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Wedekind–Fock–Havinga salt $Me(Et)N^+(All)PhI^- \cdot CHCl_3$ as historically the first object for absolute asymmetric synthesis: spontaneous resolution, structure and absolute configuration[†]

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The title salt crystallises as a conglomerate (space group $P2_12_12_1$, $Z = 4$) with one solvate $CHCl_3$ molecule forming strong shortened contact with I^- [$Cl \cdots I^-$ 3.599(2) Å]. Therefore, it undergoes spontaneous resolution by simple crystallisation with a deficiency of the conglomerator $CHCl_3$ or by an internal entrainment procedure. It exhibits the (*S*)-(+) absolute configuration and racemises in solution ($\Delta G^{\#}_{rac}$ = 26.5 kcal mol^{-1}). The salt was almost completely converted into one enantiomer by stirred crystallisation from solution (with full evaporation) or from a melt under conditions of enantiomerisation. The contribution of autocatalysis to this process is discussed.

Chiral ammonium salt $Me(Et)N^+(All)PhI^- \cdot CHCl_3$ **1** has attracted the attention of several generations of chemists and remains to be of much current interest because "...mental adjustments are required in order to deal intuitively with 'improbable' solid-state phenomena."[3] Salt **1** by right should be named for three outstanding persons who are responsible for its highly important place in the history of stereochemistry (see photos on the back cover and historical outlook[‡]).

E. Wedekind was the first to synthesise[5(*a*),(*g*)] salt **1** and to find that it incorporates crystallisation $CHCl_3$. He examined spontaneous racemisation of **1** and similar salts in solutions (its

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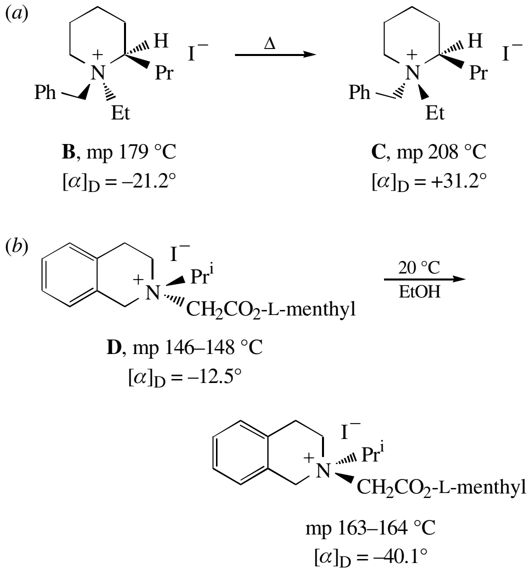
[†] Asymmetric Nitrogen. Part 84. Previous communication see ref. 1. Preliminary results of this work have been published.[2]

[‡] E. Wedekind, born on December 31, 1870, in Altona on Elbe, studied in Tübingen and Munich (thesis). In 1897–1899, he worked at the Polytechnical Institute in Riga (Russia); in 1904, he became a Professor at the Chemical Institute of Tübingen University. Over decades, he was elaborating the problems of asymmetric four-coordinated nitrogen[4] (which was earlier considered as five-coordinated). The related results obtained in Riga, Tübingen, and Strasbourg were published in 2 monographs and 60 communications in 1899–1934 (see ref. 5).

The question as to whether the four-coordinated nitrogen exists has been raised first by J. Wislicenus in 1877 [ref. 5(*a*), p. 1], and those as to three-coordinated nitrogen by A. Hantzsch and A. Werner in 1890.[6] Described in the next year by J. A. Le Bel, the optical activation of $Me(Et)N^+(Pr^n)Bu^iCl^-$ under the action of microorganisms[7(*a*)] was not confirmed later (1899).[7(*b*),(*c*)] Despite the unsuccessful attempts to resolve the Le Bel salt using the optically active acids such as tartaric, camphoric, and mandelic ones,[7(*b*)] Wedekind, in the same year, has launched an attack on solving the problem. One of the major arguments in support of the stereoisomerism of ammonium salts that Wedekind kept in mind[5(*c*)] was identity of the Menshutkin salts prepared by means of three possible ways from the corresponding *N*,*N*-dialkylaniline and alkyl iodide.[8] Studies by Wedekind of 1899 initiated the German[9] and three groups of British chemists[10] to be involved in the solution of this problem. These data on the synthesis, crystallographic characterisation, and unsuccessful attempts to resolve salts $Me(All)N^+(CH_2Ph)PhHal^-$ **A** using optically active tartaric and camphoric acids in aqueous solutions have been reported[5(*d*),(*e*)] followed by the publication of W. J. Pope *et al.*[10(*a*),(*b*)] on the resolution of salt **A** *via* camphorsulfonates in non-aqueous solutions. In 1905, M. B. Thomas and H. O. Jones first observed[10(*c*)] apparently asymmetric transformation of diastereomeric salts such as (+)-camphorsulfonate obtained from Wedekind salt **1**; when heated the latter above 50 °C in H_2O, its optical activity was changed to the sign reversal. However, the authors could not make the important fact out, and just expressed their astonishment: "It is curious that the rotatory power . . . vanish at some temperature above 50 °C and then become levorotatory...". Asymmetric transformation of a covalent diastereomeric salt was precisely detected[9] at the first time in 1905 by M. Scholtz who has synthesised derivatives of the alkaloid coniine for biological tests. In response to the Wedekind works, he has isolated diastereomerically pure salts **B** and **C** and carried out their intertransformations under short heating up to the melting [Scheme 1 (*a*)].



