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Crystal and molecular structure of the levorotatory (1*R*,2*S*)-ephedrinium (*S*)-*t*-butylsulfinylacetate: a definitive proof of the absolute configuration of enantiomeric *t*-butyl methyl sulfoxides

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Abstract

The levorotatory enantiomer of *t*-butylsulfinylacetic acid **3** was obtained in the reaction of the α-carbanion of (+)-*t*-butyl methyl sulfoxide **1** with carbon dioxide. The same enantiopure form of the acid **3** was isolated from its diastereomerically pure levorotatory salt **5** with (−)-(1*R*,2*S*)-ephedrine. The structure of this salt was determined by X-ray analysis and the absolute configuration (*S*) at sulfur was ascribed to the *t*-butylsulfinylacetate anion. Consequently, the absolute configuration (*S*) was assigned to the acid (−)-**3** and its precursor (+)-*t*-butyl methyl sulfoxide **1**.

1. Introduction

The first synthesis and assignment of the absolute configuration (*R*) to (−)-*t*-butyl methyl sulfoxide **1** were reported by Mislow and his coworkers as early as 1965.[1,2] The configurational assignment was based on the assumption that the reaction of the diastereomerically enriched (−)-O-menthyl methanesulfinate **2** with *t*-butylmagnesium chloride as well as with other alkyl and aryl Grignard reagents occurs with inversion of configuration at sulfur. Analysis of the CD spectra of (−)-**1** and a series of optically active alkyl methyl sulfoxides prepared in a similar way strengthened this view.

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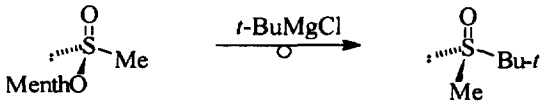


(1)

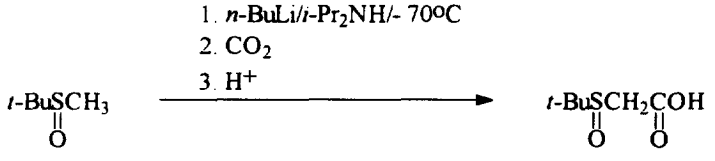
(-)-(*R*)-**2** (-)-(*R*)-**1**

Recently, the enantiopure forms of the sulfoxide **1** have been obtained by Alcudia et al.[3] in the reaction of the diastereomerically pure DAG-sulfinates with Grignard reagents and by Evans[4] and his coworkers from N-sulfinyl oxazolidinones and Grignard reagents. In both cases the nucleophilic substitution reactions have been assumed to proceed with inversion of configuration at sulfur, although in the initial work of the Spanish group[3] retention was reported.

Since nucleophilic substitution at sulfinyl sulfur may occur with retention of configuration[5] and because in our studies[6] aimed at providing unequivocal proof of retention of configuration in the reaction of chiral sulfinates with alkyl Grignard and lithium reagents the sulfoxide **1** became the configurational standard, we decided to determine its absolute configuration by the method which is unquestionable, i.e. by X-ray analysis. Unfortunately, the enantiomeric sulfoxides **1** are liquids and their absolute configurations cannot be determined directly by X-ray crystallographic measurements. However, to solve this difficulty we decided to obtain the crystalline derivative from optically active sulfoxide **1**, suitable for crystallographic analysis, in a reaction which does not occur at sulfur and does not change the configuration of the starting sulfoxide **1**. The determination of the absolute configuration of the enantiomeric sulfoxides **1** by such a combined chemical–crystallographic method is reported in this paper.

2. Results and discussion

In the first step, the α-carbanion generated from optically active *t*-butyl methyl sulfoxide **1**, partially enriched in the dextrorotatory enantiomer, was treated with carbon dioxide. The enantiomeric excess of the sulfoxide **1** was determined by the analysis of its ^{1}H NMR spectrum measured in the presence of (+)-(*R*)-*t*-butylphenylphosphinothioic acid **6** as a chiral solvating agent.[7] The work-up procedure involving lyophilization, and ion exchange chromatography afforded the expected optically active (−)-*t*-butylsulfinylacetic acid **3**.

