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N-QUATERNARY COMPOUNDS—XLIII[1]
SYNTHESIS AND CIRCULAR DICHROISM OF α-AMINO AND α-N,N,N-TRIMETHYLAMMONIO ACID AMIDES

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Abstract—CD spectra of α-trimethylammonio acid amides contain 2 or 3 absorption bands in the 200–260 nm region. CD spectra of α-amino acid amides also contain multiple bands in this region. The possible origin of the CD bands is discussed.

The amide chromophore is optically active in dissymmetric surroundings with the CO $n \rightarrow \pi^*$ band above *ca* 210 nm. α-Halopropionanilides[2-4] and related compounds, however, have two CD-bands in this region which do not coincide with the UV absorption maxima, and which have been ascribed to $n \rightarrow \pi^*$ transitions in the CO group for different conformers present in solution.[5] A similar explanation has been used to account for the two CD bands in the spectra of α-amino acids.[7]

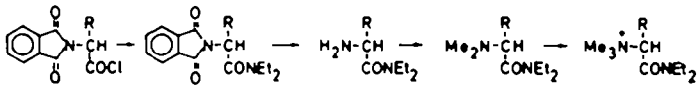
The validity of this explanation has recently been disputed; instead the origin of the higher wavelength band (at *ca* 230 nm) was attributed to an intramolecular charge transfer transition of an electron from a non-bonding orbital of the heteroatom to the π^*-antibonding orbital of the carboxyl group, which appears to explain why protonation in acid solution results in only one CD band in the region of CO absorption.[8] α-N,N,N-Trimethylammonio acids display only one CD band in this region, at *ca* 215 nm;[9] similarly α-N,N,N-trimethylammonio aldehydes were found to display one CD band in the 300 nm region corresponding to CO absorption.[10] The intramolecular charge-transfer theory,[8] however, seems to be contradicted by the recent finding that 2-alkyl substituted dicarboxylic acids give rise to two distinct CD bands.[11] In the work described herein we have investigated the dichroic absorption of some α-amino amides and their corresponding N,N,N-trimethylammonio amides.

The syntheses of the optically active amides are shown in Scheme 1. Their glycine analogues were also prepared for measurements of dipole moments. In a recent publication the synthesis of optically active amino acid amides from N-benzyloxycarbonylamino acid p-nitrophenyl ester and amines is described.[12] We have chosen as starting materials the N-phthaloyl derivatives of (S)-α-amino acids which react as acid chlorides with amines to yield amides of high optical purity.[13] The phthaloyl group was removed from the amides 2 by hydrazine treatment and the liberated amino group was reductively N,N-dimethylated. Racemisation in the reductive methylation is thought to be negligible by analogy to the same reaction for amino acids.[14] The quaternisation of the dimethylamino group in 4 was performed by means of methyl iodide in nitromethane solution.

The UV spectra of 3, 4 and the chloride analogues of 5 (Figs. 1 and 2) exhibit a relatively intense band near 200 nm, which at least in part originates from $\pi \rightarrow \pi^*$ transition, observed for example at 202 nm for N,N-diethylacetamide in cyclohexane.[15] Contributions from lone-pair transitions ($n \rightarrow \sigma^*$) of the amino group may also be involved in the case of the tertiary amines 4.[16,17]

The $n \rightarrow \pi^*$ transition is often hidden under the more intense lower lying transitions in amides.[6,15,18] The $n \rightarrow \pi^*$ band has been estimated to be situated between 231 and 233 nm in the UV spectra of tertiary amides.[15] In our case the flat part of the CD-curves from 230 to *ca* 265 nm may indicate the presence of a low-intensity long wavelength band although this was not apparent in the UV-spectra recorded.