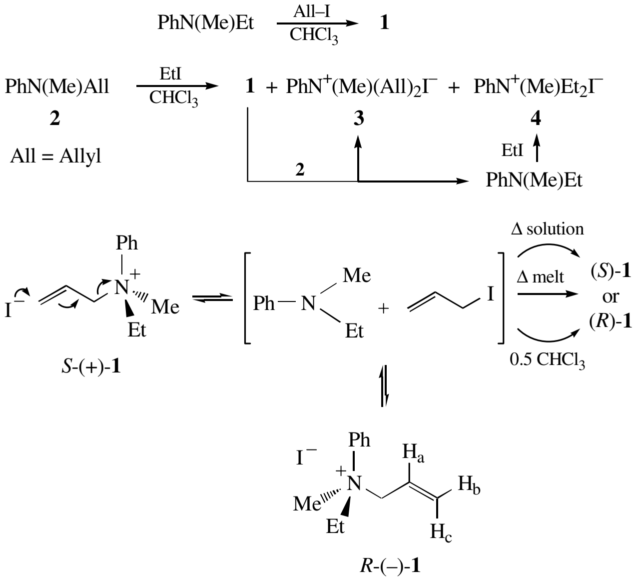
Scheme 1 Asymmetric diastereomeric transformations of the chiral ammonium salts.

Similar transformations were observed by Wedekind under mild conditions[5(*j*),(*k*)] [**D**, Scheme 1(*b*)]. It is amazing that till now the discovery of such phenomena important both in principle and in terms of technology, as asymmetric diastereomeric transformation was ascribed to H. Leuhs and J. Wutke (1913), and a well-known list of conglomerates[11] does not include many of hemihedral crystals found by Wedekind and A. L. Fock.[5,13]

A. L. Fock, born on April 28, 1856, in Böbs near Lübeck (Germany), studied (1876–1880) in Strasbourg (thesis). Since 1881, he worked with H. H. Landolt as his assistant and, since 1885, as an assistant professor at the Berlin University. Famous crystallographer, the author of the monograph "Introduction in Chemical Crystallography"[12] (translated and edited by W. J. Pope, one of the most prominent chemist of that time), Fock has performed all crystallographic studies of the Wedekind salts.[5,13] Both scientists were mad about hunting for conglomerates, and triumphed over each new find of the hemihedral crystal, in particular, of **A**[5(*d*)] and **1**.[5(*g*)] It is interesting to mention a microgoniometric study when hemihedrism was observed only for the enantiomer (–)-$Me(Pr^i)N^+(CH_2Ph)PhI^-$ (mp 132 °C) but not for the racemate (mp 133 °C).[10(*c*)] The priority in obtaining an optically active compound containing a stereogenic heteroatom is attributed to Pope and co-workers;[4,14] however, before them Wedekind and Fock have found hemihedrism (*i.e.*, homochirality) of the crystals of iodide **A**[5(*d*)] and then isomorphism of halides **A**.[5(*c*)] This fact was confirmed by Pope himself. He wrote [ref. 10(*a*), p. 1130]: "...Fock actually measured crystals of the optically active iodides", and emphasizing identity of the crystallographic parameters found by Fock for bromide (±)-**A**[5(*c*)] with those for enantiomers found by himself, he conrate depends on the type of anion: I > Br > Cl) and explained the racemisation by reversible dissociation into an amine and an allyl halide.[5(f)]

A. L. Fock pioneered microgoniometric studies of salt **1** and found the hemihedrism of its crystals;[5(a),7] *i.e.*, he found that it crystallises as a conglomerate (a mixture of homochiral crystals of the enantiomers) and hence is capable of spontaneous resolution.

E. Havinga was the first to perform spontaneous resolution of **1** and proposed the idea of spontaneous asymmetric synthesis[21] (absolute asymmetric synthesis or crystallisation-induced the second order asymmetric transformation[11]). Such a synthesis takes place under the following conditions: (*a*) the material crystallises as homochiral crystals (conglomerate); (*b*) the characteristic time of formation of the first nucleus is long; and (*c*) the rate of spontaneous or catalysed racemisation in a solution or melt is higher than the rate of crystal growth. Then, crystallisation from a supersaturated solution or a melt gives an enantiomerically pure product as a result of cloning molecules on the first nucleus formed (see, *e.g.*, refs. 3, 32 for the nucleation mechanism) from a mixture of the constant enantiomeric composition 1:1 (because of rapid racemisation). Thus, the racemate is converted into a single *d*- or *l*-enantiomer. This idea became universally recognised.[11,20,22–28] However, the total enantiomeric enrichment of the precipitate and the mother liquor in a particular experiment cannot be quantitatively evaluated from the experimental data by Havinga. It was noted by himself[21] that "...crystals contain $CHCl_3$, tend to liquate and soon become sticky renders exact quantitative determinations in small-scale experiments somewhat difficult". Moreover, Havinga's experiments "...have never been repeated" [ref. 25(*a*), p. 185], and it was noted that his results "...may not be reproducible".[24]