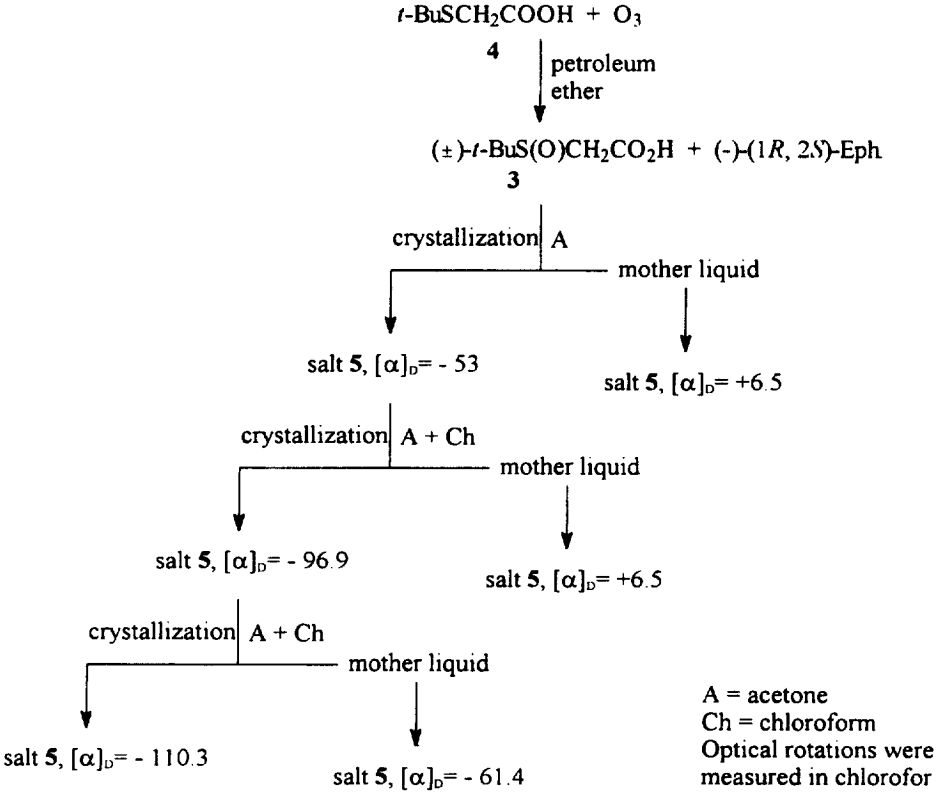


(2)

(+)-**1**, $[\alpha]_D$= +2.5 ($CHCl_3$) (-)-**3**, $[\alpha]_D$= - 18.0 ($CHCl_3$)

In the next step, an attempt was made to establish its absolute configuration by X-ray crystal structure analysis. To this end, the racemic acid (±)-**3** was obtained by oxidation (ozone) of *t*-butylsulfanylacetic acid **4** in almost quantitative yield and was found to form crystalline diastereomeric salts with (−)-(1*R*,2*S*)-ephedrine. The classical resolution procedure shown in Scheme 1 allowed the isolation after three consecutive crystallizations the diastereomerically pure salt **5** having $[\alpha]_D$=−110.3 ($CHCl_3$) and m.p. 170–173°C. Further crystallization of this salt did not change its specific rotation and melting point. Additional evidence of its full diastereomeric purity was given by its ^{1}H NMR spectra measured in the

presence of (+)-(*R*)-*t*-butylphenylphosphinothioic acid **6** as a chiral solvating agent.[7] Whereas the ^{1}H NMR spectrum of the salt having $[\alpha]_D=-96.6$ ($CHCl_3$) measured in the presence of equimolar amounts of (+)-(*R*)-**6** showed two resonance absorptions for the *t*-butyl protons at $\delta=1.2894$ and 1.2834 ppm with the intensity ratio 3.5:1, in the ^{1}H NMR spectrum of the salt **5** with $[\alpha]_D=-110.3$ ($CHCl_3$) recorded under similar conditions, only one singlet absorption at $\delta=1.2961$ ppm was obserwed. This indicated that the latter salt had been obtained in a diastereomerically pure state.



Scheme 1.

