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BETAINES DERIVED FROM AMINO AND HYDRAZINO ACIDS AS PHASE TRANSFER CATALYSTS*

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Abstract - Betaines derived from α-, β- and γ-amino acids (obtained by alkylation of the corresponding amino acids with O-methyl-N,N'-diisopropylisourea) as well as β-hydrazino acids (prepared by dehydrohalogenative hydrolysis of methyl 3-(2-alkyl-2,2-dimethylhydrazinium)propionate halides catalyse typical phase transfer reactions (dichlorocyclopropanation of styrene, N-formylation of pyrrolidine, dehydration of benzamide and phenylacetamide, Williamson synthesis of benzyl propyl ether, addition of ethoxycarbonylnitrene to 2,3-dimethylbutene-2. In most cases, the activity of zwitterionic salts is at least similar to that of typical phase transfer catalysts (tetraalkylammonium salts). The mechanism of the catalytic action of betaines is proposed.

INTRODUCTION

Numerous compounds are capable of serving as phase transfer agents (quaternary onium salts, crown ethers, cryptands, podands, N-, P-, S-oxides and others).[3-5] Many of the above mentioned catalysts are commercially available,[5] however, the search for new phase transfer agents is still underway; this is from Starks' standpoint one of characteristic developments in phase transfer catalysis (PTC).[6] The goal of these studies was to search for new stable, active and selective (including regio- and stereoselective) as well as multi-functional catalytic systems and to extend, in such a way, the synthetic possibilities of PTC. Moreover, new data concerning the catalytic properties of various classes of compounds in PTC reactions are useful for elucidation of their mechanism of action which still remains obscure.[7,8] Among the known phase transfer catalysts the readily available quaternary ammonium salts (Q^+X^-) with a bulky lipophilic cation and a hydrophobic anion are particularly widespread. These salts are, as a rule, fairly effective in various two-phase reactions involving anions.[3,4] The catalytic action of salts Q^+X^- is due to their ability to exchange the X^- anion for the reagent anion, solubilization and activation of the latter in nonpolar

*For preliminary communications, see refs. 1, 2.

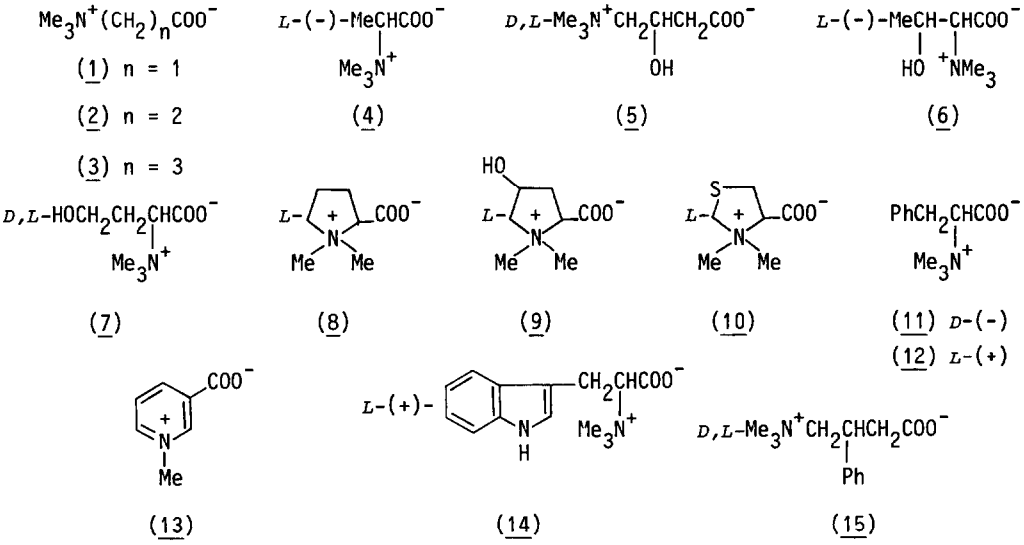
medium in the form of an ionic pair with the Q^+ cation. In the case of zwitterionic salts such an exchange fails to occur, though it is known[9] that betaine $(n\text{-}C_{12}H_{25})_3N^+CH_2COO^-$ accelerates the two-phase reaction of 1-haloalkanes with aqueous alkali: in the presence of betaine the reaction rate is 10 to 50 times higher than in the presence of a conventional catalyst of the Q^+X^- type. The promoting action of inner salts (trialkylammonium carboxylates and trialkylammonium sulphonates) in PTC dehydrochlorination,[10] halogen exchange[11] and oxidation[12] reactions has been also documented.

Now, we have synthesized a number of betaines derived from amino and hydrazino acids and studied their catalytic properties in some typical PTC reactions.

RESULTS AND DISCUSSION

Synthesis of Zwitterionic Salts

Amino acid betaines. In the present work, betaines 1-15 derived from α-, β- and γ-amino acids were studied. Commercially available glycine betaine (1), γ-butyrobetaine (3), carnitine (5) and nicotinic acid betaine (trigonelline, 13) were used. β-Alanine betaine (2) was prepared by reacting propiolactone with trimethylamine.[13] Proline betaine (stahydrine, 8) and 4-hydroxyproline betaine (betoncine, 9) were obtained by alkylation of the corresponding amino acids with O-methyl-N,N'-diisopropylisourea (MIU) as described elsewhere.[14]



Using this convenient, mild, N-regiospecific and non-racemizing method[14-18] we prepared betaines 4, 6, 7, 10-12, 14 and 15 from α-alanine, threonine, homoserine, thioproline, D- and L-phenylalanine, tryptophan and β-phenyl-γ-aminobutyric acid, respectively. The reactions of amino acids with MIU were carried out in methanol at room temperature. The reac-

tion time, product yields and physical characteristics are presented in Table 1.