Scheme 2

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cluded: "It follows that the inactive salt is not a racemic compound but is . . . a mere mechanical mixture of the two component salts" [ref. 10(*b*), pp. 835–836]. The components of this mixture are enantiomorphous crystals (Figure 1)[10(b)] like in case of the Pasteur salt. Thus, a breakthrough in the stereochemistry of asymmetric heteroatoms took place on the verge of the centuries (1899–1901) due to efforts of Wedekind, Fock, Pope, S. J. Peachey and A. W. Harvey.

Wedekind has also synthesised[5(h)] optically active analogues of **A**, *i.e.* salts (+)- and (–)-$Me(Pr)N^+(CH_2Ph)PhI^-$ **E**, which were later prepared[15] by the reductive transformation of iodides (+)-**A** → (+)-**E**. The absolute configurations of (*S*)-(–)-**E** and (*S*)-(+)-As-analogue were determined[16(a)] using the method of quasi-racemates[11] by comparison with (*S*)-(+)-P-analogue studied[16(b)] by X-ray diffraction analysis. The salts like (+)-**A**[15(a)] and other[15(b),(c)] were used for the transfer of chirality from N to C by the Stevens reaction[15(a),(c)] and Hofmann cleavage.[15(b)]

The really opposite situation was with three-coordinated nitrogen. In all instances the resolution of compounds ranging from the Tröger base (V. Prelog, P. Wieland, 1944) to the chiral dialkoxyamine with the open-chained asymmetric nitrogen (R. G. Kostyanovsky *et al.*, 1979)[17(d),(e)] and systems with the sterically hindered nitrogen inversion[1] were carried out using chiral reagents. Only then did we find out the crystallographic identity of the enantiomers and racemate of a bis-naphtho analogue of the Tröger base[18] (which was found to be a conglomerate like those found by Fock and Pope!) we succeeded in spontaneous resolution, again at the verge of the centuries, and obtained the above synthetic product, each individual crystal of which was optically active, $[\alpha]_D^{20} = 1100–1200°$ (*c* 0.1, MeOH).

It is incomprehensible why either Wedekind or Pope, who realised the point perfectly well, never measured the optical rotation for the individual crystals of the salts under study. Only half a century later it was done by Havinga.

E. Havinga born on May 7, 1909, in Amersfoort (the Netherlands), studied theoretical physics at the Utrecht University (with H. A. Kramers) and organic chemistry (thesis "Monolayers: Structure and Chemical Reactions", 1939, under the supervision of F. Kögl), worked in the laboratory of medicinal chemistry at Utrecht, then became full professor and director of the laboratory of organic chemistry at the University of Leiden (1949–1979). His scientific interest ranged from physical organic chemistry to bioorganic chemistry including photochemistry and the chemistry of vitamin D, conformational analysis and peptide chemistry, catalysis and enzymatic reactions. He was gifted with incredible capacity for working and also with versatile talents outside chemistry. An outstanding teacher of organic chemistry (the number of theses prepared under his supervision amounts to 166), he was also an excellent tennis player, art-lover and masterly pianist who inspired the Dutch composer W. Aerts to write "Thirteen variations and coda on a theme of E. Havinga in E minor".

In his last year, Havinga has described his academic career in the essay "Enjoying Organic Chemistry, 1927–1987".[19] He was "a pioneer in optical activity from chiral crystals..." (see ref. 20). In fact, a new epoch of exploring the chirality phenomena has begun from his studies on salt **1**.[21] The whole flood of theoretical and experimental researches was initiated by his precisely formulated idea of spontaneous asymmetric synthesis and conditions for its accomplishment. The Havinga effect named the stereospecific autocatalysis by M. Calvin,[22] has been thoroughly investigated in theoretical aspects.[23] The ideas of Havinga were successfully realised.[11,24–27] Over the past decade it was shown that the efficiency of the crystallisation-induced asymmetric transformation depends critically on stirring and evaporation rates.[3,28] The main test sample is the salt $NaClO_3$ capable of crystallising in chiral cubic space group $P2_13$. Three years after translation of Fock's book[12(b)] Pope has found[10(e)] optical activity of the crystal of this salt ($\alpha = 3.6°\ mm^{-1}$ at 546 nm) and has shown that in 3137 crystals obtained by simple crystallisation, the left–right relation is practically equal to 1:1. After 92 years, D. K. Kondepudi *et al.*[28] and then J. M. McBride *et al.*[3] have repeated this experiment and have demonstrated that its result was dramatically changed under conditions of stirred crystallisation (100–1000 rpm) to give either only left or only right crystals.