The X-ray crystal structure determination carried out on a single crystal of the above salt revealed unequivocally that the absolute configuration at the stereogenic sulfur atom in the acid **3** anion is (*S*) as it is clearly seen from Fig. 1 which shows the thermal ellipsoidal plot of the salt (−)-**5** with the atom numbering scheme. The unit cell and hydrogen bonds, which are formed between the carboxylic group of the acid **3** anion and hydroxy and ammonium groups of the ephedrinium cation with the corresponding O4–H4···O2, N1–H11···O3 and N1–H12···O3 distances of 1.92(5), 1.95(3) and 1.93(3), respectively, are shown in Fig. 2. Interestingly, the sulfinyl oxygen atom is not involved in the hydrogen bond formation.

Finally, to correlate the absolute configuration of the acid **3** with that of the sulfoxide **1**, the salt (−)-**5** was acidified and the enantiopure *t*-butylsulfinylacetic acid (−)-**3** was isolated whose absolute configuration is (*S*). Taking into account the fact that the acid (−)-(*S*)-**3** was obtained from the sulfoxide (+)-**1** in the reaction (Eq. 2) which occurs at the α-carbon atom without bond breaking around sulfur, the absolute configuration (*S*) should be ascribed to the sulfoxide (+)-**1** and correspondingly (*R*) to the sulfoxide (−)-**1**. In this way we confirmed unequivocally the original configurational assignments to enantiomeric *t*-butyl methyl sulfoxides **1** proposed by Mislow and dispelled some recent doubts

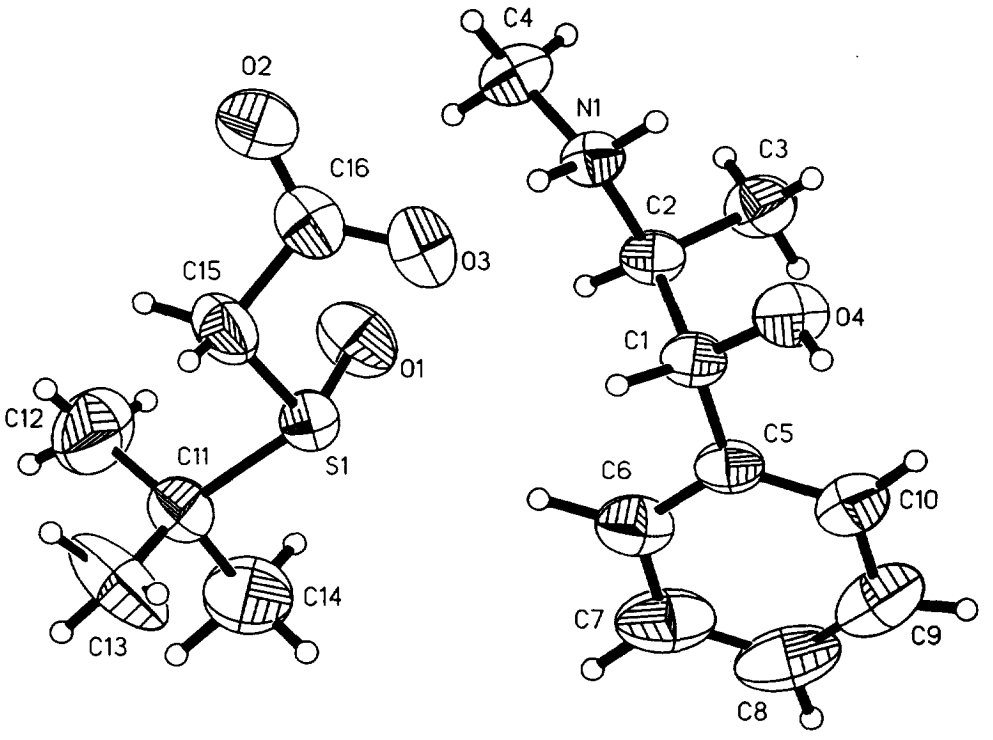
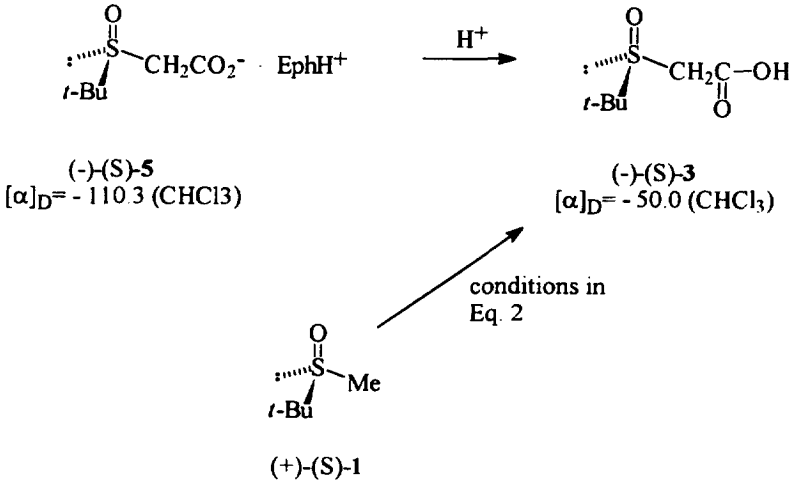


