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The Crystal Structure of Succinylcholine Iodide

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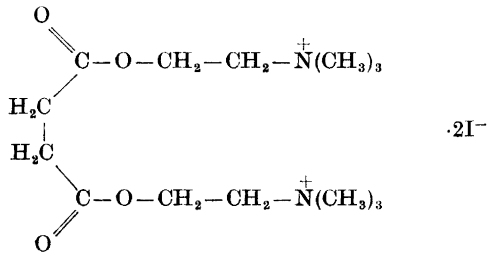
Succinylcholine iodide crystallizes in space group $P2_1$ with a unit cell having dimensions: $a=12.90$, $b=8.221$, $c=9.676$ Å, $\beta=98.2°$. $Z=2$. The structure determination was based upon visually estimated three-dimensional X-ray data. The final R-value is 0.098. The conformation of the succinylcholine ions is far from centrosymmetric, but the two chemically identical but crystallographically independent choline moieties of each ion have the same nearly *gauche* conformation. Ionic forces seem to be the dominant feature in the structural packing.

The investigation of the crystal structure of succinylcholine iodide



was undertaken as a part of a study of compounds acting as neuromuscular blocking agents. The conformation of the succinylcholine ion is of interest, as a connection may exist between this and its biological action. Since, however, the conformation in solution may be different from that found in a crystal, a series [1] of succinylcholine salts forming non-isostructural crystals is being investigated to examine the variation in conformation arising from different surroundings of the succinylcholine ion.

EXPERIMENTAL

Succinylcholine iodide, $C_{14}H_{30}O_4N_2I_2$, was prepared by mixing saturated aqueous solutions of succinylcholine chloride and potassium iodide. The resulting precipitate was purified by recrystallization from 95 % ethanol, and single crystals were grown

by slow evaporation of a 50 % ethanol solution. M.p. 250–255° (decomp., determined on a Leitz melting point microscope). The crystals are monoclinic needles elongated in the *b*-direction. The unit cell dimensions measured from precession films are $a=12.90\pm0.02$, $b=8.221\pm0.010$, $c=9.676\pm0.014$ Å, $\beta=98.2°\pm0.2°$. Systematic extinction of $0k0$ diffracted spectra when k was odd indicated the space group $P2_1$ or $P2_1/m$; the structure solution showed the former to be correct. The calculated density for two formula units per unit cell is 1.78 g/cm³ and the density measured by flotation in a mixture of C_2H_5I and CCl_4 is 1.76 g/cm³. The linear absorption coefficient, μ (Mo$K\alpha$), is 31.5 cm^{-1}.

All X-ray data were measured from a needle with the dimensions $0.16\times0.28\times0.40$ mm³, using Mo$K\alpha$ radiation, $\lambda=0.7107$ Å. The reflections hKl, $K=0-5$, were recorded by equi-inclination Weissenberg multiple film techniques. The reflections $hk0$ and $0kl$ were recorded by the precession method and used to correlate the levels hKl. All intensities were estimated visually, corrected for Lorentz and polarization factors and for variations in spot shape [2] and finally scaled together to form a set of 1145 independent non-zero reflections. No corrections for extinction or absorption were applied.

DETERMINATION AND REFINEMENT OF THE STRUCTURE

The structure was solved by the heavy atom method. The co-ordinates of the iodine atoms were obtained from the three-dimensional Patterson synthesis, and the positions of the other twenty non-hydrogen atoms were postulated from a three-dimensional Fourier synthesis calculated using the phases from the contributions of the iodine atoms.

The refinement started with three cycles of Fourier refinement and was continued and completed using the full matrix least squares method, with

Table 1. Final positional parameters and $10^4\times$ their e.s.d. in parentheses.