The UV spectra of **5b** and **5c** in Fig. 2 exhibit two bands contrary to the spectrum of the chloride analogue of **5c**. The long wavelength bands at 245 nm originate from iodide absorption, probably associated with interaction with the solvent,[19] and have no correspondence in the CD spectra. This long wavelength band, which is also observed in the spectra of tetra-*t*-butylammonium iodide, is shifted *ca* 25 nm towards shorter wavelengths on changing to



1a, R=Me 2 3 4 5
b, R=CHMe2
c, R=CH2CHMe2
d, R=H

Scheme 1.

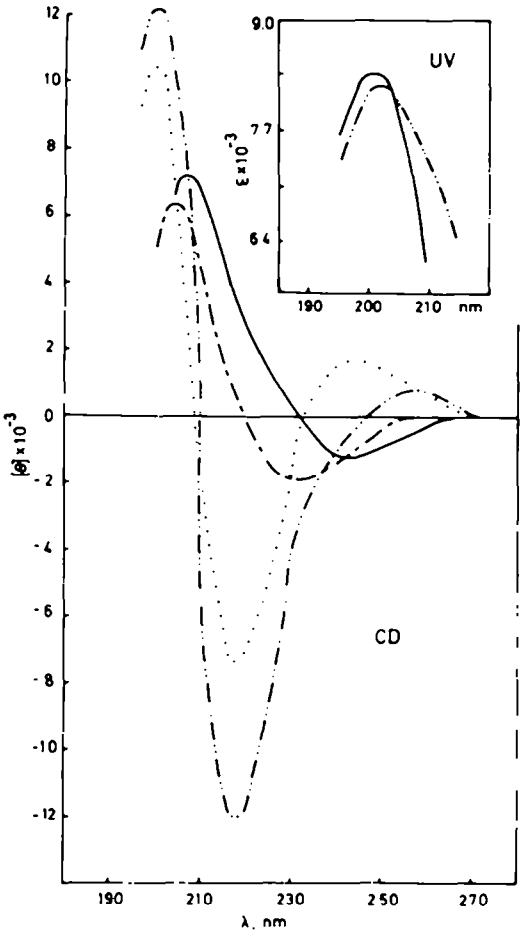


Fig. 1. CD curves: (*S*)-α-Amino-*N'*,*N'*-diethyl-γ-methylvaleramide **3c** in hexane ——— and in methanol — — —. (*S*)-α-*N*,*N*-Dimethylamino-*N'N'*-diethyl-γ-methylvaleramide **4c** in hexane —·— and in methanol ····.