Fig. 1. Thermal ellipsoidal plot of the levorotatory salt **5** of t-butylsulfinylacetic acid **3** with (1*R*,2*S*)-ephedrine with atom numbering scheme.

concerning their correctness.[3] It also means that inversion of configuration at sulfur always occurs in the reaction of optically active sulfinates with Grignard reagents (the Andersen method).[6] Moreover, it confirms the previous assigment of the *R* absolute configuration for the levorotatory enantiomer of methyl *t*-butyl sulfoxide reported by Kagan et al.[8]



(3)

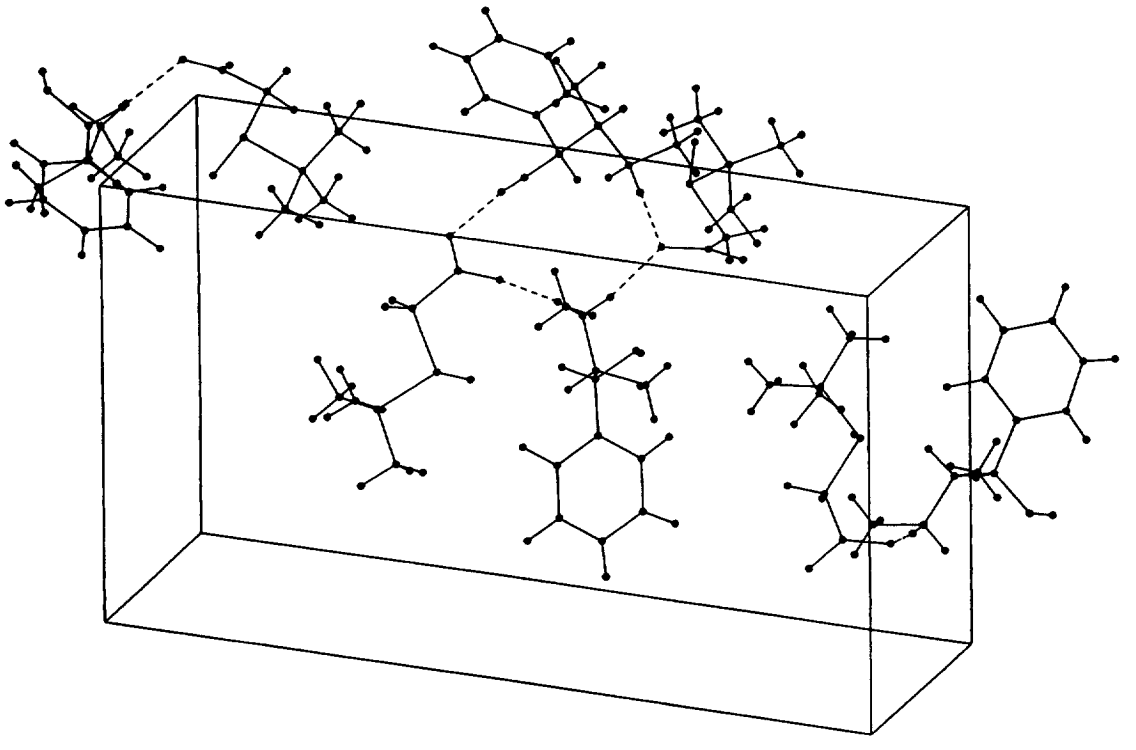


Fig. 2. The unit cell and hydrogen bonding system.