	x/a	*y/b*	*z/c*
I(1)	0.2348 (3)	0.5303 (8)	0.5847 (3)
I(2)	0.1221 (2)	1.0 (–)	0.1405 (3)
C(1)	0.4437 (42)	0.8977 (96)	0.4652 (58)
C(2)	0.4159 (36)	0.9551 (74)	0.6058 (48)
O(3)	0.4645 (30)	0.8913 (62)	0.7189 (40)
O(4)	0.3302 (22)	1.0129 (76)	0.5899 (28)
C(5)	0.2866 (39)	1.0725 (77)	0.7251 (50)
C(6)	0.2042 (31)	0.9845 (88)	0.7534 (40)
N(7)	0.0988 (25)	1.0144(102)	0.6783 (33)
C(8)	0.1002 (30)	1.0137(120)	0.5218 (41)
C(9)	0.0329 (70)	0.8640(161)	0.7146 (96)
C(10)	0.0488 (66)	1.1572(146)	0.7156 (86)
C(1′)	0.4165 (32)	1.0097(119)	0.3502 (42)
C(2′)	0.4305 (41)	0.9135(100)	0.2128 (54)
O(3′)	0.4348 (28)	1.0067 (92)	0.1084 (38)
O(4′)	0.4249 (26)	0.7700 (58)	0.2032 (34)
C(5′)	0.4246 (37)	0.6966 (78)	0.0678 (49)
C(6′)	0.3215 (53)	0.6600 (96)	0.0104 (67)
N(7′)	0.2643 (24)	0.5189 (98)	0.0531 (31)
C(8′)	0.2613 (33)	0.5348(122)	0.2143 (42)
C(9′)	0.3112 (71)	0.3471(128)	0.0137 (87)
C(10′)	0.1520 (30)	0.4973 (99)	–0.0113 (39)

individual isotropic temperature factors for all atoms for three cycles and then with anisotropic temperature factors for the iodine atoms and individual isotropic temperature parameters for all other atoms for further two

Table 2. Final thermal parameters and their e.s.d. The anisotropic temperature factor are defined by the equation
T.F. $=\exp[-1/4(h^2a^{*2}B_{11}+k^2b^{*2}B_{22}+l^2c^{*2}B_{33}+2hka^*b^*B_{12}+2hla^*c^*B_{13}+2klb^*c^*B_{23})]$.

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
I(1)	5.24(.17)	3.36(.96)	2.81(.12)	0.22(.23)	1.52(.11)	0.18(.18)
I(2)	3.06(.11)	4.71(.99)	2.44(.11)	0.13(.21)	0.88(.09)	0.00(.18)
	Atom	B	Atom	B	Atom	B
	C(1)	4.0(1.2)	C(8)	2.8(0.8)	C(5′)	2.6(1.0)
	C(2)	3.0(1.0)	C(9)	6.0(1.9)	C(6′)	2.5(1.2)
	O(3)	4.7(0.9)	C(10)	4.6(1.2)	N(7′)	2.4(0.6)
	O(4)	3.4(0.6)	C(1′)	3.3(0.9)	C(8′)	2.9(0.9)
	C(5)	3.6(1.1)	C(2′)	3.5(1.1)	C(9′)	4.2(1.7)
	C(6)	2.6(0.9)	O(3′)	5.8(0.9)	C(10′)	2.9(0.8)
	N(7)	2.7(0.7)	O(4′)	3.2(0.7)		

Table 3. Bond lengths and their e.s.d. $\times 10^2$ in parentheses.

	Å	
C(1)—C(1′)	1.45	(9)
C(1)—C(2)	1.53	(8)
C(1′)—C(2′)	1.58	(9)
C(2)—O(3)	1.29	(6)
C(2′)—O(3′)	1.27	(9)
C(2)—O(4)	1.19	(6)
C(2′)—O(4′)	1.19	(9)
O(4)—C(5)	1.57	(6)
O(4′)—C(5′)	1.44	(6)
C(5)—C(6)	1.35	(8)
C(5′)—C(6′)	1.40	(8)
C(6)—N(7)	1.47	(5)
C(6′)—N(7′)	1.47	(10)
N(7)—C(8)	1.51	(5)
N(7′)—C(8′)	1.57	(5)
N(7)—C(9)	1.57	(14)
N(7′)—C(9′)	1.60	(13)
N(7)—C(10)	1.41	(13)
N(7′)—C(10′)	1.51	(5)

Table 4. Bond angles and their e.s.d. in parentheses.