Ideas presented in the second section of Havinga's paper[21] were almost not cited. The readers (not exclusive of the authors of this work) seem to be so stunned when perceiving the first part of the paper that they lose sight of the second one though it is not less interesting. Havinga assumes that in the system of molecules interoriented in a certain manner (crystal or monolayer), an enantiomeric excess may be preferable, in terms of free energy, than a racemate. It is well known for crystals (existence of conglomerates) but not for solutions, and Havinga proposes the following model. It may be that 3D achiral molecules of the type of $HO(CH_2)_n(X)C(Y)(CH_2)_nOH$ are capable of 2D (two-dimensional, or dipty) chiral self-association to form a mono-layer at the H_2O–air interface. When the molecules are oriented in such a manner that one of HO group is directed into H_2O phase, its oxidation (*e.g.*, with permanganate) can result in the formation of a 3D chiral product. This fantasy was partly realised. Remarkable absolute 2D → 3D asymmetric synthesis was described[29] still in Havinga times. A large monocrystal of achiral tiglic acid (space group $P\bar{1}$) was cut in two along the planes ($\bar{2}$ 1 0) and (2 $\bar{1}$ 0), each part was coated with an epoxide resin (not touching the edges) and treated with an oxidant (Figure 2). In result both enantiomeric products were obtained in yields 40–60% with ee > 95%.

By now, numerous data on the homochiral self-association of molecules in monolayers[30] and 2D chiral systems[31] are obtained. In case of 2D chiral molecule of 1-nitronaphthalene, the formation of decamer clusters of the composition of 8l2d and diptychiral enantiomer 8d2l are found. Similarly to the 3D chiral enantiomers of the Pasteur salt, they are sorted out but scanning tunneling microscopy[31] was used instead of an optical microscope and forceps.

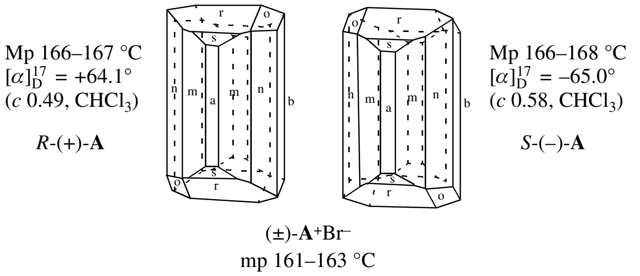

Figure 1 The enantiomorphous crystals of salt **A**.

Therefore we analysed, reproduced, supplemented and developed the above results.

We examined two versions of the synthesis of **1** on an 0.1 mol scale (Scheme 2)§ and found that only iodoallylation at the final stage [the advantages of this synthesis were noted previously[5(a),(d)]] affords pure product **1**, which is nonhygroscopic [in accordance with data from ref. 10(*c*) and in contrast to data from refs. 5(*a*),(*d*)]. In the second version of the synthesis, disproportionation by-products[3,4] are formed (*cf.* ref. 33), which were isolated and identified. Thus, we found that the data by Wedekind are reproducible; however, the version of synthesis is of crucial importance. It is likely that this fact is responsible for discrepant results by Fock concerning studies of α,β,γ-salts obtained in different manners.[5,13] Unfortunately, the procedure used for the synthesis of **1** was also not specified in refs. 19, 24.

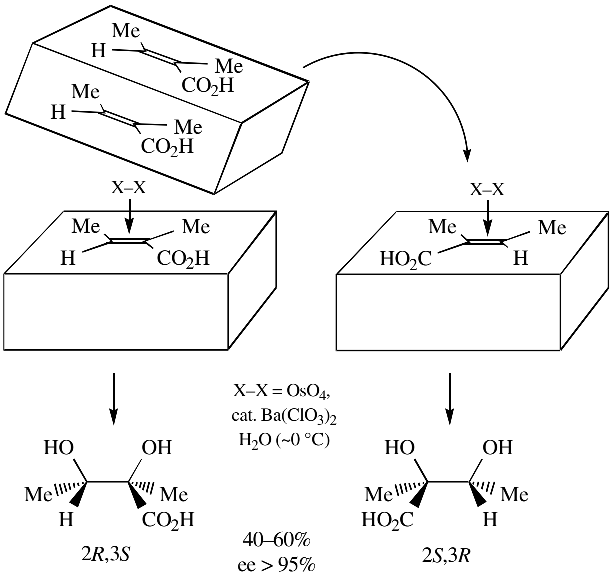

Figure 2 2D → 3D Absolute asymmetric synthesis in tiglic acid bishydroxylation.

Well-formed bright transparent crystals of (+)- or (–)-**1** (weighing as much as 0.1 g) were prepared by crystallisation from thoroughly purified dry chloroform at –6 °C. These crystals were somewhat different in the specific rotation (a crystal was cut in half to perform these measurements). The chiral space group $P2_12_12_1$ and the absolute configuration S-(+)-**1** were found by X-ray diffraction analysis using a portion of the crystal with maximum $[\alpha]_D$ 28.8° (c 0.8, CHCl$_3$). The barrier $\Delta G^{\#}$ = 26.5 kcal mol^{-1} at 25 °C in CHCl$_3$ was found from the kinetics of racemisation. Thus, we supported the data by Fock on the crystallisation of compound as a conglomerate, which are based on the hemihedrism of the crystals, the data by Wedekind on the spontaneous racemisation of (+)-**1** and the results by Havinga on the spontaneous resolution of **1**.

