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Structure, Solid-State Photochemistry and Reactivity in Asymmetric Synthesis of 3,4-Bis(diphenylmethylene)-N-methylsuccinimide

BY FUMIO TODA* AND KOICHI TANAKA

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790, Japan

AND ZAFRA STEIN AND ISRAEL GOLDBERG*

School of Chemistry, Sackler Faculty of Exact Sciences, Tel-Aviv University, 69978 Ramat-Aviv, Israel

Abstract

The synthesis and structural features of 3,4-dihydro-3,4-bis(diphenylmethylene)-N-methylsuccinimide [3,4-bis-(diphenylmethylene)-1-methyl-2,5-pyrrolidinedione $(6b)$, $C_{31}H_{23}NO_2$, $M_r = 441.53$] are described. $(6b)$ crystallizes at room temperature in three polymorphic forms: (A) monoclinic, $P2_1$, $a = 11.640(3)$, $b = 9.257(2)$, $c = 12.103(4)$ Å, $\beta = 114.83(1)°$, $V = 1183.6(6)$ Å^3, $Z = 2$, $F(000) = 464$, $D_x = 1.239$ g cm^{-3}, $\mu = 0.72$ cm^{-1}, $R_F = 0.077$ for 1560 observations $[I > 3\sigma(I)]$; (B) orthorhombic, $Pbcn$, $a = 9.964(1)$, $b = 20.181(3)$, $c = 11.622(3)$ Å, $V = 2337.0(7)$ Å^3, $Z = 4$, $F(000) = 928$, $D_x = 1.255$ g cm^{-3}, $\mu = 0.73$ cm^{-1}, $R_F = 0.044$ for 1466 observations $[I > 3\sigma(I)]$; (C) monoclinic, $P2_1/n$, $a = 9.485(3)$, $b = 11.014(2)$, $c = 22.945(3)$ Å, $\beta = 98.62(2)°$, $V = 2369.9(9)$ Å^3, $Z = 4$, $F(000) = 928$, $D_x = 1.238$ g cm^{-3}, $\mu = 0.72$ cm^{-1}, $R_F = 0.060$ for 2200 observations $[I > 3\sigma(I)]$. The $(6b)$ molecule adopts a helical (prochiral) configuration with approximate C_2 symmetry in order to accommodate the steric hindrance between the aryl substituents; the conformation is very similar in the three polymorphs. Transformations between the different polymorphs can be induced easily, and it is possible to vary the amount of chiral polymorph in the crystallization mixture by seeding techniques and the use of acidic additives. Crystalline $(6b)$ undergoes a photocyclization reaction to yield N-methyl-1,1,4-triphenyl-1,2-dihydronaphthalene-2,3-dicarboximide $(8b)$. In the observed conformation of $(6b)$, the intramolecular distances between the unsaturated carbon sites which join during the photochemical reaction are within 3.27–3.38 Å. The solid-state photoreaction of the chiral
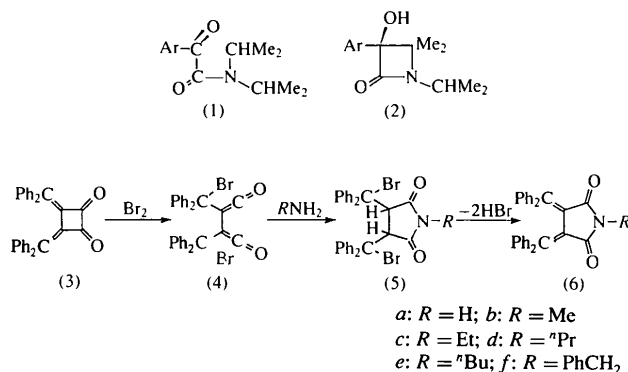
polymorph A gives an optically active molecular product $(8b)$ of 64% enantiomeric excess (e.e.), and represents a chiral enrichment process assisted by the crystal medium. The corresponding photochemical reactions with the racemic polymorphs B and C yield racemic $(8b)$.