C(1′)—C(1)—C(2)	115°	(6°)
C(1)—C(1′)—C(2′)	106°	(7°)
C(1)—C(2)—O(3)	119°	(5°)
C(1′)—C(2′)—O(3′)	113°	(7°)
C(1)—C(2)—O(4)	110°	(4°)
C(1′)—C(2′)—O(4′)	124°	(6°)
O(3)—C(2)—O(4)	127°	(5°)
O(3′)—C(2′)—O(4′)	123°	(6°)
C(2)—O(4)—C(5)	117°	(3°)
C(2′)—O(4′)—C(5′)	119°	(5°)
O(4)—C(5)—C(6)	113°	(5°)
O(4′)—C(5′)—C(6′)	109°	(5°)
C(5)—C(6)—N(7)	121°	(5°)
C(5′)—C(6′)—N(7′)	123°	(6°)
C(6)—N(7)—C(8)	111°	(3°)
C(6′)—N(7′)—C(8′)	107°	(6°)
C(6)—N(7)—C(9)	104°	(6°)
C(6′)—N(7′)—C(9′)	114°	(5°)
C(6)—N(7)—C(10)	116°	(6°)
C(6′)—N(7′)—C(10′)	118°	(5°)
C(8)—N(7)—C(9)	108°	(6°)
C(8′)—N(7′)—C(9′)	112°	(6°)
C(8)—N(7)—C(10)	109°	(6°)
C(8′)—N(7′)—C(10′)	105°	(3°)
C(9)—N(7)—C(10)	109°	(6°)
C(9′)—N(7′)—C(10′)	100°	(6°)

cycles. The form-factors for all atoms were taken from *International Tables for X-ray Crystallography*.[3] Unit weight was given to each observed reflection, and no unobserved reflections were included in the refinement. The final reliability index R is 0.098. The observed structure amplitudes and calculated structure factors are given in Table 6. Nearly all calculations have been performed on the IBM 7094 computer at the NEUCC installation in Copenhagen with the use of the integrated program system *X-RAY 63*.[4]

Attempts to determine the absolute chirality of the succinylcholine ion have not been made, as it is of no significance in relation to the present problem and crystals of each chirality may exist in any batch.

DESCRIPTION AND DISCUSSION OF THE STRUCTURE

The final positional and thermal parameters together with their estimated standard deviations are given in Tables 1 and 2, and in Tables 3 and 4 the inter-atomic distances and angles are shown. A detailed discussion of these results seems of little value since the influence of the iodine atoms gives rise to very high standard deviations (0.05 – 0.14 Å on inter-atomic distances and 3° – 7° on angles).

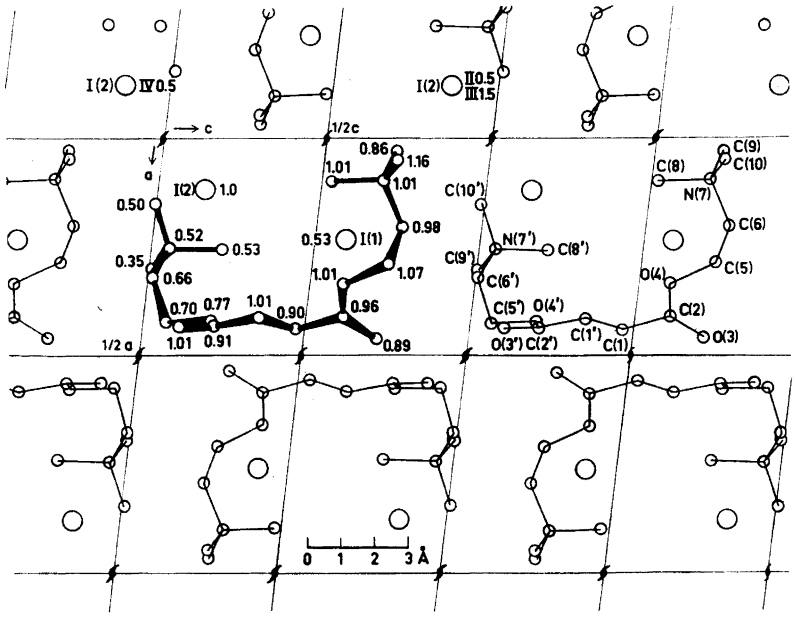


Fig. 1. The structure viewed along the b-axis. The numbers show the y co-ordinates (y/b) of the atoms. The use of roman numerals is as in Table 5. The atomic numbering used in this paper is shown.