Table 1. Synthesis of Betaines by Reacting Amino Acids with O-methyl-N,N'-diisopropylurea

Amino acid	Reaction time, days	Betaine	Yield, %	m.p., °C	$[\alpha]^{25}_{546}$, deg.	Found, % / Calculated, % C	H	N	Molecular formula
L-α-alanine	13	4	17	240 (decomp.)	-21.4 (c=0.49, H_2O)	48.8 / 48.3	9.9 / 10.1	9.6 / 9.4	$C_6H_{13}NO_2 \cdot H_2O$
L-threonine	30	6	27	208	-62.1 (c=0.66, H_2O)	49.9 / 49.5	9.2 / 9.5	8.3 / 8.2	$C_7H_{15}NO_3 \cdot 0.5H_2O$
homoserine	3	7	68	241-242 (decomp.)	-	52.6 / 52.2	9.5 / 9.4	9.0 / 8.7	$C_7H_{15}NO_3$
L-thioproline	3	10	60	173-174 (decomp.)	-93.5 (c=2.0, EtOH)	36.0 / 36.5	7.2 / 7.7	6.8 / 7.1	$C_6H_{11}NO_2 \cdot 2H_2O$
D-β-phenyl-α-alanine	13	11	37	220-221 (decomp.)	-76.7 (c=0.87, H_2O)	64.0 / 64.0	8.7 / 8.5	6.2 / 6.2	$C_{12}H_{17}NO_2 \cdot H_2O$
L-β-phenyl-α-alanine	13	12	44	220-222 (decomp.)	+77.2 (c=0.79, H_2O)	63.7 / 64.0	8.7 / 8.5	6.1 / 6.2	$C_{12}H_{17}NO_2 \cdot H_2O$
L-tryptophan	17	14	24	249 (decomp.)	+117.6 (c=0.56, H_2O)	67.0 / 68.2	7.3 / 7.4	11.2 / 11.4	$C_{14}H_{18}N_2O_2$
β-phenyl-γ-amino-butyric acid	5	15	65	189-191	-	67.9 / 67.8	9.4 / 9.2	5.8 / 6.1	$C_{13}H_{19}NO_2 \cdot 0.5H_2O$

^1H NMR spectroscopy data for betaines 2, 4, 6, 8-12, 14 and 15 are given in Table 2. Signal assignment was done based on literature data[19] describing NMR spectra for betaines 1-3, 8, 9 (as hydrochlorides), 7 (as a free base) and a number of other amino acid betaines from marine algae. The spectrum of 7 coincides with that given in ref. 19. The structures of previously unknown betaines 4, 10-12, 14 and 15 were also confirmed by ^{13}C NMR and fast atom bombardment (FAB) mass spectroscopy data (Table 3). Both $[M+1]^+$ peaks and those of cluster ions $[2M+1]^+$ characteristic of betaines were observed in FAB mass spectra.

β-Hydrazino acid betaines. Betaines derived from β-hydrazino acids - 3-(2-alkyl-2,2-dimethylhydrazinium)propionates (27-36) were prepared using the general procedure[20-22] based on the quaternization of methyl 3-(2,2-dimethylhydrazino)propionate (16)[23,24] with alkyl or aralkyl halides followed by treatment of the corresponding products (17-26) with a strongly

Table 2. ^{1}H NMR Spectral Data for Amino Acid Betaines

Compound	Solvent/Standard	Chemical shift, δ, ppm
2[a]	D_2O/DSS	2.68(t,2H,CH_2COO), 3.11(s,9H,$N(CH_3)_3$), 3.57(t,2H,CH_2N)
4	D_2O/DSS	1.56(dt,3H,$^{3}J_{H,H}$=7Hz, $^{3}J_{H,}{}^{14}{}_{N}$=2.5Hz,CH_3CH), 3.20(s,9H,$N(CH_3)_3$), 3.84(q,1H,J=7Hz,CH_3CH)
6	D_2O/DSS	1.29(d,3H,J=6Hz,CH_3CH), 3.29(s,9H,$N(CH_3)_3$), 3.56(d,1H,J=10Hz, CHCOO), 4.33(m,1H,CHOH)
8[a]	DMSO-d_6/TMS	2.05-2.50(m,4H,-CH_2CH_2-), 3.08(s,3H,NCH_3), 3.32(s,3H,NCH_3), 3.64 (t,2H,NCH_2), 4.05(^{2}t,^{2}1H,NCHOH)
9[a]	DMSO-d_6/TMS	2.04(dq,1H,3-H), 2.47(dq,1H,3-H), 3.01(s,3H,NCH_3), 3.21(q,1H,5-H), 3.26(s,3H,NCH_3), 3.89(q,1H,5H), 3.98(d,1H,2-H), 4.38(m,1H,4-H), 5.46(s,1H,OH)
10	DMSO-d_6/TMS	3.23(q,1H,3-H), 3.30(s,3H,NCH_3), 3.40(s,3H,NCH_3), 3.47(q,1H,3-H), 4.03(q,1H,2-H), 4.57(d,1H,5-H^{3}), 4.65(d,1H,5-H^{3})
11, 12[b]	D_2O/DSS	3.31(s,9H,$N(CH_3)_3$), 3.31(m,2H,$PhCH_2$), 4.20(dd,1H,CHN), 7.40 (bs,5H,Ph)
14	D_2O/DSS	3.20(s,9H,$N(CH_3)_3$), 3.20(m,2H,CH_2CH), 3.89(dd,1H,$CHCH_2$), 7.1-7.8 (m,5H,Ph)
15	D_2O/DSS	2.49(d,2H,J=7Hz,-CH_2COO), 3.00(s,9H,$N(CH_3)_3$), 3.33-4.04(m,3H, NCH_2CH), 7.38(s, 5H,Ph)

[a]For the spectrum of hydrochloride, see ref. 19; [b]The spectra of enantiomeric 11 and 12 are identical.

