buehner M., Chandrasekhar K., Ford G. C., Hackert M. L., Liljas A., Rossmann M. G., Smiley J. E., Allison W. S., Everse J., Kaplan N. O., Taylor S. S.: Proc. Natl. Acad. Sci. U.S.A. *70*, 1968 (1973).
2. Eventoff W., Rossmann M. G., Taylor S. S., Torff H. J., Meyer H., Keil W., Kiltz H. H.: Proc. Natl. Acad. Sci. U.S.A. *74*, 2677 (1977).
3. Christianson D. W., Lipscomb W. N.: Proc. Natl. Acad. Sci. U.S.A. *83*, 7568 (1986).
4. Roderick S. L., Banaszak L. J.: J. Biol. Chem. *261*, 9461 (1986).
5. Riordan J. F.: Mol. Cell. Biochem. *26*, 71 (1979).
6. Krechl J., Böhm S., Smrčková S., Kuthan J.: Collect. Czech. Chem. Commun. *54*, 673 (1989).
7. Krechl J., Smrčková S., Pavlíková F., Kuthan J.: Collect. Czech. Chem. Commun. *54*, 2415 (1989).
8. Hoffmann R.: J. Chem. Phys. *39*, 1397 (1963).
9. Kratochvíl B., Ondráček J., Hašek J., Csordás L.: Collect. Czech. Chem. Commun. *53*, 3131 (1988).
10. Pople J. A., Gordon M.: J. Am. Chem. Soc. *89*, 4253 (1967).
11. Pinner A.: *Die Imidoäther und ihre Derivate*. Oppenheim, Berlin 1892.

Translated by the author (J. Krechl).