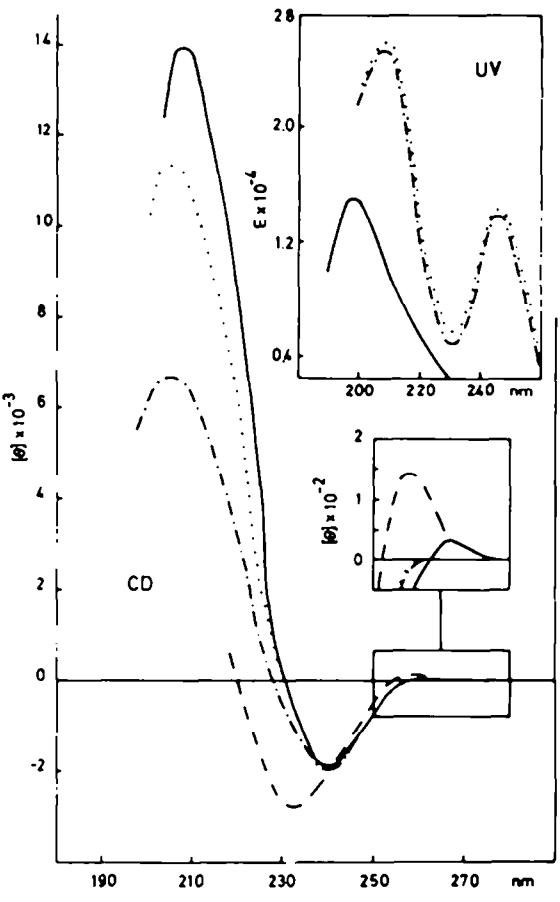


Fig. 2. CD curves: (*S*)-α-*N*,*N*-Dimethylamino-*N'*,*N'*-diethyl-β-methylbutyramide **4b** hydrochloride in methanol ———. (*S*)-α-N,N,N-trimethylammonio-*N'*,*N'*-diethyl-β-methylbutyramide iodide **5b** —·—·. (*S*)-α-*N*,*N*,*N*-trimethylammonio-*N'*,*N'*-diethyl-γ-methylvaleramide iodide **5c** ····, and (*S*)-α-*N*,*N*,*N*-trimethylammonio-*N'*,*N'*-diethyl-γ-methylvaleramide chloride ——— in acetonitrile.

methanolic solution. Corresponding shifts are not observed in the CD spectrum.

The CD spectra of **3** and **4** were recorded in hexane and in methanol, those of **5** in acetonitrile. The spectra within each series were closely related, the spectra of **3c** and **4c** are shown in Fig. 1 and the complete data are given in Table 1. The sodium D-line rotation of the ammonio amides **5a** and **5b** was negative whereas the rotation of **5c** was positive. The dichroic absorption of **5a** in acetonitrile however, could not be recorded with certainty, whereas **5b** and **5c** gave well defined CD curves (Fig. 2).

From the above discussion of the UV spectra the 200 nm positive CD bands of **3** and **5**, and possibly those of **4** as well, may be assigned to the $\pi \rightarrow \pi^*$ carbonyl transition of the tertiary amide group. The negative bands of **3** and **5** at 230–250 nm are probably associated with the $n \rightarrow \pi^*$ transition. The weak long wavelength positive band observed in some spectra of **5** (Fig. 2) may be interpreted as the very long wavelength part of the intense positive band at shorter wavelengths, overlapped by a more narrow negative 230 nm band as shown by a mathematical treatment.[20] Alternatively it could arise in a similar way from carbonyl $n \rightarrow \pi^*$ transitions of two or more conformers. Transitions from the ammonium group are excluded since all its electrons are in bonding orbitals. Thus, though long wavelength bands are observed (Fig. 2) in the spectra of **5** this cannot be taken as an unequivocal indication of a conformational equilibrium.

Table 1. Dichroic absorption; λ_{max}/nm and $\Delta\varepsilon_{max}$

Solvent MeOH **3a**: 234(−0.23), 205(+1.23). **3b**: 232 (−0.79), *ca* 205(+).† **3c**: 231(−0.64), 204(+2.12). **4a**: 239(+1.10), 218(−1.16), *ca* 200(+).† **4a**/HCl: 246(+0.03). **4b**: 247(+1.30), 218(−1.63), *ca* 200(+).† **4b**/HCl: 258(+0.05), 231(−0.91). **4c**: 244(+0.59), 218(−2.43), 202(+3.47).

Solvent hexane **3a**: 241(−0.35), 206(+1.30). **3b**: 242(−0.54), *ca* 205(+).† **3c**: 243 (−0.40), 207(+2.40). **4a**: 254(+0.15), 218(−1.33), *ca* 200(+).† **4b**: 254(+0.57). **4c**: 257(+0.24), 218(−3.99), 202(+4.03).

Solvent MeCN **5a**/Cl⁻: 250(+0.06), 233(−0.66), *ca* 205(+).† **5b**: 240(−0.64), 205(+2.20). **5c**/Cl⁻: 267(+0.01), 240(−0.59), 208(+4.64). **5c**: 240(−0.59), 205(+3.75).

†The maxima were not reached or the values are uncertain.