Considering chloroform incorporated in **1** as a conglomerator,[2] we removed CHCl$_3$ by evacuation (1 torr) (signals of CHCl$_3$ in the ^{1}H NMR spectra were monitored in [^{2}H$_6$]acetone). The crystallisation of the sample from EtOH–Et$_2$O with the addition of a half-molar amount of the conglomerator CHCl$_3$ (at –6 °C) afforded S-(+)-**1** in 20–35% yield, ee 61–70%. Next, we separated **1** by the internal entrainment procedure.[2(c)] In essence, this technique is a version of spontaneous resolution because the single crystal used for seeding was taken from a starting racemic mixture. A well-formed crystal (1–3 mg) was taken from the sample of **1** (150 mg). This crystal was used as a seed in the crystallisation (with self-evaporation) of this sample from a supersaturated solution in CHCl$_3$ at 20–25 °C. The crystals of (+)-**1** or (–)-**1** were separated in 30–35% yields and ee 70–75% after 3–5 days. In an analogous experiment, the precipitate contained a small amount of the solvent after two weeks. After the removal of the solvent in vacuo (10 torr), the starting material was completely recovered to an optically active form (ee 21%). This experiment was repeated with crystallisation for a month at –6 °C followed by the solvent removal in vacuo (10 torr). Surprisingly, this experiment also afforded optically active **1** (ee 16%). Hence, it follows that an autocatalytic effect of enantiomerisation of **1** occurs in the formation of a solid phase. A similar effect was observed previously[17(d),(e)] for the asymmetric diastereomeric transformation of 1-α-carboxyethyl-3,3-bis(trifluoromethyl)diaziridine (αS, 1S, 2S) → (αS, 1R, 2R). At the inversion barrier $\Delta G^{\#}$ = 22.5 kcal mol^{-1} (at 25 °C in acetone), crystallisation even at –80 °C gave only the first diastereomer. Analogously, the crystallisation (–6 °C) of N,N'-dinitroso-N,N'-dimethylethylenediamine [an equilibrium 1:1 mixture of *syn–syn* and *syn–anti* rotamers (NO with respect to MeN); the barrier of hindered rotation about the N–N bond $\Delta G^{\#}$ = 23.3 kcal mol^{-1}] gave only the first rotamer (relevant

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§ ^{1}H and ^{13}C NMR spectra were measured at 400.13 and 100.61 MHz, respectively; optical activity was studied on a Polamat A polarimeter.

1 was obtained from PhN(Me)Et and allyl iodide (12 h at 20 °C), yield 82%; from **2** and EtI (1 month at 6 °C, in the dark), yield 36.6%, mp 79–80 °C (CHCl$_3$); for selected monocrystal $[\alpha]_D^{20}$ = –28.8°, $[\alpha]_{578}$ = –29.4°, $[\alpha]_{546}$ = –33.8° (c 0.8, CHCl$_3$). ^{1}H NMR (400.13 MHz, [^{2}H$_6$]acetone) δ: 1.1 (t, 3H, MeC, ^3J 7.0 Hz), 3.85 (s, 3H, MeN), 4.41 (m, 2H, CH_2Me, ABX$_3$ spectrum, $\Delta\nu$ 66.0 Hz, ^2J –13.7 Hz, ^3J 7.0 Hz), 5.05 (m, 2H, CH_2CH, ABX spectrum, $\Delta\nu$ 40.6 Hz, ^2J –13.1 Hz, $^3J_{AX}$ 7.7 Hz, $^3J_{BX}$ 6.4 Hz), 5.49 (dd, 1H, H$_b$, $^3J_{ab}$ 10.1 Hz, $^2J_{ac}$ 2.0 Hz), 5.69 (m, 1H, H$_a$), 5.80 (dd, 1H, H$_c$, $^3J_{ac}$ 16.8 Hz, $^2J_{bc}$ 2.0 Hz), 7.66 and 8.21 (m, 5H, Ph), 8.38 (s, 1H, CHCl$_3$) {for CHCl$_3$ ^{1}H NMR ([^{2}H$_6$]acetone) δ: 7.95}. ^{13}C NMR ([^{2}H$_6$]acetone) δ: 8.17 (qt, *Me*CH$_2$, ^1J 129.3 Hz, ^2J 2.9 Hz), 47.02 (q, MeN, ^1J 143.9 Hz), 63.04 (t, *C*H$_2$Me, ^1J 143.9 Hz), 69.67 (t, *C*H$_2$CH, ^1J 146.7 Hz), 79.22 (d, CHCl$_3$, ^1J 215.1 Hz), 125.12 (d, *C*H=CH$_2$, ^1J 159.8 Hz), 127.83 (t, *C*H$_2$=CH, ^1J 159.1 Hz), 122.36, 129.9, 130.0 and 141.32 (d, d, d and s, Ph, ^1J 162.8, 164.2 and 164.0 Hz). Found (%): N 3.20. Calc. for C$_{12}$H$_{20}$NI·CHCl$_3$ (%): N, 3.32.