Introduction

Several successful examples of the so-called 'absolute' asymmetric synthesis (Green, Lahav & Rabinovich, 1979; Vaida, Popovitz-Biro, Leiserowitz & Lahav, 1990) by solid-state photoirradiation, applied to chiral crystals of achiral compounds, have accumulated in recent years (*e.g.* Sakamoto *et al.*, 1993; Roughton, Muneer & Demuth, 1993; Sekine, Hori, Ohashi, Yagi & Toda, 1989; Kaupp & Haak, 1993, and references therein). Molecules, which in solution equilibrate rapidly between inverted configurations, adopt in a chiral crystalline environment (even in the absence of external chiral inducing agents) a chiral arrangement, and this chirality can be subsequently frozen by photoreaction to give a molecularly chiral product. A suitable example is provided by the N,N-dialkylarylglyoxamide system (1). Crystalline solids of selected derivatives of (1) yield, upon irradiation, the corresponding derivatives of optically active β-lactams (2) of very high optical purity in almost quantitative yields (Scheme 1; Toda & Miyamoto, 1993; Toda, Soda & Yagi, 1987). The photoreaction and ring closure involves the two carbonyl groups of (1). The formation of chiral crystals of (1) was found to be very sensitive to the nature of the substituent, and could be obtained only for the glyoxamide which is substituted with an isopropyl group on the N atom, and for selected substitutions on the aryl ring (the *meta*-substituted compounds revealed a higher propensity to

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* Authors to whom correspondence should be addressed.

form chiral solids and yield optically active β-lactams, than the other isomers). An asymmetric distortion of the molecular structure may also enhance in certain cases the formation of chiral materials. Such a constraint can be achieved, for example, in biaryl systems, or in molecules overcrowded by aryl groups. The observed transformation of racemic crystals of 1,1'-binaphthyl to chiral ones provides a pioneering reference in this context (Wilson & Pincock, 1975). This idea led us to the preparation of a series of new succinimide derivatives (6) from 3,4-bis(diphenylmethylene)cyclobutanedione (3), in which the steric hindrance between the two inner phenyl groups causes a helical twist of the molecular structure (Scheme 1). Structural investigations of the (6b) derivative have confirmed that this compound has indeed an asymmetric molecular structure, and that it forms a chiral polymorph in addition to two racemic ones. Irradiation of the chiral crystal of (6b) gave an optically active photocyclization product. Interconversion among the chiral and the racemic crystals, and the X-ray structures of these materials have been investigated in detail, and are presented below.

30 min. Subsequent evaporation of the solvent and crystallization from acetone yielded a mixture of three types of crystals, chiral crystals A as orange hexagonal plates, racemic crystals B (m.p. 575 K) as orange rectangular plates, and racemic crystals C (m.p. 580 K) as yellow rectangular plates in ca 1:1:1 ratio (total 8.0 g, 93% yield). By heating to 533 K, A was converted to C before melting. The different crystal types could be resolved mechanically. The A, B and C crystals showed the same spectral data: IR 1740, 1690 and 1565 cm^{-1}; UV 257 (ε, 50 600), 309 (35 000) and 398 nm (21 500); ^{1}H NMR δ 3.0 (s, Me, 3H), 6.4–7.5 (m, Ph, 20H). Analysis: calc. for C$_{31}$H$_{23}$O$_2$N: C 84.33, H 5.25, N 3.17; found for crystal A: C 84.18, H 5.19, N 3.19.

Preparation of 3,4-bis(diphenylmethylene)succinimide (6a), and its various derivatives N-ethyl- (6c), N-n-propyl- (6d), N-n-butyl- (6e) and N-benzyl-3,4-bis(diphenylmethylene)succinimide (6f). Ammonia gas was bubbled into a solution of (3) (2.0 g, 4.85 mmol) and Br$_2$ (2.0 g, 12.5 mmol) in CCl$_4$ (100 ml) for 30 min at room temperature. The resulting solution was evaporated, after crystallization from acetone, using crystals of (6a) as orange prisms (0.7 g, 34% yield, m.p. 551–553 K). Replacement of the ammonia reagent by a suitable amine derivative allows the synthesis of (6c) as yellow prisms (quantitative yield, m.p. 558 K), (6d) as yellow prisms (47% yield, m.p. 5361 K), (6e) as yellow needles (81% yield, m.p. 517 K), and (6f) (85% yield, m.p. 512–514 K). Neither (6a) nor (6c–f) formed chiral crystals.