The interpretation of the CD spectra of **4** is complicated by the uncertainty as to the position of the amine $n \rightarrow \sigma^*$

transition (which should not be confused with the intramolecular charge-transfer transition suggested by Polónski[8]). The n $\rightarrow \sigma^*$ transition appears to be at longer wavelengths in secondary and tertiary amines than in primary amines; in the CD spectra of some tertiary amines rather high intensity bands ($[\theta] = 4000$–8000) have been observed at 220–225 nm in addition to bands at shorter wavelengths.[16,21,22] It cannot be excluded that corresponding transitions are involved in the dichroic absorption of **4** below 230 nm (Fig. 1). The spectra of **4** are rather different from those of **3** and **5**. The CD spectrum of **4b** as its hydrochloride in methanol, however, is similar to the CD spectra of **3** and **5**. Electric dipole coupling[23] between the n $\rightarrow \sigma^*$ amine and the $\pi \rightarrow \pi^*$ amide transitions should also be considered. Such coupling should give rise to a couplet which appears to be present in the spectra of **4**.

The long wavelength positive bands of **4** probably originate from n $\rightarrow \pi^*$ transitions. It is uncertain, however, whether bands of similar origin are involved in the negative bands at shorter wavelengths, indicating a conformational equilibrium.

The series **3** and **4** appears to have opposite signs for the long wavelength CD bands (Fig. 1) which might suggest a different conformational distribution in the two series. The dipole moments for the series **3** and **4** (see Experimental section), determined in benzene solution, were not much different from the value 3.75 D reported[24] for *N,N*-diethylacetamide (dioxane) and therefore the dipole moments seem to offer little additional conformational information.

EXPERIMENTAL

CD curves were recorded with Jasco Automatic Spectropolarimeters Models J-10 and J-40. The cell lengths were 0.1–30 mm and the temperature 27°C. UV spectra were recorded on a Cary-118 spectrophotometer.

Dipole moments. Dielectric constants were measured at 25°C in a Weilheim Dipolmeter DM 01 on four different solutions of each compound. The concentrations were in the range 35–140 mg in 35 g of benzene. No correction for atomic polarisation was made in the calculation of the dipole moments.[25] Dipole moments: 3.78 D (**3a**), 3.72 D (**3b**), 3.67 D (**3c**) and 3.82 D (**3d**); 3.45 D (**4a**), 3.50 D (**4b**), 3.36 D (**4c**) and 3.55 D (**4d**).

(S) - N - *Phthaloylalanine* - *diethylamide* **2a**. (*S*) - *N* - Phthaloylalanyl chloride[10] (0.1 mol) was dissolved in methylene chloride (30 ml) and benzene (150 ml) was added; the soln was then cooled to 5°C and diethylamine (0.2 mol) dissolved in benzene (50 ml) was added dropwise. The reaction mixture was left for 2 days at room temperature before the solvents were evaporated. The residue was treated with $CHCl_3$ (250 ml) and the solution was washed with aq Na_2CO_3 before drying. Evaporation left the non-crystalline title compound (24 g) which was used as such. For analytical purposes part of the material was further purified by chromatography on a silica gel (0.2–0.5 mm) column using methanol:benzene (1:2) as eluant. The product was a colourless glass-like material which did not crystallise [lit.[26], m.p. 85°C for the racemate]. (Found: C, 65.78; H, 6.50. Calc. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61%); $[\alpha]_D = -43.7°$ (c = 1.2 in MeOH).

(S) - N - *Phthaloylvalinediethylamide* **2b** was prepared as above from (*S*)-*N*-phthaloylvalyl chloride.[10] The product (93%) was made to crystallise by rubbing it with a glass rod. This material was used without further purification; for analytical purposes a sample was recrystallised from n-pentane; m.p. 60°C. (Found: C, 67.59; H, 7.44. Calc. for $C_{17}H_{22}N_2O_3$: C, 67.52; H, 7.33%); $[\alpha]_D$ – 150° (c = 1.3 in MeOH).

(S) - N - *Phthaloylleucine* - *diethylamide* **2c** was obtained as above from (*S*)-*N*-phthaloylleucyl chloride[27] in 91% yield, m.p. 68°C (pet. ether). (Found: C, 68.52; H, 7.59. Calc. for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.64%); $[\alpha]_D = -53.5°$ (c = 1.1 in MeOH).