3. Experimental

Melting points were determined on a Boethius PHMK apparatus and were uncorrected. NMR spectra (200 MHz) were recorded with a Bruker AC 200 spectrometer. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter. Reactions were monitored by TLC chromatography (Merck Kieselgel $60F_{254}$). Column chromatography was done on Merck $60F_{254}$ silica gel (70–230 mesh).

3.1. Reaction of (+)-t-butyl methyl sulfoxide 1 with carbon dioxide — preparation of (−)-t-butylsulfinylacetic acid 3

To a stirred solution of diisopropylamine (0.4 g, 4 mmol) in 50 mL of dry THF, a solution of *n*-butyllithium (4 mmol) in hexane was added at −78°C. After stirring for 20 min at this temperature, a solution of (−)-**1**, $[\alpha]_D$=+2.5 (c=1.0, $CHCl_3$), (0.37 g, 3.1 mmol) was added. The reaction mixture was stirred for 20 min at −78°C and then carbon dioxide was passed through the reaction solution for 15 min. After slowly raising the temperature to ca. 20°C, the solvents were removed in vacuo. To the residue, 5 mL of 1 N NaOH was added and the water solution was extracted with ether (2×15 mL). Lyophilization of the water phase afforded a solid residue from which the acid (−)-**3** was liberated by ion exchange chromatography; 75 mg (20%), $[\alpha]_D$=−18.0 (c=1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$), δ=1.35 (s, 9H, $(CH_3)_3C$), 3.40 and 3.64 (AB system, J_{AB}=15.05 Hz, 2H, CH_2), 4.4–4.60 (s, 1H, COO*H*). ^{13}C NMR ($CDCl_3$), δ=30.9, 48.1, 118.3. HRMS (EI), M^+: calcd for $C_6H_{12}O_3S$ 164.0429; found 164.0432.

3.2. Synthesis of racemic t-butylsulfinylacetic acid 3

A three-neck round-bottomed flask was charged with *t*-butylsulfinylacetic acid (13 g, 88 mmol) and petroleum ether (300 mL). A stream of ozone (rate 0.1 mol/h) was passed through the above solution at room temperature. The sulfinylacetic acid **3** formed during the reaction was deposited on the walls of the reaction flask. After 90 min the solvent was removed by decantating and the remaining white solid was dissolved in methylene chloride (50 mL). Then, petroleum ether (100 mL) was added and the solution was cooled in a refrigerator for 1 h. The analytically pure acid (±)-**3**, deposited as white crystals, was isolated after decantation of the solvents, 11.5 g, 80%. Its spectral and analytical data (^{1}H and ^{13}C NMR, HRMS) fully supported the structure **3**.

3.3. Preparation of the levorotatory salt 5 of (−)-(S)-t-butylsulfinylacetic acid 3 with (−)-(1R,2S)-ephedrine

The racemic acid **3** (1.64 g, 10 mmol) and (−)-(1*R*,2*S*) ephedrine (1.65 g, 10 mmol) were dissolved in acetone (12.5 mL) and the solution was kept at 3–5°C in a refrigerator for 2 h. The white crystals of the salt **5** formed were isolated by removal of the solvent by decantation [1.9 g, $[\alpha]_D=-52.95$ (c=1.7, $CHCl_3$)]. Next, they were dissolved at ca. 30°C in a mixture of acetone (50 mL) and chloroform (15 mL) and kept in a refrigerator for 12 h. The white crystals formed were filtered off and dried in vacuo [0.81 g, $[\alpha]_D=-96.9$ (c=0.65, $CHCl_3$)]. The crystalline salt **5** was again dissolved at ca. 30°C in a mixture of acetone (40 mL) and chloroform (15 mL) and left to crystallize at room temperature for 48 h. Filtration gave the diastereomerically pure salt **5** [0.3 g, $[\alpha]_D=-110.3$ (c=0.35, $CHCl_3$), m.p. 170–173°C]. ^{1}H NMR ($CDCl_3$): δ=1.10 (d, *J*=6.75 Hz, 3H, $N^+CH(CH_3)CH$), 1.26 (s, 9H, $(CH_3)_3C$), 2.80 (s, 3H, N^+CH_3), 3.37–3.50 (m, 3H, CH_2CO_2 and $N^+(CH_3)CH(CH_3)$), 5.37 (d, *J*=1.35 Hz, 1H, CH(OH)Ph), 7.24–7.43 (m, 5H, aromatic). ^{13}C NMR ($CDCl_3$): δ=15, 23.01, 31, 42.07, 52.8, 61.5, 70.5, 108.3, 125.8, 127.2, 128.2, 217.4. HRMS (EI) M^+: calcd for the acid **3** anion $C_6H_{11}O_3S$ 163.0429; found 163.0432; M^+ calcd for the amine cation $C_{10}H_{16}NO$ 166.1232; found 166.1231.