Solid-state photochemistry

Photoreaction of (6b) *in the solid state.* Single pieces of the chiral and racemic crystals A, B and C were powdered for this reaction in order to study separately the behavior of the individual polymorphs. Irradiation of 7 mg of powdered A for 50 h, and crystallization of the product from a small amount of isopropanol, yielded colorless prisms of (8b) (5 mg, 71% yield, m.p. 541–547 K) in 64% e.e. {[α]$_D$ +108° (ca 0.05, CHCl$_3$)}. Spectal data of (8b): IR 1750 and 1685 cm^{-1}; UV 244 (ε 13 700) and 309 nm (13 600); ^{1}H NMR δ 2.9 (s, Me, 3H), 4.7 (s, CH, 1H) and 6.8–7.5 (m, Ph, 19H). Irradiation of powdered B and C, under similar experimental conditions, yielded racemic (8b) with 40–50% yield (m.p. 558–560 K).

Photoreaction of (6a) *and* (6c–f) *in the solid state.* Irradiation of powdered solids (6c–f) for 50 h yielded the corresponding photocyclization products as colorless crystals of (8c) (10% yield, m.p. 535–538 K), (8d) (29% yield, m.p. 494–496 K), (8e) (70% yield, m.p. 497–498 K) and (8f) (60% yield, m.p. 499–502 K), respectively. Products (8c–f) showed very similar IR and UV spectra to those of (8b); those of the (8f) derivative were reported previously (Toda, Nakaoka, Yuwane & Todo, 1973). Analyses: (8c), calc. for C$_{32}$H$_{25}$O$_2$N: C 84.37, H 5.53, N 3.08; found: C 84.22, H 5.42, N 2.95. (8d), calc.

Experimental

General considerations

Photoreactions were carried out by irradiation of powdered crystals using a high-pressure Hg lamp at room temperature. Melting points are uncorrected. IR, UV and ^{1}H NMR spectra were measured in Nujol mulls, CHCl$_3$ and CDCl$_3$, respectively. The optical purity of (8b) was determined by HPLC, using a column containing an optically active solid phase, Chiralpak AS (available from Daicel Chemical Industries Ltd, Himeji, Japan), and a mixture of hexane–ethanol (95:5) as eluant. Elemental analyses were performed on the Perkin–Elmer 2400 CHN elemental analyzer.

Synthesis

Preparation of 3,4-bis(diphenylmethylene)-N-methyl-succinimide (6b). A solution of (3) (8.0 g, 19.4 mmol), Br$_2$ (8.0 g, 50 mmol) and CH$_3$NH$_2$ (20 g, 645 mmol) in CCl$_4$ (250 ml) was stirred at room temperature for

Table 1. *Summary of crystal data, data collection, solution and refinement details for* (6b) ($C_{31}H_{23}O_2N$, $M_r = 441.53$) *in the various polymorphs A, B and C*

Crystal	A	B	C
Crystal data			
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_1$	$Pbcn$	$P2_1/n$
a (Å)	11.640 (3)	9.964 (1)	9.485 (3)
b (Å)	9.257 (2)	20.181 (3)	11.014 (2)
c (Å)	12.103 (4)	11.622 (3)	22.945 (3)
α (°)	90.0	90.0	90.0
β (°)	114.83 (1)	90.0	98.62 (2)
γ (°)	90.0	90.0	90.0
Z	2	4	4
V (Å³)	1183.6 (6)	2337.0 (7)	2369.9 (9)
$F(000)$	464	928	928
D_x (Mg m⁻³)	1.239	1.255	1.238
No. of reflections for cell parameters	25	25	24
2θ range for cell parameters (°)	8.3–11.0	9.2–12.3	8.4–11.1
μ (cm⁻¹)	0.72	0.73	0.72
Crystal form	Hexagonal plates	Rectangular plates	Rectangular plates
Crystal size (mm)	0.25 × 0.25 × 0.15	0.30 × 0.30 × 0.10	0.35 × 0.25 × 0.10
Crystal color	Orange	Orange	Yellow
Data collection			
Diffractometer		Enraf–Nonius CAD-4	
No. of measured reflections	2193	2480	3911
No. of independent reflections	2094	2237	3602
R_{int}	0.07	0.0	0.03
No. of observed reflections, $F > 6\sigma(F)$	1565	1466	2201
$2\theta_{max}$ (°)	50	54	50
Range of h, k, l	−13–13 0–11 0–14	0–12 0–25 0–14	−11–11 0–13 0–27
No. of standard reflections	3	3	3
Intensity variation (%)	16	2.5	3
Refinement			
Refinement on	F	F	F
R	0.077	0.044	0.060
wR	0.075	0.046	0.061
S	1.84	1.10	1.23
No. of reflections used	1560	1466	2200
No. of parameters used	312	161	313
H-atom treatment		Not refined	
Weighting scheme		$w = 1/\sigma^2(F_o)$	
$(\Delta/\sigma)_{max}$	0.07	0.02	0.01
$|\Delta\rho|_{max}$ (e Å⁻³)	0.33	0.24	0.26
Source of atomic scattering factors		*International Tables for X-ray Crystallography* (1974, Vol. IV).	