2 was obtained from *N*-methylaniline and allyl bromide in abs. MeOH (boiling for 20 h), yield 80%, bp 80 °C (5 torr). ^{1}H NMR (CDCl$_3$) δ: 2.94 (s, 3H, Me), 3.92 (dt, 2H, CH$_2$, ^3J 5.0 Hz, ^4J 1.7 Hz), 5.14 (dq, 1H, H$_b$, $^1J_{ab}$ 10.1 Hz, $^2J_{bc}$ = ^4J = 1.7 Hz), 5.18 (dq, 1H, H$_c$, $^3J_{ac}$ 17.1 Hz, $^2J_{bc}$ = ^4J = 1.7 Hz), 5.85 (ddt, 1H, H$_a$, $^3J_{\mathrm{H_aCH_2}}$ 5.0 Hz, $^3J_{ab}$ 10.1 Hz, $^3J_{ac}$ 17.1 Hz), 6.7, 6.73 and 7.24 (m, 5H, Ph).

3 was identified in the mixture with **1** and **4**. ^{13}C NMR ([^{2}H$_6$]acetone) δ: 47.2 (q, MeN, ^1J 144.0 Hz), 69.05 (t, *C*H$_2$CH, ^1J 147.0 Hz), 125.0 (d, *C*HCH$_2$, ^1J 160.0 Hz), 127.8 (t, *C*H$_2$CH, ^1J 159.0 Hz), 122.0, 129.7, 130.4 and 140.9 (d, d, d, and s, Ph, ^1J 163.0, 164.0 and 164.1 Hz).

4, mp 102–104 °C (MeOH–Et$_2$O), identified with the sample obtained from PhNEt$_2$ and MeI. ^{1}H NMR ([^{2}H$_6$]acetone) δ: 1.15 (t, 6H, MeC, ^3J 7.0 Hz), 3.83 (s, 3H, MeN), 4.37 (m, 4H, 2CH_2Me, ABX$_3$ spectrum, $\Delta\nu$ 47.0 Hz, ^2J –14.1 Hz, ^3J 7.0 Hz), 7.65, 7.70 and 8.12 (m, 5H, Ph). ^{13}C NMR ([^{2}H$_6$]acetone): 8.42 (qt, *Me*CH$_2$, ^1J 127.9 Hz, ^2J 2.9 Hz), 46.95 (q, MeN, ^1J 142.4 Hz), 64.38 (t, *C*H$_2$Me, ^1J 146.8 Hz), 122.82, 130.36, 130.64 and 141.81 (d, d, d and s, Ph, ^1J 162.8, 164.2 and 164.8 Hz).

Asymmetric transformation of (±)-**1** *by stirred crystallisation from a melt*. The single crystal (4.5 mg) was taken from the sample of (±)-**1** (200 mg). The sample and a teflon-coated magnetic stirring bar (l = 8 mm, 6 mm in diameter) were put in a molybdenic glass ampoule (l = 10 cm, 1 cm in diameter), and the single crystal was put in a side arm of the ampoule. The ampoule was evacuated (1 Torr) and cooled with liquid nitrogen. Then, the ampoule was heated to room temperature and filled with CHCl$_3$ vapour, then cooled again and sealed. The sample was heated to melting point, then cooled to 75 °C. The crystal from the arm was transferred to the ampoule, and stirred (800–1000 rpm). After 2–5 h, full sample crystallisation occurred. The ampoule was opened, the sample dissolved in CHCl$_3$ and the optical rotation of the solution was measured. The experiment was repeated three times with the following results: $[\alpha]_D^{18}$ = +28.0, –28.2 and +28.4° (c 0.8, CHCl$_3$), ee 97.2, 97.9 and 98.5%, respectively.

data will be published elsewhere). Nevertheless, an increase in the degree of asymmetric conversion with temperature should be expected. W. A. Bonner, commenting the work by Havinga as early as 1972, wrote:[25(*a*)] "...With gradual evaporation of the solvent, all of the original racemate might in principle crystallise as the (–)-isomer, provided that the (+)-isomer has not itself undergone chance nucleation in the meantime." Indeed, highly enriched (+)-**1**, ee 31%, can be obtained by crystallisation from boiling chloroform up to almost complete evaporation. In stirred crystallisation[3,28] (500–600 rpm), ee increased up to 51% and became even higher, up to 95%, on the addition of a single crystal from the starting mixture at the step of semi-evaporation. Stirred crystallisation from a melt (in a sealed ampoule with $CHCl_3$ vapour) with the addition of a single crystal to the melt cooled to 75 °C gave a somewhat greater effect (ee 98.5%). Thus, the racemic mixture of **1** was almost fully converted into one enantiomer, and the idea proposed by Havinga was completely supported.