3.4. Isolation of (−)-(S)-t-butylsulfinylacetic acid 3 from the salt (−)-5

The salt **5** [50 mg, $[\alpha]_D=-110.3$ (c=0.35, $CHCl_3$)] obtained as above was dissolved in water (10 mL) and acidified with sulfuric acid to pH 2. Lyophilization of the solution gave a white powder which was extracted with ether (4×15 mL). Evaporation of the solvent in vacuo gave the analytically pure acid **3**, [17 mg, $[\alpha]_D=-50.0$ (c=2.1, $CHCl_3$)]. Its spectral and analytical data (^{1}H and ^{13}C NMR, HRMS) fully supported the structure **3**.

3.5. Crystal structure of (−)-(1R,2S)-ephedrinium (S)-t-butylsulfinylacetate 5

The crystal and molecular structure of the salt (−)-**5** was determined using data collected on a CAD4 diffractometer. The compound crystallized in the orthorhombic system, in space group $P2_12_12_1$. An asymmetric part of the unit cell constitutes one anion and one cation. Crystal data and experimental details are shown in Table 1. Intensity data were collected at room temperature using a diffractometer with graphite monochromatized CuKα radiation. Lattice constants were refined by least-squares fit of 25 reflections in θ range 21.79–27.72°. Because the decline in intensities of three standard reflections (−2, 3, −8; −3, 3, 4; −1, −5, −7) was 7.9% during 51.0 h of exposure time, the DECAY correction was applied.[10] A total of 3387 observed reflections (with $I \geq 3\sigma(I)$) were used to solve the structure by

Table 1
Crystal data and experimental details

Moleular formula		$C_{16}H_{27}NO_4S$
$[\alpha]_D$		- 110.3($CHCl_3$)
Space group		$P2_12_12_1$
a (Å)		6.821(20
b (Å)		12.312(3)
c (Å)		21.685(4)
V (Å^3)		1821.1(8)
Z		4
D_c (g/cm^3)		1.202
μ (cm^{-1})		16.75
Crystal dimensions (mm)		0.35, 0.3, 0.4
Maximum 2θ (°)		150
Radiation, λ (Å)		CuKα, 1.54178
Scan mode		ω/2θ
Scan width (°)		0.71+0.14*tanθ
hkl ranges	h =	-8 0
	k =	-15 0
	l =	-27 27
DECAY correction		
	minimum	1.00003
	maximum	1.04184
	average	1.02068
No. of reflections:		
	unique	3522
	with $I \geq 3\sigma(I)$	3387
No. of parameters refined		309
Largest diff. peak (eÅ^{-3})		0.461
Largest diff. hole (eÅ^{-3})		-0.701
R		0.0453
R_w		0.0475
η		1.04(4)[9]
Absolute configuration at		
	S1 atom	S
	C1 atom	R
	C2 atom	S

direct methods and to refine it by full matrix least-squares using *F*s. Hydrogen atoms were found on a difference Fourier map and refined with isotropic thermal parameters. Anisotropic thermal parameters were refined for all nonhydrogen atoms. The final refinement converged to R=0.0453 with weight $1/(\sigma^2(F) + 0.000079 * F^2)$ for 309 refined parameters, with inclusion of extinction parameter was 0.0086(9)).[9]

The structural solution was carried out with the Enraf–Nonius SDP crystallographic computing package[10] and SHELXS-86 program;[11] structure refinement with SHELXTL package.[12] Full crystallographic data, with values of F_{obs} and F_{calc}, are deposited at the Cambridge Crystallographic Data Centre.[13]

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