N-*Phthaloylglycine*-*diethylamide* **2d** was prepared according to the literature.[28]

(S) - α - *Amino* - N',N' - *diethylpropionamide* **3a**. A solution of (*S*) - *N* - phthaloylalanine - diethylamide (0.086 mol) and hydrazine hydrate (0.098 mol) in abs. ethanol (216 ml) was stirred at room temp. overnight and then heated for 2 h at 70°C. The phthaloyl hydrazide which precipitated from the cold (5°C) solution was removed, and the filtrate was concentrated at reduced pressure. The residual material was redissolved in methylene chloride (150 ml), the solution left at 5°C overnight and the precipitate removed before evaporation and fractional distillation of the residue; the title compound was obtained in 63% yield, b.p. 70–71°C/0.25 mmHg. (Found: C, 57.97; H, 11.00. Calc. for $C_7H_{14}N_2O$: C, 58.30; H, 11.18%); $[\alpha]_D = -6.6°$ (c = 1.3 in MeOH).

(S) - α - *Amino* - N',N' - *diethyl* - β - *methylbutyramide* **3b** was prepared as above from (*S*) - *N* - phthaloylvaline - diethylamide in 71% yield, b.p. 72°C/0.15 mmHg. (Found: C, 62.15; H, 11.24. Calc. for $C_9H_{20}N_2O$: C, 62.73; H, 11.70%); $[\alpha]_D = +53.5°$ (c = 1.0 in MeOH).

(S) - α - *Amino* - N',N' - *diethyl* - γ - *methylvaleriamide* **3c** was obtained as above from (*S*) - *N* - phthaloylleucine - diethylamide in 70% yield, b.p. 80°C/0.05 mmHg. (Found: C, 64.56; H, 11.84. Calc. for $C_{10}H_{22}N_2O$: C, 64.47; H, 11.90%); $[\alpha]_D = +11.5°$ (c = 1.0 in MeOH).

α - *Amino* - N',N' - *diethylacetamide* **3d** was prepared as above from *N*-phthaloylglycine-diethylamide in 44% yield, b.p. 78–80°C/0.35 mmHg[lit.[28] b.p. 66°C/0.5 mmHg].

(S) - α - N,N - *Dimethylamino* - N',N' - *diethylpropionamide* **4a**. A solution of (*S*) - α - amino - *N',N'* - diethylpropionamide (0.043 mol) in methanol (150 ml), water (30 ml), and 35% formalin (70 ml) was hydrogenated at atmospheric pressure over 5% Pd/C (5 g) until the hydrogen consumption had ceased. The catalyst was then filtered off and conc. HCl (6 ml) added to the filtrate before evaporation at reduced pressure. The residue was extracted with chloroform (120 ml), and the chloroform extracts evaporated. The residue slowly crystallised in the cold and was washed with ether and recrystallised from acetone. The HCl salt of **4a** thus obtained had m.p. 143–144°C. (Found: C, 51.52; H, 9.83. Calc. for $C_9H_{20}N_2O$·HCl: C, 51.79; H, 10.14%). The free base **4a** was generated by addition of trimethylamine (0.05 mol) in methanol (10 ml) to a solution of **4a**·HCl (0.033 mol) in methanol (25 ml) followed by addition of ether (250 ml). The precipitate was filtered, the filtrate evaporated and the residue fractionally distilled. The title compound was obtained in an overall yield of 50%, b.p. 92–94°C/10 mmHg. (Found: C, 63.29; H, 12.00. Calc. for $C_9H_{20}N_2O$: C, 62.74; H, 11.70%); $[\alpha]_D = -43.0°$ (c = 1.3 in MeOH).