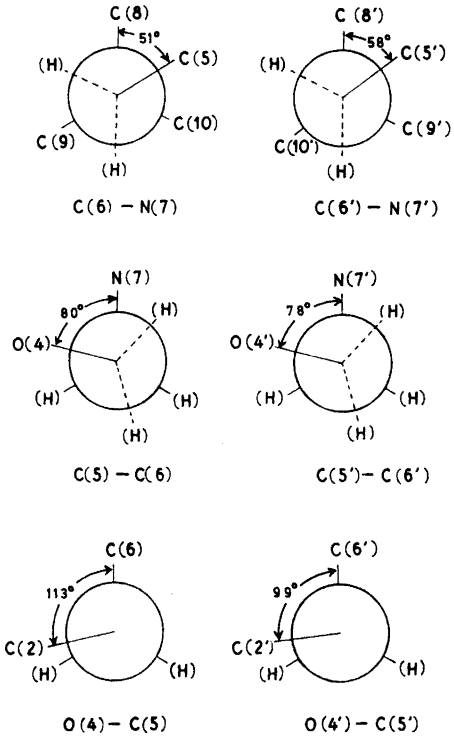


Fig. 2. The conformation of the choline moieties as viewed down the bond indicated below each figure. The dihedral angles are given.

Formally the succinylcholine ion is centrosymmetric, and the molecular symmetry $\bar{1}$ is found in the crystal structures of succinylcholine perchlorate and succinylcholine picrate.[1] But in this structure the conformation of the succinylcholine ions is far from this (*cf.* Fig. 1). Nevertheless the two choline moieties in each ion show approximately the same nearly *gauche* conformation (Fig. 2). This or the enantiomeric conformation of the system $O-C-C-N^+$ is found in a great number of crystal structures.[5] Recently Chothia and Pauling [6] reported two conformations of acetyl-α-methylcholine in a single crystal, one nearly *gauche* and one midway between *eclipsed* and *trans*. The intramolecular $N^+\cdots O$ and $C\cdots O$ distances in succinylcholine iodide are: $N(7)\cdots O(4)$ 3.22 Å, $N(7')\cdots 0(4')$ 3.14 Å, $(C8)\cdots O(4)$ 2.95 Å and $C(8')\cdots O(4')$ 2.88 Å.

The atomic arrangement in the ester groups deviates somewhat from planarity, and the conformation about the two independent groups of each ion differs in the same way from the most common [7] ester conformation. The alcohol moieties are situated *s-cis* to the C=O groups, but the β-carbon atoms in the acid moieties are *s-trans* to the carbonyl groups. As illustrated in Fig. 3 the twists of the ions arise through deviations (up to about 45°) from the expected *trans* conformation in the succinyl backbone.

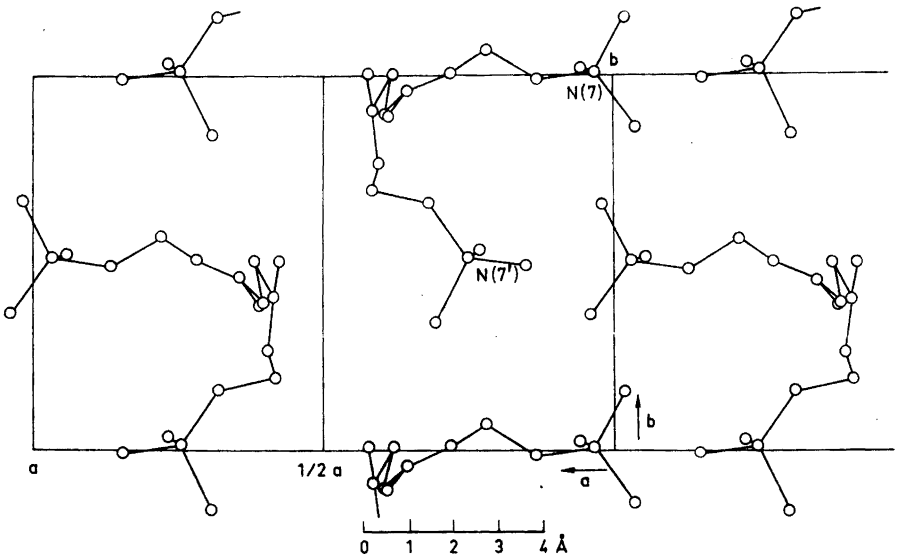


Fig. 3. Succinylcholine ions viewed along the c^*-axis.