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters in polymorph A of* (6b) (Å²)

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
N(1)	0.8465 (5)	0.0653	0.6543 (6)	0.056 (3)
C(2)	0.7702 (8)	−0.0618 (13)	0.6038 (11)	0.076 (5)
C(3)	0.9815 (7)	0.0651 (12)	0.7015 (6)	0.048 (3)
O(4)	1.0386 (5)	−0.0454 (9)	0.7090 (6)	0.074 (3)
C(5)	1.0226 (7)	0.2175 (11)	0.7304 (7)	0.044 (3)
C(6)	1.1368 (6)	0.2642 (11)	0.7403 (6)	0.042 (3)
C(7)	1.2479 (7)	0.1643 (11)	0.7780 (7)	0.044 (3)
C(8)	1.2802 (6)	0.0829 (13)	0.8801 (7)	0.056 (3)
C(9)	1.3896 (8)	−0.0066 (12)	0.9224 (8)	0.069 (4)
C(10)	1.4635 (7)	−0.0060 (13)	0.8596 (9)	0.073 (5)
C(11)	1.4316 (8)	0.0733 (16)	0.7573 (9)	0.077 (4)
C(12)	1.3252 (8)	0.1630 (13)	0.7178 (8)	0.066 (4)
C(13)	1.1616 (7)	0.4144 (11)	0.7193 (7)	0.047 (3)
C(14)	1.0763 (7)	0.4942 (11)	0.6179 (7)	0.050 (3)
C(15)	1.1016 (9)	0.6346 (12)	0.6026 (8)	0.069 (5)
C(16)	1.2103 (10)	0.7023 (12)	0.6813 (11)	0.078 (5)
C(17)	1.2980 (8)	0.6248 (13)	0.7782 (10)	0.073 (5)
C(18)	1.2738 (7)	0.4839 (12)	0.7956 (8)	0.059 (4)
C(19)	0.7976 (8)	0.1993 (11)	0.6515 (7)	0.056 (4)
O(20)	0.6854 (5)	0.2256 (10)	0.6182 (6)	0.075 (3)
C(21)	0.9091 (6)	0.3028 (11)	0.7144 (7)	0.046 (3)
C(22)	0.9006 (6)	0.4290 (11)	0.7640 (7)	0.045 (3)
C(23)	0.7771 (6)	0.5099 (11)	0.7271 (7)	0.043 (3)
C(24)	0.7026 (7)	0.5365 (12)	0.6047 (7)	0.056 (4)
C(25)	0.5922 (7)	0.6175 (13)	0.5742 (8)	0.066 (4)
C(26)	0.5542 (7)	0.6598 (13)	0.6577 (9)	0.070 (4)
C(27)	0.6286 (8)	0.6390 (14)	0.7801 (8)	0.073 (5)
C(28)	0.7418 (7)	0.5560 (13)	0.8125 (7)	0.062 (4)
C(29)	1.0108 (6)	0.4987 (11)	0.8643 (6)	0.042 (3)
C(30)	1.0841 (7)	0.4186 (12)	0.9680 (7)	0.053 (3)
C(31)	1.1828 (8)	0.4898 (15)	1.0660 (7)	0.065 (4)
C(32)	1.2057 (8)	0.6326 (14)	1.0582 (9)	0.071 (4)
C(33)	1.1341 (8)	0.7105 (12)	0.9562 (9)	0.070 (5)
C(34)	1.0349 (7)	0.6439 (11)	0.8603 (7)	0.049 (3)

for $C_{33}H_{27}O_2N$: C 84.40, H 5.80, N 2.98; found C 84.33, H 5.39, N 2.88. (8e) calc. for $C_{34}H_{29}O_2N$: C 84.44, H 6.04, N 2.90; found: C 84.41, H 5.93, N 2.78. (8f), calc. for $C_{37}H_{27}O_2N$: C 85.85, H 5.26, N 2.71; found: C 85.77, H 5.12, N 2.70. (6a) was inert to similar irradiation.