Salt **1** was studied by X-ray diffraction analysis,[¶] initially, with the use of a random crystal and, subsequently, with a crystal known to be optically active in order to determine the absolute configuration. The crystal structure of **1** contains the (*S*)-(+) quaternary ammonium cation, the iodide anion and the solvate chloroform molecule [Figure 3(*a*)].

The most striking features of **1** were found within the crystal packing analysis. In addition to the weak Cl···H contacts [Cl···H 2.83 Å, Cl···H–C 172 and 137°, for Cl(2) and Cl(3), respectively] between the $CHCl_3$ molecule and the allyl hydrogens of the cation [even shorter intramolecular constants Cl···H (2.59 Å) were observed for the Ti complexes],[34] the former also takes part in the formation of shortened contacts with the I^- anion. The $CHCl_3$ molecule is assembled with the I^- not only by the short H(13)···I contact [H(13)···I(1′) ($-1-x$, $^1/_2+y$, $^1/_2-z$) 2.81 Å, C(13)–H(13)···I(1′) 148°] but also by 'long' and 'short' I···Cl contacts [C(13)–Cl(3)···I(1) 3.599(2) Å, C(13)–Cl(3)–I(1) 168.6(1)°; Cl(1)···I(1″) ($-^1/_2-x$, $1-y$, $^1/_2+z$) 3.889(2) Å, C(13)–Cl(1)···I(1″) 155.1(1)°] [Figure 3(*b*)]. Thus, the crystal packing in **1** can be described as a 3D framework formed by the $CHCl_3$ molecule and the I^- anion assembled by short I···H and I···Cl contacts, with quaternary ammonium cations located in the framework cavities [Figure 3(*c*)].

It is noteworthy that according to CCDB (release 2000) the Cl(3)···I(1) contact in **1** is one of the shortest for the Cl···I^- type. Taking into consideration the difference in the van der Waals radii of I and Cl atoms (0.26 Å),[35(*a*)] this contact is comparable with the Cl···Cl one in the crystal of chlorine (3.294 Å).[35(*b*)]

The recent topological analysis of the electron density function [$\rho(r)$] within the quantum theory of 'Atoms in molecules' (QTAM)[36(*a*)] have shown that such a type of the halogen··· halogen shortened contacts can be described as a donor–acceptor interaction of a lone pair with an antibonding orbital.[36(*b*),(*c*)] The assumption of such a character for the I(1)···Cl(3) interaction will imply the elongation of the corresponding C–Cl bond, while the observed C(13)–Cl(3) bond length is practically the same [1.761(3) Å] as the remaining [1.768(3) and 1.766(3) Å].

In order to investigate the character of short I···Cl contacts, we performed the QTAM analysis in the $HCl_2C–Cl_a\cdots I^-$ fragment on the basis of calculations at the MP2 level of theory (Gaussian 94) using the 6-31G* basis for Cl, C and H atoms