The molecular packing is rather compact, and many intermolecular distances corresponding to van der Waals contacts are observed. But the ionic forces seem to be the dominant feature in the structure. Table 5 lists a series of close contacts to I^-. Since the bonds N(7) – C(8), N(7) – C(9), and N(7) – C(10) are directed towards an I^- and since this is also the case for the bonds N(7′) – C(8′) and N(7′) – C(10′), the positive charge of the nitrogen atoms seems to be delocalized to the whole quaternary ammonium group. In addition four I^- ions are nested between the carbon atoms around N(7) and three are situated in the same way around N(7′). Many of the distances from these iodide ions to the methyl carbon atoms are equal to or somewhat less than the sum of the respective van der Waals radii, 4.2 Å (= 2.0 + 2.2).[8]

Table 5. Close contacts between CH_3-groups and iodide ions, together with the N–C···I angles. The positions of the ions are: I (x, y, z); II ($-x$, $y+\frac{1}{2}$, $1-z$); III ($-x$, $y-\frac{1}{2}$, $1-z$); IV ($-x$, $y-\frac{1}{2}$, $-z$).

C(8)···$I(2)_I$	3.73 Å	∠ N(7)–C(8)···$I(2)_I$	176°
C(9)···$I(2)_{II}$	3.97 Å	∠ N(7)–C(9)···$I(2)_{II}$	172°
C(10)···$I(2)_{III}$	3.95 Å	∠ N(7)–C(10)···$I(2)_{III}$	169°
C(8′)···$I(1)_I$	3.64 Å	∠ N(7′)–C(8′)···$I(1)_I$	173°
C(10′)···$I(2)_{IV}$	3.58 Å	∠ N(7′)–C(10′)···$I(2)_{VI}$	172°

The shorter $N^+\cdots I^-$ distances are about 4.5 Å; obviously the steric influence from the carbon atoms in the quaternary ammonium groups prevents the existence of close direct $N^+\cdots I^-$ contacts.

Table 6. Observed and calculated structure factors for succinylcholine iodide. The column headings are the index h, $|F_o|$ and $|F_c|$.

Table 6. Continued.