Crystal structure analyses

The three polymorphic crystal types of (6b), A–C, suitable for X-ray diffraction were prepared by recrystallization from acetone. The X-ray diffraction measurements were carried out at room temperature (ca 298 K)

on an automated CAD-4 diffractometer equipped with a graphite monochromator, using Mo $K\alpha$ ($\lambda = 0.7107$ Å) radiation. Intensity data were collected by the ω–2θ scan mode with a constant scan speed 4° min⁻¹ and scan range $(0.90 + 0.35 \tan\theta)°$. Possible deterioration of the analyzed crystal was tested by detecting periodically, every 60 min, the intensities of three standard reflections from different zones of the reciprocal space. It was found negligible for crystals B and C. The standard intensities of crystal A exhibited a linear decrease (of ca 16% during the entire experiment), which required an appropriate correction for this data set. No corrections for absorption or secondary extinction effects were applied. Enraf–Nonius CAD-4 software was used for the diffraction measurements (Enraf–Nonius, 1989). A local *CADINT* program was used for data reduction. Crystal data, and data collection, solution and refinement details are summarized in Table 1.

The crystal structures were solved by direct methods. Their refinements are carried out by full-matrix least-squares, including the potential and anisotropic thermal parameters of the non-H atoms. All H atoms were introduced in calculated positions, the methyls being treated as rigid groups. The final refinements were based on observations with $F_o \geq 6\sigma(F_o)$ and experimental

Table 3. *Fractional atomic coordinates and equivalent isotropic displacement parameters in polymorph B of (6b) (Å²)*

$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j.$$

	x	y	z	U_{eq}
N(1)	0	0.5757 (1)	1/4	0.0405 (8)
C(2)	0	0.6480 (2)	1/4	0.0623 (14)
C(3)	0.0868 (2)	0.5380 (1)	0.3169 (2)	0.0393 (6)
O(4)	0.1714 (2)	0.5633 (1)	0.3780 (1)	0.0537 (6)
C(5)	0.0595 (2)	0.4674 (1)	0.2887 (2)	0.0349 (6)
C(6)	0.1480 (2)	0.4177 (1)	0.3124 (2)	0.0344 (6)
C(7)	0.2536 (2)	0.4230 (1)	0.4021 (2)	0.0368 (6)
C(8)	0.3829 (2)	0.4000 (1)	0.3789 (2)	0.0483 (7)
C(9)	0.4830 (2)	0.4031 (1)	0.4616 (2)	0.0569 (9)
C(10)	0.4547 (3)	0.4276 (1)	0.5696 (2)	0.0568 (9)
C(11)	0.3274 (2)	0.4488 (1)	0.5951 (2)	0.0534 (8)
C(12)	0.2270 (2)	0.4467 (1)	0.5123 (2)	0.0449 (7)
C(13)	0.1515 (2)	0.3550 (1)	0.2451 (2)	0.0363 (6)
C(14)	0.1570 (2)	0.3573 (1)	0.1255 (2)	0.0429 (7)
C(15)	0.1711 (2)	0.2992 (1)	0.0629 (2)	0.0543 (8)
C(16)	0.1776 (2)	0.2390 (1)	0.1178 (2)	0.0600 (9)
C(17)	0.1705 (2)	0.2362 (1)	0.2367 (2)	0.0552 (9)
C(18)	0.1593 (2)	0.2939 (1)	0.3003 (2)	0.0452 (6)

The molecules are located on a C_2 axis at $0, y, 0.25$.

Table 4. *Fractional atomic coordinates and equivalent isotropic displacement parameters in polymorph C of (6b) (Å²)*