Table 3. $^{13}C\{^{1}H\}$ NMR[a] and FAB Mass Spectral Data for Amino Acid Betaines

Compound	Chemical shift, δ, ppm	m/z(rel. abundance, %)	
		$[M+1]^+$	$[2M+1]^+$
4	13.8(CH_3), 52.6(t,$^{1}J(^{13}C,^{14}N)$~3.5Hz, $N(CH_3)_3$), 74.9(CH), 174.2 (^{3}COO)	132(100)	263(20)
6	-	162(100)	323(11)
10	31.0(5-C), 46.9(NCH_3), 53.2(NCH_3), 68.5(2-C), 78.2(4-C), 169.8(COO)	162(100)	323(26)
11, 12[b]	34.0(CH_2), 53.3($N(CH_3)_3$), 81.3(CH), 128.8, 130.3, 130.7, 136.2(C_6H_5), 172.0(COO)	208(100)	415(9)
14	24.0(CH_2), 53.2($N(CH_3)_3$), 80.2(CH), 108.6, 113.3, 119.5 (two signals), 120.7, 123.3, 126.0, 127.8 (ring carbons), 172.6(COO)	247(100)	493(25)
15	39.8(CH), 45.6(CH_2COO), 55.0(t,$^{1}J(^{13}C,^{14}N)$~3.5Hz,$N(CH_3)_3$), 71.5(t,$^{1}J(^{13}C,^{14}N)$~3.5Hz,NCH_2), 128.9, 130.6, 142.5(C_6H_5), 179.5(COO)	222(100)	443(5)

[a]Solvent - D_2O, internal standard - dioxane; [b]NMR and FAB MS of enantiomeric 11 and 12 are identical.

basic anion-exchange resin (Amberlite IRA-400) in OH^- form.

$$Me_2N\text{-}NHCH_2CH_2COOMe \xrightarrow{R\text{-}X} R\text{-}\overset{Me}{\overset{|}{\underset{Me}{\overset{|}{N^+}}}}\text{-}NHCH_2CH_2COOMe\ X^- \xrightarrow[(OH^-)]{\text{Amberlite IRA-400}} R\text{-}\overset{Me}{\overset{|}{\underset{Me}{\overset{|}{N^+}}}}\text{-}NHCH_2CH_2COO^- \cdot nH_2O$$

16 17-26 27-36

R = Me (17, 27), Et (18, 28), Pr (19, 29), i-Pr (20, 30), n-C_6H_{13} (21, 31), n-$C_{10}H_{21}$ (22, 32), n-$C_{12}H_{25}$ (23, 33), n-$C_{16}H_{33}$ (24, 34), $PhCH_2$ (25, 35), $PhCH_2CH_2$ (26, 36);
X = I (17, 19, 20), Br (18, 21-24, 26), Cl (25); n = 0 (29, 34, 35), 1 (28, 31-33), 2 (27, 30, 36).

Alkylation of hydrazinopropionate 16 with R-X was carried out using stoichiometric quantities of reagents in acetonitrile, ethanol, methanol, acetone or without solvent. The reaction proceeds exclusively at the tertiary nitrogen atom. The reaction conditions, yields and physico-chemical characteristics of salts 17-26 are summarized in Table 4; ^1H NMR spectral data for these products confirming their structures are listed in Table 5.

Table 4. Synthesis of Methyl 3-(2-alkyl-2,2-dimethylhydrazinium)propionates (17-26) by Alkylation of Methyl 3-(2,2-dimethylhydrazino)propionate (16)

Alkylating agent	Solvent (ml per 1 mol of 16)	Reaction conditions	Product	Yield, %	m.p., °C
MeI	MeOH (100)	reflux, 1 h	17	92	126[a]
EtBr	EtOH (100)	reflux, 2.5 h	18	73	95-97
PrI	without solvent	room temp., 16 h	19	71	68-70
i-PrI	without solvent	room temp., 16 h; 110°C, 5 h	20	68	74.5-75.5
n-$C_6H_{13}Br$	MeCN (220)	room temp., 24 h	21	67	75-76
n-$C_{10}H_{21}Br$	without solvent	90°C, 42 h	22	70	oil
n-$C_{12}H_{25}Br$	MeCN (1000)	75°C, 15 h	23[b]	-	-
n-$C_{16}H_{33}Br$	without solvent	80°C, 3 days	24	57	55-60
$PhCH_2Cl$	without solvent	room temp., 14 h	25	84	130-131
$PhCH_2CH_2Br$	acetone (100)	room temp., 16 h; reflux, 2 h	26	66	144-145

[a]Ref. 24, m.p. 125.5-126.5°C; [b]Product 23 without isolation was converted to the corresponding betaine 33 (see Table 5).