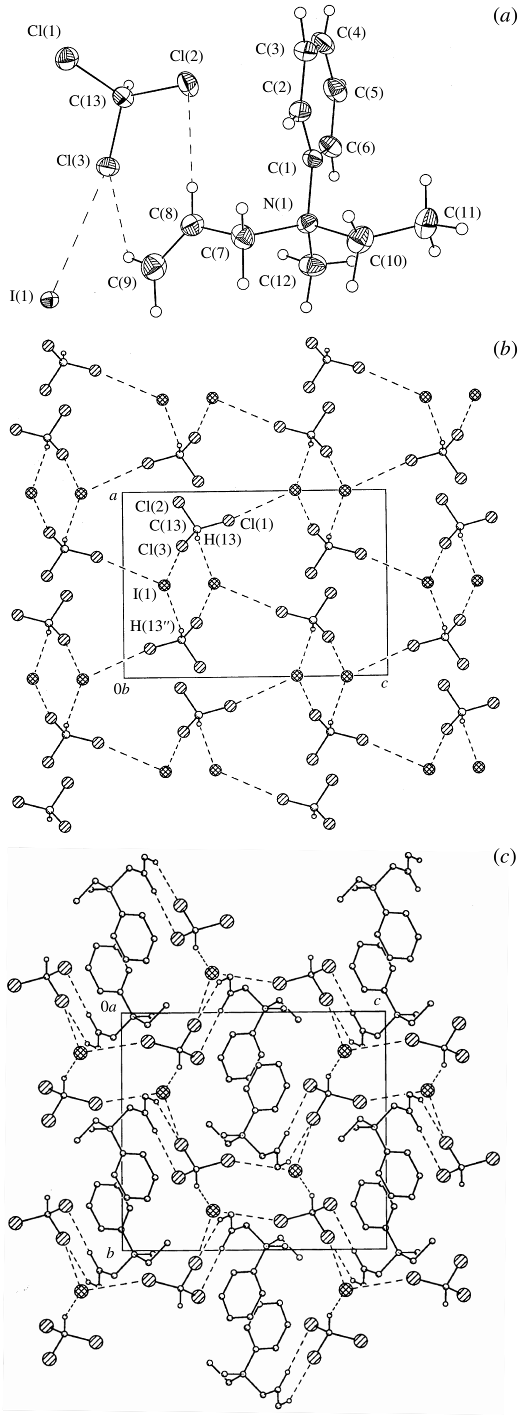

Figure 3 (*a*) The view of **1** [ellipsoids plot (50%)] illustrating the contents of the unit cell. The main bond lengths (Å): N(1)–C(1) 1.490(3), N(1)–C(7) 1.546(3), N(1)–C(10) 1.541(3), N(1)–C(12) 1.490(3), C(13)–Cl(1) 1.768(3), C(13)–Cl(2) 1.766(3), C(13)–Cl(3) 1.761(3); bond angles (°) C(1)–N(1)–C(12) 113.6(2), C(12)–N(1)–C(10) 109.3(2), C(1)–N(1)–C(10) 109.3(2), C(12)–N(1)–C(7) 107.3(2), C(1)–N(1)–C(7) 111.0(2), C(10)–N(1)–C(7) 105.9(2), Cl(1)–C1(3)–Cl(2) 110.2(1), Cl(1)–C(13)–Cl(3) 110.6(2), Cl(2)–C(13)–Cl(3) 111.1(2). (*b*) H···I^- and I^-···Cl contacts. (c) The crystal structure of **1**.

[¶] *Crystallographic data for* **1**: crystals of $(C_{12}H_{18}N)(I)(CHCl_3)$ are orthorhombic at 100 K, space group $P2_12_12_1$, $a = 9.8591(6)$ Å, $c = 13.7637(9)$ Å, $V = 1710.5(2)$ Å^3, $Z = 4$, $M = 422.54$, $d_{calc} = 1.641$ g cm^{-3}, μ(MoKα) = = 23.26 cm^{-1}, $F(000) = 832$. The intensities of 17743 reflections were measured with a Smart 1000 CCD diffractometer at 100 K [λ(MoKa) = = 0.71072 Å, ω-scans with a 0.3° step in ω and 10 s per frame exposure, $2\theta < 60°$], and 4878 independent reflections ($R_{int} = 0.0296$) were used in the further refinement. The absorption correction was carried out semi-empirically from equivalents using the Sadabs program. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation. The absolute (+)-configuration of the N(1) atom in **1** was confirmed by estimating the Flack absolute parameter which, in case of (*S*) configuration of N(1), has a value close to zero with a rather small *e.s.d.*, 0.00(2). The refinement converged to $wR_2 = 0.0611$ and GOF = 1.062 for all independent reflections [$R_1 = 0.0234$ was calculated against F for 4623 observed reflections with $I > 2\sigma(I)$]. The number of the refined parameters was 218 (the ratio of the refined parameters for observed reflections was more than 20). All calculations were performed using SHELXTL PLUS 5.0 on IBM PC AT. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2001. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/78.

and 3-21G* for I atoms. This calculation leads to the geometry of the I···Cl contact (Cl_a···I, C–Cl_a···I equal to 3.476 Å and 177.87°, respectively) similar to that found for I(1)···Cl(3) in **1**. In spite of the shorter I···Cl contact observed in the *ab initio* calculation of HCl_2C–Cl_a···I^- the C–Cl_a bond, instead of the expected elongation, is significantly shortened (1.752 Å) in comparison with remaining (1.784 Å).

The QTAM analysis of the HCl_2C–Cl···I^- revealed that critical points (CP) (3,–1) (the necessary and sufficient condition of the chemical bond[36(*a*)]) are observed on C–Cl and C–H bonds as well as on the I···Cl contact. All bonds in the $HCCl_3$ molecule are characterised by negative values of the laplacian of $\rho(r)$ [$\nabla^2\rho(r)$] and local energy density $E(r)$ in CP (3,–1); that is, the characteristic of the shared type of interaction. On the contrary, the I···Cl contact is characterised by positive values of both $\nabla^2\rho(r)$ and $E(r)$ in CP (3,–1) thus indicating the closed-shell type of this interaction. It is noteworthy that the values of $\rho(r)$ (0.085 eÅ^{-3}) and $\nabla^2\rho(r)$ (0.839 eÅ^{-5}) for CP (3,–1) of the I···Cl contact are close to those obtained earlier for the Cl···Cl contact in chlorine (0.062 eÅ^{-3}, 0.805 eÅ^{-5})[36(*b*)] and ClF (0.135 eÅ^{-3}, 1.06 eÅ^{-5})[36(*c*)] crystals. Taking into account that the value of $\rho(r)$ correlates with the bond order,[36(*a*)] this observation means that the I···Cl interaction is characterised by the comparable strengths with the Cl···Cl (3.294 Å)[35(*b*)] one in the chlorine crystal. The same conclusion can also be made on the basis of the Cl···Cl and I···Cl contacts.

An analysis of the C–Cl bond polarity by means of the difference of bonded radii [the distance from the nucleus to CP (3,–1)] have revealed that the C–Cl_a bond is characterised by the lowest one (0.14 Å) in comparison with remaining C–Cl bonds (0.22 Å). Thus, the observed shortening, instead of the expected elongation, of the C–Cl_a bond is the result of the reverse polarity, which is induced by the iodine negative charge.

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