(S) - α - N,N - *Dimethylamino* - N',N' - *diethyl* - β - *methylbutyramide* **4b** was similarly prepared from (*S*) - α - amino - *N',N'* - diethyl - β - methylbutyramide in 57% yield, b.p. 116–118°C/16 mmHg. (Found: C, 65.82; H, 12.08. Calc. for $C_{11}H_{24}N_2O$: C, 65.96; H, 12.08%); $[\alpha]_D = +14.4°$ (c = 2.1 in MeOH). The HCl-salt of **4b** had m.p. 216°C (acetone). (Found: C, 55.90; H, 10.80. Calc. for $C_{11}H_{24}N_2O$·HCl: C, 55.79; H, 10.64%).

(S) - α - N,N - *Dimethylamino* - N',N' - *diethyl* - γ - *methylvaleramide* **4c** was similarly prepared from (*S*) - α - amino - *N',N'* - diethyl - γ - methylvaleramide in 55% yield, b.p. 122–124°C/18 mmHg. (Found: C, 67.13; H, 11.94. Calc. for $C_{12}H_{26}N_2O$: C, 67.22; H, 12.22%); $[\alpha]_D = +19.2°$ (c = 2.0 in MeOH).

α - N,N - *Dimethylamino* - N',N' - *diethylacetamide* **4d** was similarly prepared from α - amino - *N',N'* - diethylacetamide in 51% yield, b.p. 96°C/20 mmHg. (Found: C, 60.66; H, 11.60. Calc. for $C_8H_{18}N_2O$: C, 60.74; H, 11.47%).

(S) - α - N,N,N - *Trimethylammonio* - N',N' - *diethylpropionamide iodide* **5a**. A solution of (*S*) - α - *N,N* - dimethylamino - *N',N'* - diethylpropionamide (0.005 mol) and methyl iodide (0.02 mol) in nitromethane (25 ml) was heated in a pressure bottle at 40°C for 20 h. The volume of the solution was then reduced to *ca* 10 ml, and ether (150 ml) was added. The precipitated title compound was recrystallised from isopropanol; yield 58%, m.p. 228°C. (Found: C, 38.64; H, 7.60. Calc. for

$C_{16}H_{23}IN_2O$: C, 38.23; H, 7.38%); $[\alpha]_D = -39.7°$ (c = 1.0 in 0.1 N HCl). Excess freshly prepared silver chloride was added to a solution of the iodide **5a** (2.0 g) in water (90 ml). The mixture was stirred for 1 h before filtration.

(S) - α - N,N,N - *Trimethylammonio* - N',N' - *diethyl-propionamide chloride* was obtained from the filtrate after freeze-drying: m.p. 194°C (acetone). (Found: C, 53.60; H, 10.20. Calc. for $C_{16}H_{33}ClN_2O$: C, 53.92; H, 10.40%).

(S) - α - N,N,N - *Trimethylammonio* - N',N' - *diethyl* - β - *methylbutyramide iodide* **5b** was prepared as above from (*S*) - α - *N,N* - dimethylamino - *N',N'* - diethyl - β - methylbutyramide in 95% yield, m.p. 201–202°C (i-PrOH). (Found: C, 42.31; H, 7.87. Calc. for $C_{12}H_{27}IN_2O$: C, 42.10; H, 7.95%); $[\alpha]_D = -9.8°$ (c = 1.0 in 0.1 N HCl).

(S) - α - N,N,N - *Trimethylammonio* - N',N' - *diethyl* - γ - *methylvaleramide iodide* **5c** was prepared as above from (*S*) - α - *N,N* - dimethylamino - *N',N'* - diethyl - γ - methylvaleramide in 88% yield, m.p. 200–201°C (i-PrOH). (Found: C, 44.15; H, 8.17. Calc. for $C_{13}H_{29}IN_2O$: C, 43.82; H, 8.20%); $[\alpha]_D = +11.5°$ (c = 1.1 in 0.1 N HCl). Part of the iodide **5c** was converted as above to (*S*) - α - *N,N,N* - trimethylammonio - *N',N'* - diethyl - γ - methylvaleramide chloride, m.p. 161°C (acetone). (Found: C, 59.00; H, 11.00. Calc. for $C_{13}H_{29}ClN_2O_2$: C, 58.96; H, 11.04%).

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