Table 5. ^{1}H NMR Spectral Data for Methyl 3-(2-alkyl-2,2-dimethylhydrazino)propionates[a]

Compound	Solvent/ standard	Chemical shift, δ, ppm
18	D_2O/DSS	1.35(t,3H,J=7Hz,$\underline{CH_3}CH_2$), 2.63(t,2H,J=6Hz,$\underline{CH_2}COOMe$), 3.26(s,6H,$N(CH_3)_2$), 3.27(t,2H,J=6Hz,$NHCH_2$), 3.59(q,2H,J=7Hz,$CH_3\underline{CH_2}$), 3.71(s,3H,$COOCH_3$)
19	D_2O/DSS	0.98(t,3H,J=7Hz,$\underline{CH_3}CH_2$), 1.81(m,2H,$CH_3\underline{CH_2}CH_2$), 2.63(t,2H,J=6Hz, $\underline{CH_2}COOMe$), 3.28(s,6H,$N(CH_3)_2$), 3.28(t,2H,J=6Hz,$N\underline{H}CH_2$), 3,48(m,2H, $CH_3CH_2\underline{CH_2}$), 3.72(s,3H,$COOCH_3$)
20	D_2O/DSS	1.41(d,6H,J=6Hz,$CH(\underline{CH_3})_2$), 2.63(t,2H,J=6Hz,$\underline{CH_2}COOMe$), 3.20(s,6H, $N(CH_3)_2$), 3.30(t,2H,J=6Hz,$NHCH_2$), 3.72(s,3H,$COOCH_3$), 3.98(m,1H,$\underline{CH}(CH_3)_2$
21	D_2O/DSS	0.88(t,3H,$\underline{CH_3}(CH_2)_5$, 1.35(m,6H,$CH_3(\underline{CH_2})_3(CH_2)_2$), 1.77(m,2H, $CH_3(CH_2)_3\underline{CH_2}CH_2$), 2.61(t,2H,J=6Hz,$\underline{CH_2}COOMe$), 3.27(t,2H,J=6Hz,$NHCH_2$), 3.28(s,6H,$N(CH_3)_2$), 3.52(m,2H,$CH_3(CH_2)_4\underline{CH_2}$), 3.73(s,3H,$COOCH_3$)
22	$CDCl_3$/HMDSO	0.86(t,3H,$\underline{CH_3}(CH_2)_9$), 1.26(m,14H,$CH_3(\underline{CH_2})_7(CH_2)_2$), 1.80(m,2H, $CH_3(CH_2)_7\underline{CH_2}CH_2$), 2.67(t,2H,J=6Hz,$\underline{CH_2}COOMe$), 3.23(m,2H,$NHCH_2$), 3.52 (s,6H,$N(CH_3)_2$), 3.63(m,2H,$CH_3(CH_2)_8\underline{CH_2}$), 3.69(s,3H,$COOCH_3$)
24	D_2O/DSS	0.86(t,3H,$\underline{CH_3}(CH_2)_{15}$), 1.24(m,26H,$CH_3(\underline{CH_2})_{13}(CH_2)_2$), 1.75(m,2H, $CH_3(CH_2)_{13}\underline{CH_2}CH_2$), 2.58(t,2H,$\underline{CH_2}COOMe$), 3.27(t,2H,$NHCH_2$), 3.34(s,6H, $N(CH_3)_2$), 3.50(m,2H,$CH_3(CH_2)_{14}\underline{CH_2}$), 3.66(s,3H,$COOCH_3$), 7.21(t,1H, J=7.5Hz,NH)
25	D_2O/DSS	2.67(t,2H,J=6Hz,$\underline{CH_2}COOMe$), 3.29(s,6H,$N(CH_3)_2$), 3.44(t,2H,J=6Hz,$NHCH_2$), 3.73(s,3H,$COOCH_3$), 4.71(s,2H,$PhCH_2$), 7.59(s,5H,Ph)
26	$CDCl_3$/TMS	2.67(t,2H,J=6Hz,$\underline{CH_2}COOMe$), 3.20(m,4H,$NHCH_2$ and CH_2Ph), 3.59(s,6H, $N(CH_3)_2$), 3.71(s,3H,$COOCH_3$), 3.90(m,2H,NCH_2), 7.35(s,5H,Ph), 7.42 (t,1H,J=8Hz,NH)

[a]For the spectrum of 17, see ref. 25.

Dehydrohalogenative hydrolysis of hydrazinium propionates 17-26 was carried out by passing aqueous solutions of these salts through a column packed with a strongly basic anion-exchanger (Amberlite IRA-400 or IRA-401) in OH^- form. In all cases, the corresponding betaines were obtained, their yields, melting points and elemental analysis data being given in Table 6. ^{1}H NMR spectra data confirming the structures of zwitterionic salts 27-36 are given in Table 7.

Table 6. Hydrazino Acid Betaines 28-36[a]

Compound	Yield, %	M.p., °C	Found, %			Molecular formula	Calculated, %		
			C	H	N		C	H	N
28	71	182-185	47.4	10.1	16.0	$C_7H_{16}N_2O_2 \cdot H_2O$	47.2	10.2	15.7
29	89	188-193	55.0	10.6	15.9	$C_8H_{18}N_2O_2$	55.1	10.4	16.1
30	61	188-191	45.8	10.4	13.0	$C_8H_{18}N_2O_2 \cdot 2H_2O$	45.7	10.6	13.3
31	74	185	56.0	11.0	11.7	$C_{11}H_{24}N_2O_2 \cdot H_2O$	56.4	11.2	12.0
32	34	176-178	61.7	11.7	9.9	$C_{15}H_{32}N_2O_2 \cdot H_2O$	62.0	11.8	9.6
33	55	195-196	64.2	12.4	9.3	$C_{17}H_{36}N_2O_2 \cdot H_2O$	64.1	12.0	8.8
34	40	100-102	70.4	12.2	7.6	$C_{21}H_{44}N_2O_2$	70.7	12.4	7.9
35	77	180-182	64.6	8.3	12.5	$C_{12}H_{18}N_2O_2$	64.8	8.2	12.6
36	72	164-167	57.4	8.7	10.4	$C_{13}H_{20}N_2O_2 \cdot 2H_2O$	57.3	8.9	10.3