$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j.$$

	x	y	z	U_{eq}
N(1)	0.2508 (3)	0.1934 (3)	0.5041 (1)	0.061 (1)
C(2)	0.3659 (5)	0.1584 (6)	0.4711 (2)	0.088 (2)
C(3)	0.2769 (4)	0.2385 (4)	0.5608 (2)	0.057 (1)
O(4)	0.3944 (3)	0.2548 (3)	0.5877 (1)	0.087 (1)
C(5)	0.1333 (3)	0.2523 (3)	0.5803 (1)	0.049 (1)
C(6)	0.1173 (4)	0.2518 (3)	0.6378 (1)	0.050 (1)
C(7)	0.2369 (4)	0.2757 (4)	0.6858 (1)	0.052 (1)
C(8)	0.3117 (5)	0.3841 (4)	0.6902 (2)	0.067 (2)
C(9)	0.4180 (5)	0.4052 (4)	0.7375 (2)	0.080 (2)
C(10)	0.4517 (5)	0.3189 (6)	0.7799 (2)	0.086 (2)
C(11)	0.3798 (5)	0.2105 (6)	0.7751 (2)	0.103 (2)
C(12)	0.2730 (5)	0.1888 (4)	0.7289 (2)	0.081 (2)
C(13)	−0.0212 (4)	0.2223 (4)	0.6578 (1)	0.053 (1)
C(14)	−0.0947 (4)	0.1188 (4)	0.6383 (2)	0.062 (2)
C(15)	−0.2204 (5)	0.0894 (4)	0.6597 (2)	0.085 (2)
C(16)	−0.2716 (5)	0.1635 (6)	0.6993 (2)	0.098 (2)
C(17)	−0.1980 (5)	0.2659 (5)	0.7199 (2)	0.090 (2)
C(18)	−0.0713 (4)	0.2948 (4)	0.6997 (2)	0.070 (2)
C(19)	0.1074 (4)	0.1808 (3)	0.4817 (2)	0.054 (1)
O(20)	0.0667 (3)	0.1400 (2)	0.4332 (1)	0.069 (1)
C(21)	0.0276 (4)	0.2335 (3)	0.5268 (1)	0.049 (1)
C(22)	−0.1075 (4)	0.2790 (3)	0.5141 (1)	0.048 (1)
C(23)	−0.2074 (4)	0.2398 (3)	0.4613 (1)	0.049 (1)
C(24)	−0.2288 (4)	0.1182 (4)	0.4482 (2)	0.066 (2)
C(25)	−0.3229 (5)	0.0810 (4)	0.3990 (2)	0.077 (2)
C(26)	−0.3956 (5)	0.1662 (5)	0.3632 (2)	0.074 (2)
C(27)	−0.3776 (4)	0.2871 (5)	0.3759 (2)	0.073 (2)
C(28)	−0.2853 (4)	0.3248 (4)	0.4253 (2)	0.060 (2)
C(29)	−0.1605 (4)	0.3734 (3)	0.5511 (1)	0.050 (2)
C(30)	−0.0789 (4)	0.4760 (4)	0.5684 (2)	0.058 (1)
C(31)	−0.1309 (5)	0.5668 (4)	0.6011 (2)	0.071 (2)
C(32)	−0.2633 (6)	0.5548 (5)	0.6179 (2)	0.088 (2)
C(33)	−0.3448 (5)	0.4545 (5)	0.6010 (2)	0.087 (2)
C(34)	−0.2965 (4)	0.3645 (4)	0.5672 (2)	0.063 (2)

weights $w = 1/\sigma^2(F_o)$, minimizing $w(\Delta F)^2$. The final electron difference-density maps did not show any unusual features, confirming the correctness of the structural models. The absolute configuration of structure

A has not been determined. Programs used to solve and refine the structures are *SHELXS86* (Sheldrick, 1985) and *SHELX76* (Sheldrick, 1976), respectively. Geometry calculations were done with *PARST* (Nardelli, 1983), and the diagrams were prepared using *ORTEPII* (Johnson, 1976). A Silicon Graphics 4D/120GTX computer system was used for all calculations. Final fractional atomic coordinates are given in Tables 2–4.* The atom numbering scheme used is depicted in Fig. 1.