h,3,9	7 513 491	-9 297 300	0 284 266	-5 185 170	h,5,5	-2 178 182
2 211 185	8 161 156	-8 501 495	1 398 415	-4 161 101	-5 317 356	-1 451 464
4 380 364	9 191 155	-7 172 181	2 689 703	-3 181 192	-4 512 481	0 418 360
6 247 196	10 150 162	-6 552 505	4 444 449	-2 381 337	-3 358 355	1 615 523
8 209 143	11 355 269	-5 766 719	5 423 386	-1 343 370	-2 734 585	2 331 327
7 222 188		-4 246 265	7 184 162	1 352 339	-1 658 615	3 265 277
h,4,2		-3 315 276	8 172 113	2 205 178	0 400 463	4 535 431
h,3,10	-11 162 138	-2 290 262	10 217 213	7 182 182	1 144 160	5 208 203
-10 230 180	-10 268 310	-1 301 286		8 199 56	2 255 300	
-9 306 368	-9 392 342	0 814 805	h,4,7		3 378 345	h,5,6
-7 242 266	-8 195 196	1 559 508	-12 222 219	h,4,10	4 611 552	-5 258 261
-6 228 140	-7 783 778	2 322 272	-11 236 307	-6 271 276	5 452 520	-4 276 284
-5 210 119	-6 457 457	3 693 656	-9 424 415	-4 266 302	6 151 248	-3 312 302
-1 353 364	-5 353 334	4 370 329	-8 374 368	-3 275 305	7 384 386	-2 254 226
1 314 287	-4 374 263	5 244 275	-5 179 211	-1 213 210		-1 455 542
2 362 378	-3 547 531	6 149 109	-4 291 309	1 184 120	h,5,3	0 297 285
	-2 464 435	7 186 234	-3 611 608	3 211 126	-5 334 467	1 355 346
h,3,11	-1 1005 1040	8 195 193	-2 310 334	5 254 216	-4 223 261	2 225 211
-5 272 207	0 243 233	9 344 346	-1 457 447		-3 220 234	3 241 243
-3 421 431	1 908 944	11 259 270	0 477 472	h,4,11	-2 455 415	5 273 251
-2 258 135	2 725 710	12 218 167	1 226 195	-9 206 207	-1 242 256	7 326 343
	3 285 322		2 251 227	-8 247 179	0 345 346	
h,3,12	4 435 390	h,4,5	3 155 110	-6 231 250	1 171 156	h,5,7
-8 271 248	5 142 144	-13 218 226	4 178 165	-5 207 206	2 554 518	-6 544 535
-7 240 246	6 326 313	-12 389 154	5 200 221	-2 181 142	-1 627 572	-5 292 320
-6 235 162	7 415 389	-11 240 262	6 207 204	0 349 330	0 670 558	-4 241 245
	8 329 328	-10 516 587	8 294 252		2 744 705	-3 293 253
h,4,0	9 285 275	-9 194 180	9 198 148	h,4,12	3 537 465	-2 235 256
2 643 829	10 461 469	-8 236 260		-2 239 236	4 263 262	-1 201 168
3 588 581		-7 149 167	h,4,8		5 273 216	0 277 241
4 455 501	h,4,3	-6 217 268	-13 214 224	h,5,0	6 261 255	2 300 259
5 172 180	-12 311 365	-5 495 454	-12 196 62	2 403 456	7 152 145	3 367 349
6 564 544	-11 300 346	-4 683 651	-11 178 186	3 762 805	8 215 252	5 250 211
7 178 214	-10 156 160	-3 200 205	-10 173 92	4 214 286		
8 545 601	-9 510 359	-2 774 763	-9 190 181	5 623 673	h,5,4	h,5,8
9 362 456	-8 233 255	-1 570 595	-8 164 169	6 308 431	-7 155 265	-8 239 317
11 200 239	-7 315 269	0 388 374	-7 236 241	7 210 293	-6 218 267	-7 233 212
	-6 443 352	1 395 383	-6 200 228		-5 362 355	-4 220 194
h,4,1	-5 336 340	2 288 290	-5 452 447	h,5,1	-4 210 237	-3 231 267
-13 243 283	-4 541 482	3 232 262	-4 218 214	-8 306 468	-3 762 658	-2 331 325
-11 244 252	-3 835 795	4 362 308	-3 345 336	-7 258 418	-2 631 555	0 377 386
-10 179 171	-2 230 268	5 168 187	-2 391 369	-6 177 268	-1 224 231	1 350 345
-9 158 229	-1 715 714	6 346 338	-1 205 228	-5 169 262	0 452 422	
-8 258 256	0 503 493	7 411 360	0 169 152	-4 187 312	1 446 366	h,5,9
-7 333 400	1 372 410	9 190 111	1 287 270	-3 242 334	2 332 323	-5 278 297
-6 370 351	2 233 282		2 174 172	-2 428 427	3 313 275	-4 306 376
-5 544 537	3 386 367	h,4,6	3 489 459	-1 343 394	4 256 273	-2 284 240
-4 592 567	4 307 325	-10 170 132	4 333 305	0 523 509	5 264 263	
-3 435 440	5 710 711	-9 254 247	6 268 240	1 603 615	6 567 558	h,5,10
-2 764 792	6 343 310	-8 167 171		2 275 290	8 240 276	-1 277 255
-1 368 398	7 150 181	-7 384 418	h,4,9	3 492 482		0 250 199
0 812 890	8 406 363	-6 439 425	-11 198 119	4 265 299	h,5,5	
1 162 162	9 183 177	-5 143 102	-10 235 302	5 263 258	-8 241 276	
2 402 431	10 155 131	-4 645 623	-9 210 199	7 207 280	-7 505 603	
3 940 895		-3 393 376	-8 215 197	9 246 286	-6 546 495	
4 632 580	h,4,4	-2 324 337	-7 297 346		-4 365 361	
6 647 616	-10 178 186	-1 126 29	-6 166 154		-3 284 301	

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