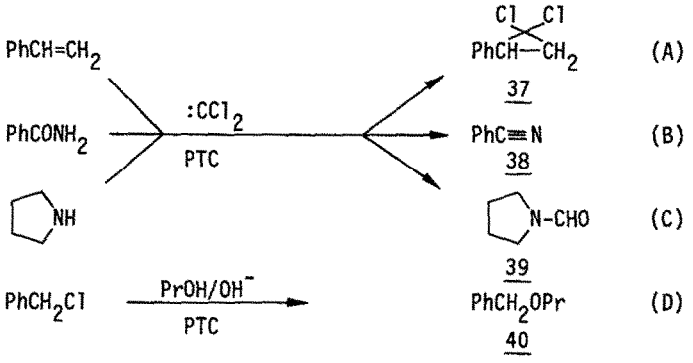
[a]Betaine 27 was obtained in 85% yield (m.p. 252-254°C) as described previously.[22]

Table 7. ^{1}H NMR Spectral Data for Betaines 28-36[a]

Compound	Solvent/ standard	Chemical shift, δ, ppm
28	DMSO-d_6/TMS	1.28(t,3H,J=7Hz,CH_3), 1.99(t,2H,J=6Hz,CH_2COO), 2.26(t,2H,J=6Hz,$NHCH_2$), 3.34(s,6H,$N(CH_3)_2$), 3.50(q,2H,J=7Hz,NCH_2), 7.2(bs,1H,NH)
29	D_2O/DSS	0.97(t,3H,J=7Hz,CH_3), 1.82(m,2H,NCH_2CH_2), 2.37(t,2H,J=6Hz,CH_2COO), 3.17(t,2H,$NHCH_2$), 3.27(s,6H,$N(CH_3)_2$), 3.47(t,2H,J=9Hz,NCH_2)
30	D_2O/DSS	1.40(d,6H,J=6Hz,$(CH_3)_2CH$), 2.36(t,2H,J=6Hz,CH_2COO), 3.17(t,2H,J=6Hz, $NHCH_2$), 3.17(s,6H,$N(CH_3)_2$), 3.96(heptet,1H,J=6Hz,$CH(CH_3)_2$)
31	D_2O/DSS	0.86(t,3H,CH_3), 1.34(m,6H,$CH_3(CH_2)_3$), 1.79(m,2H,NCH_2CH_2), 2.36(t,2H, J=6Hz,CH_2COO), 3.15(t,2H,J=6Hz,$NHCH_2$), 3.24(s,6H,$N(CH_3)_2$), 3.5(m,2H,CH_2N)
32	D_2O/DSS	0.84(t,3H,CH_3), 1.28(m,14H,$CH_3(CH_2)_7$), 1.74(m,2H,NCH_2CH_2), 2.34(t,2H,J= 6Hz,CH_2COO), 3.12(t,2H,J=6Hz,$NHCH_2$), 3.25(s,6H,$N(CH_3)_2$), 3.43(m,2H,CH_2N)
33	D_2O/DSS	0.86(t,3H,CH_3), 1.20(m,18H,$CH_3(CH_2)_9$), 1.73(m,2H,NCH_2CH_2), 2.32(t,2H, CH_2COO), 3.11(m,2H,$NHCH_2$), 3.28(s,6H,$N(CH_3)_2$), 3.47(m,2H,CH_2N)
34	DMSO-d_6/TMS	0.84(t,3H,CH_3), 1.23(m,26H,$CH_3(CH_2)_{13}$), 1.60(m,2H,NCH_2CH_2), 2.47(t,2H, CH_2COO), 3.14(m,2H,$NHCH_2$), 3.33(s,6H,$N(CH_3)_2$), 3.40(m,2H,CH_2N)
35	D_2O/DSS	2.40(t,2H,J=6Hz,CH_2COO), 3.25(s,6H,$N(CH_3)_2$), 3.32(t,2H,J=6Hz,$NHCH_2$), 4.69(s,2H,CH_2Ph), 7.58(s,5H,Ph)
36	D_2O/DSS	2.39(t,2H,J=6Hz,CH_2COO), 3.16(m,2H,CH_2Ph), 3.21(t,2H,J=6Hz,$NHCH_2$), 3.35(s,6H,$N(CH_3)_2$), 3.75(m,2H,CH_2N), 7.37(s,5H,Ph)

[a]Betaine 27 spectrum, see ref. 22.

Catalytic properties of betaines. Amino acid betaines 1-15 were tested as catalysts in the well-known[3,4] two-phase reactions involving dichlorocarbene: dichlorocyclopropanation of styrene, dehydration of benzamide and N-formylation of pyrrolidine (reactions A-C, respectively). Moreover, in the presence of some betaines the Williamson synthesis of benzyl propyl ether (reaction D) was carried out.



Results of studying reactions A-D are summarized in Table 8. It should be noted that, as shown in the experiments, betaines in the reactions involving alkali can be used both as free bases and as hydrochlorides (yielding betaines *in situ*), their catalytic properties being essentially the same. The highest catalytic activity was displayed in reactions A-C by betaines derived from β-alanine (2), threonine (6), homoserine (7), proline (8), phenylalanine (11, 12), tryptophan (14), β-hydroxy- and β-phenyl-γ-aminobutyric acid (5 and 15). In the presence of these zwitterionic salts, products 37-39 are formed in yields close to those achieved with conventional phase transfer catalysts. PTC O-alkylation (reaction D) is effectively catalysed by betaines 11 and 12, the activity of the inner salts 4, 14 and 15 being considerably lower (Table 8).

Catalytic properties of betaines 27-36 derived from β-hydrazino acids were tested in reactions A and D, in dehydration of phenylacetamide to phenylacetonitrile (reaction E) as well as in the reaction of 2,3-dimethylbutene-2 with ethoxycarbonylnitrene generated in a two-phase CH_2Cl_2/H_2O system by treating ethyl N-(*p*-nitrobenzene)sulphocarbamate with potassium carbonate[26] (reaction F).

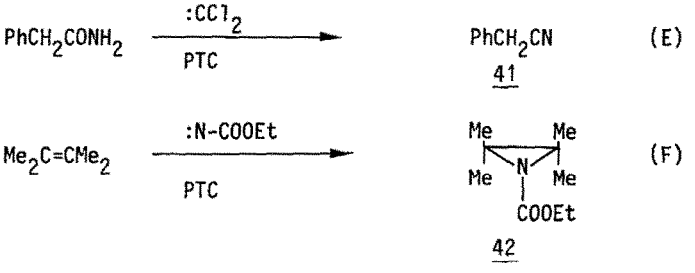


Table 8. PTC Reactions in the Presence of Amino Acid Betaines 1-15

Catalyst	Reaction A[a]		Reaction B[a]	Reaction C[a]		Reaction D[a]
	time, h	yield of 37, %[b]	yield of 38, %[b]	time, h	yield of 39, %[b]	yield of 40, %[b]
1·HCl	3.0	64	-	3.0	40	-
2	1.0	96	78	3.0	31	-
3	6.5	12	-	5.0	24	-
4	6.5	100	83	6.5	57	17
5·HCl	4.5	100	86	3.0	33	-
6	4.0	76	88	6.0	49	-
7	4.5	100	100	3.0	37	-
8	2.5	97	90	1.0	64	-
9	2.5	7	31	5.0	36	-
10		-	50	5.0	9	-
11 (12)[c]	4.0	73	84	6.0	55	88
13·HCl	6.5	8	13	5.0	15	-
14	4.0	83	88	6.0	48	5
15	4.0	95	84	6.0	62	19
without catalyst	4.5	4	12	6.0	6	0.2

[a]For reaction conditions, see Experimental; [b]GLC data; [c]Enantiomeric 11 and 12 displayed essentially equal activity.

Betaines 27-36 are very effective in reactions A and E, moreover their catalytic activity is comparable with or even somewhat higher than that of benzyltriethylammonium chloride - one of the most frequently employed catalyst in PTC reactions involving dichlorocarbene (see Table 9). Hydrazino acid betaines also catalyse the Williamson reaction, however in this case their activity is lower than that of the conventional phase transfer catalyst $Bu_4\overset{+}{N}H\overset{-}{SO_4}$.

Table 9. PTC Reactions in the Presence of Hydrazino Acid Betaines 27-36

Catalyst	Reaction A[a]		Reaction D[a]	Reaction E[a]	
	time, h	yield of 37, %[b]	yield of 40, %[b]	time, min	yield of 41, %[b]
27	2.5	59	-	-	
28	0.5	64	-	-	
29	0.5	75	15	15	100
30	0.5	58	15	50	88
31	0.5	100	17	30	100
32	0.5	98	15	-	
33	0.5	81	-	-	
34	0.5	80	-	-	
35	2.5	70	-	60	100
36	2.5	31	-	15	72
without catalyst	4.5	4	0.1	60	3
$Et_3\overset{+}{N}CH_2Ph\ \overset{-}{Cl}$	0.5	71	-	15	72
$Bu_4\overset{+}{N}H\overset{-}{SO_4}$		-	51	-	

[a]Reaction conditions, see Experimental; [b]GLC data.

As regards reaction F, addition of saturated aqueous solution of K_2CO_3 to 2,3-dimethylbutene-2 and nitrene precursor (p-$O_2NC_6H_4SO_3NHCOOEt$) in CH_2Cl_2 containing catalytic amounts of betaine 31 gives aziridine 42 in 48% yield during 30 minutes. Similar results were gained with $Bu_4\overset{+}{N}HSO_4^-$ (one of the most effective phase transfer agents[3,4]) used as catalyst. In the absence of catalyst under the same conditions, the yield of adduct 42 was 19%.

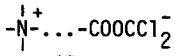
The catalytic activity found for the betaines in PTC reactions requires an explanation, as the ion-exchange mechanism (extractive or interphase) postulated for quaternary onium salts[4,7,8,27] cannot be realized in the case of zwitterionic salts. The catalytic action of quaternary onium salts in reactions involving dichlorocarbene has been explained[27,28] by the binding of CCl_3^- anion (generated at interface *via* chloroform deprotonation) resulting in a lipophilic ion pair which serves as a source of $:CCl_2$ in homogeneous organic medium.

If a similar mechanism operates in the presence of zwitterionic catalysts, the bis-ion pair 43 must serve as the source of $:CCl_2$. Migration of 43 to the bulk of organic phase is improbable because of the hydrophobic "carboxylate" part of the molecule anchored at the interface. The "onium" part of 43 is much more lipophilic, thus such bis-ion pair possibly acts as a "fishing-rod" capable of tearing the CCl_3^- anion from the interface and transferring CCl_3^- into the bulk of organic phase. Subsequent generation of $:CCl_2$ and its interaction with the substrate in this case must occur as in the case of conventional catalysts. The conversion of 43 to 44 was followed by Cl^- exchange for the more lipophilic CCl_3^- thus resuming the catalytic cycle.

43 44

However, another explanation is possible when considering the catalytic action of betaines in PTC reactions involving dichlorocarbene. Alkaline hydrolysis of chloroform is known to proceed *via* free $:CCl_2$ formation.[29] This fact explains[27,28] why PTC reactions with dichlorocarbene are effectively catalysed by trialkylamines irreversibly binding $:CCl_2$ to give an ylide, which in the bulk of organic phase acts as a base generating $:CCl_2$ in homogeneous medium.

Similar dichlorocarbene binding to carboxylate anion at the interface obviously occurs in the presence of zwitterionic salts. Moreover, the starting betaine converts to the more lipophilic inner salt 45 which possibly migrates into the bulk of organic phase and acts like ylide, a putative intermediate in reactions catalysed by tertiary amines. Such mechanism of catalytic action appears more plausible for betaines than CCl_3^- anion transfer from



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the interface, as there is no marked relationship between the lipophilicity of the "onium"

part of hydrazinium betaines and their activity (table 9). Moreover, the catalytic activity of betaines acting as "fishing-rod" must apparently grow with the distance between the poles of dipole 43. However, comparision of properties of amino acid betaines (prepared from α-, β- and γ-amino acids, respectively) in reactions A-C failed to reveal such dependence (Table 8). Moreover, in reaction C the catalytic activity decreased in the order 1>2>3, i.e. with the lengthening of the chain connecting the quaternary nitrogen atom and the carboxylate anion. The above two variants of betaine catalysis are also possible for reactions involving ethoxycarbonylnitrene. As to the Williamson reaction, which in the absence of catalyst fails to occur, alkoxide anion transfer from the interface into the organic phase with the aid of the onium fragment of betaine appears only possible.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker WH-90/DS spectrometer at 90 and 22.63 MHz, respectively. FAB mass spectra were registered on a Kratos MS-50 apparatus equipped with an Ion Tech. Ltd. FAB 11NF Source using argon as ionization gas and thioglycerine as matrix. GLC analysis was carried out on a Chrom 5 instrument with flame-ionization detector and glass column (1.2 m × 3 mm) packed with 5% OV-17 on Chromosorb W-HP (80-100 mesh). Melting points were measured on a Boetius apparatus and are uncorrected.
Optical rotations were measured on a Carl Zeiss Polamat polarimeter.

Synthesis of amino acid betaines (General procedure exemplified for the preparation of 1,1-dimethyl-4-thiazolidinium-2-carboxylate,10). A mixture of L-thioproline (13.3 g, 0.1 mol), O-methyl-N,N'-diisopropylisourea (63.2 g, 0.4 mol) and methanol (100 ml) was stirred at room temperature. The reaction mixture was gradually heated to *ca.*30°C and thioproline was completely dissolved. The stirring was continued for 72 h and the N,N'-diisopropylurea precipitate was filtered off. The filtrate was evaporated to dryness under reduced pressure, the residue was extracted with water, the nondissolved urea was filtered off and the solution was reevaporated to dryness *in vacuo*. The treatment with water was continued to complete separation of diisopropylurea. The obtained oily product solidifying on trituration with acetone was recrystillized from a ethanol-acetone (6:1) mixture to afford betaine 10 (0.7 g, yield: 60%). Betaines 4, 6, 7-12, 14 and 15 were prepared similarly (Tables 1-3).

Alkylation of methyl 3-(2,2-dimethylhydrazino)propionate (16) (General procedure exemplified for the reaction of 16 with ethyl bromide). A mixture of 16 (146.2 g, 1 mol), ethyl bromide (109 g, 74.7 ml, 1 mol) and ethanol (100 ml) was heated under reflux for 2.5 h. The solvent was evaporated under reduced pressure, the residue solidifying on cooling was recrystallized from an acetone-MEK-ethyl acetate (150:300:100 ml) mixture to afford 18 as colourless crystals (187 g, yield: 73%). Alkylations of 16 with other alkylating agents were carried out similarly (Tables 4, 5).

Preparation of 3-(2-alkyl-2,2-dimethylhydrazinium)propionates (27-36) (General procedure exemplified for the synthesis of 29). A solution of salt 19 (31.62 g, 0.1 mol) in water (20 ml) was introduced into a glass column packed with 200 ml of ion-exchange resin IRA-400 in OH^- form and eluted with water (1 l). The eluate was evaporated to dryness under reduced pressure and the residue was treated with acetone containing a small amount of ethanol or isopropanol. The solid product was filtered off, washed on the filter with acetone, dried at 50°C. Recrystallization from n-butanol-MEK afforded betaine 29 as colourless crystals (15.58 g, yield: 89%). Betaines 27, 28, 30-36 were prepared similarly, compounds 28, 32-34 and 36 were eluted with a water-ethanol (2:1) mixture (Tables 5, 6).

General procedures for PTC reactions in the presence of betaines

Dichlorocyclopropanation of styrene (reaction A). A mixture of styrene (1.67 mmol), chloroform (2.5 ml), 50% aqueous NaOH (1.5 ml) and catalyst (1 mol. %) was stirred ar room temperature until maximum content of 1,1-dichloro-2-phenylcyclopropane was attained (GLC control). For results see Tables 8, 9.

Dehydration of benzamide (reaction B) and phenylacetamide (reaction E). A mixture of $PhCONH_2$ (0.5 mmol), $CHCl_3$ (2.5 ml), 50% aq. NaOH (1 ml) and catalyst (5 mol. %) was stirred at room temperature for 2.5 h. Dehydration of phenylacetamide was carried out under similar conditions using $PhCH_2CONH_2$ (1 mmol), $CHCl_3$ (2 ml), 50% aq. NaOH (1 ml) and catalyst (5 mol. %). For results see Tables 8, 9.

N-Formylation of pyrrolidine (reaction C). The reaction was performed under conditions similar to those described above for the reaction A using pyrrolidine in place of styrene. For results see Table 8.

Synthesis of benzyl propyl ether (reaction D). A mixture of $PhCH_2Cl$ (1 mmol), PrOH (1.25 mmol), CH_2Cl_2 (2 ml), 50% aq. NaOH (1 ml) and catalyst (5 mol. %) was stirred for 5 h at room temperature with GLC monitoring. For results see Tables 8, 9.

Addition of ethoxycarbonylnitrene to 2,3-dimethylbutene-2 (reaction F). A saturated aqueous solution of K_2CO_3 (1 ml) was added dropwise to a solution of 2,3-dimethylbutene-2 (4 mmol), ethyl N-(*p*-nitrobenzene)sulphocarbamate (2 mmol) and catalyst 31 (5 mol. %) in CH_2Cl_2 (8 ml). The resulting mixture was stirred at room temperature for 30 min. GLC yield of 1-ethoxycarbonyl-2,2,3,3-tetramethylaziridine: 48%.

REFERENCES

1. Goldberg,Yu.Sh.; Ābele,E.M.; Kalviņš,I.J; Bremanis,G.A.; Shymanska,M.V.; Lukevics,E. *Dokl. Akad. Nauk SSSR* **1987**, *294*, 1387-1390.
2. Goldberg,Yu.Sh.; Ābele,E.M., Kalviņš,I.J.; Trapenciers,P.T.; Shymanska,M.V.; Lukevics,E. *Zh. Org. Khim.* **1987**, *23*, 1561-1563.
3. Starks,C.M.; Liotta,C. *Phase Transfer Catalysis. Principles and Technique;* Academic Press: New York, 1978.
4. Dehmlow,E.V.; Dehmlow,S.S. *Phase Transfer Catalysis;* Verlag Chemie: Weinheim, 1983.
5. Freedman,H.H. *Pure Appl. Chem.* **1986**, *58*, 857-868.
6. Starks,C.M. *Israel J. Chem.* **1985**, *26*, 211-215.
7. Rabinovitz,M.; Cohen,Y.; Halpern,M. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*,960-970.
8. Montanari,F.; Landini,D.; Rolla,F. In *Topics in Current Chemistry. Host Guest Chemistry II;* Vögtle,F. Ed.; Springer Verlag: Berlin, 1982; pp 147-200.
9. See Reference 3; pp 67, 127.
10. U.S. Patent 3 754 044; *Chem. Abstr.* **1970**, *72*, 78366e.
11. Japan Kokai JP 82 64 625; *Chem. Abstr.* **1982**, *97*, 127020.
12. Brunelet,T.; Gelbard,G. *J. Chem. Res. (S)* **1985**, 264-265.
13. Gresham,T.L.; Jansen,J.E.; Shawer,F.W.; Bankert,R.A.; Fiedorek,F.T. *J. Am. Chem. Soc.* **1951**, *73*, 3168-3171.
14. Musich,J.A.; Rapoport,H. *J. Org. Chem.* **1977**, *42*, 139-141.
15. Musich,J.A.; Rapoport,H. *J. Am. Chem. Soc.* **1978**, *100*, 4865-4872.
16. Mathias,L.J. *Synthesis* **1979**, 561-576.
17. Andersson,L.; Kühler,T.; Nilsson,M. *Synthesis* **1981**, 468-469.
18. Hertzberg,T.; Kühler,T.; Nilsson,M. *Acta Chem. Scand. Ser. B* **1986**, *B40*, 387-389.
19. Blunden,G.; Gordon,S.M.; Crabb,T.A.; Roch,O.G.; Rowar,M.C.; Wood,B. *Magn. Reson. Chem.* **1986**, *24*, 965-971.
20. Belgian Patent 880 831; *Chem. Abstr.* **1981**, *94*, 120876c.
21. Ger. Offen. DE 3 418 652; *Chem. Abstr.* **1985**, *102*, 95258b.
22. Kemme A.; Bleidelis,J.; Kalviņš,I.; Eremeyev,A. *Latv. PSR Zin. Akad. Vestis* **1983**, 215-218.
23. Kost,A.N.; Suminov,S.I. *Zh. Org. Khim.* **1965**, *1*, 1341-1348.
24. Zapevalova,N.P.; Ovsyannikova,L.A.; Sokolova,T.A. *Izv. Akad. Nauk SSSR. Ser. Khim.* **1966**, 2200-2204.
25. Hiller,S.A.; Eremeyev,A.V.; Kalviņš,I.J.; Liepiņš,E.E.; Semenikhina,V.G. *Khim. Geterotsikl. Soed.* **1975**, 1625-1631.
26. Senō,M.; Namba,T.; Kise,H. *J. Org. Chem.* **1978**, *43*, 3345-3348.
27. Mąkosza,M. *Pure Appl. Chem.* **1975**, *43*, 439-462.
28. Mąkosza,M.; Fedoryński,M. *Zh. Vses. Khim. Obshch. im. D.I.Mendeleeva* **1979**, *24*, 466-474.
29. Kirmse,W. *Carbene Chemistry*; Academic Press: New York & London, 1964.