An effort has also been made to crystallographically characterize the chiral and racemic products obtained by irradiation of powdered A, B and C. Crystals of the racemic (8b) (single polymorph), obtained by recrystallization of the powdered samples, were found to be monoclinic with $a = 9.289$ (4), $b = 25.926$ (3), $c = 9.932$ (1) Å, $\beta = 98.86$ (2)°, space group $P2_1/c$. However, single crystals of optically active (8b) suitable for X-ray diffraction analysis could not be obtained. No useful correlations of the topological features associated with the photochemical transformation are, therefore, feasible. The crystallographic analysis confirmed the chemical identity of (8b) as indicated in Scheme 2; the detailed results will be published elsewhere.
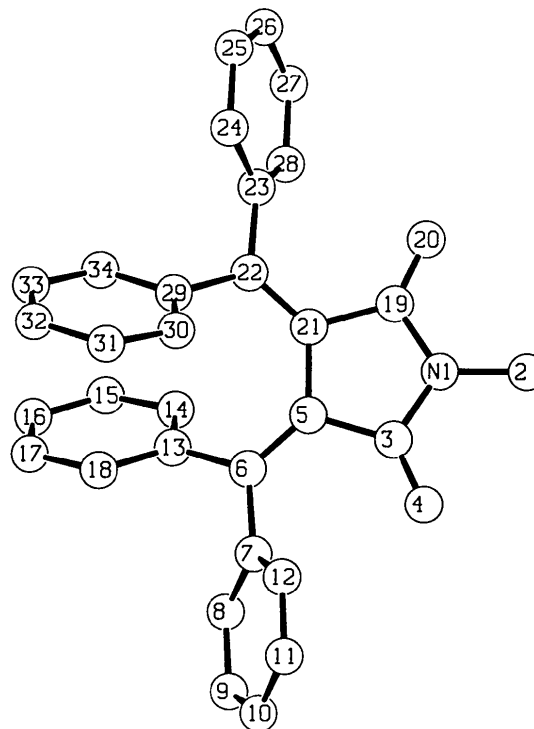
Fig. 1. Scheme of the atomic labels used in this study. In structure B the fragments C(3) through C(18) and C(19) through C(34) are related by crystallographic symmetry.

Results and discussion

During earlier investigations it has been observed that the two inner phenyl groups in the 3,4-bis(diphenylmethylene)cyclobutanedione system (3) partly overlap, and that their shielded 10 H appear at a higher magnetic field in the ^{1}H NMR spectrum than protons of the outer phenyl groups (Toda, Ishihara & Akagi, 1969; Toda & Akagi, 1971; Winter & Toda, 1975). However, attempts to prepare chiral phases of this compound were unsuccessful. It was anticipated at this stage that replacement of the cyclobutanedione central ring by a five-membered analog may cause a more severe hindrance between the inner phenyl rings, and enforce a helical configuration of the molecular framework. Correspondingly, the synthesis of the succinimide derivatives (6a–f) was attempted by treating (3) with ammonia or a primary amine in CCl_4 in the presence of Br_2. The reaction route, involving the possible intermediates (4) and (5), is shown in Scheme 1 (Toda & Fujita, 1972).

In solution, (6a–f) do not exhibit properties of optical activity. Crystallizations from acetone and other common solvents were used to obtain pure solid materials. Recrystallization of the crude (6b) product from acetone gave a mixture of chiral crystals as orange hexagonal plates (A, a conglomerate of the two chiral forms), and two different types of racemic crystals as orange (B, m.p. 575 K) and yellow (C, m.p. 570 K) rectangular plates, approximately in a 1:1:1 ratio. Form A was found to convert to form C before melting, by heating to 533 K on a hot plate. During this process the color change from orange to yellow, during the thermal racemization, spreads dramatically from one end of the crystal to the other with retention of the crystal morphology. The nature of this transformation could not be, however, fully characterized (differential scanning calorimetry scans did not show absorption peaks below 570 K).

Further recrystallizations of pure A, pure B or pure C from acetone usually gave mixtures of the different forms. For example, from 100 mg samples of either A, B, or C one could obtain mixtures of A (21 mg) and C (61 mg), B (62 mg) and C (7 mg), and B (48 mg) and C (33 mg), respectively. The composition of the crystallizing material can easily be modified by seeding techniques, or by introducing various additives into the crystallization mixtures. Both ways were particularly useful in our attempts to obtain larger amounts of the chiral form A. Thus, recrystallization of 100 mg of C from 20 ml of acetone, in the presence of a small seed of A, yielded 66 mg of the A form. Table 5 also illustrates the effect of various additives in the recrystallization process of pure B-type crystals. The results indicate that recrystallizations of B in the presence of an acidic additive often yield significant amounts of the chiral crystalline form, while no A crystals were formed in repeated recrystallization experiments from pure acetone. These findings have not been fully accounted for, as yet.

Table 5. *Recrystallization of the racemic polymorph* B *(100 mg) from acetone (10 ml) in the presence of an additive (0.1 g)*

Additive	Composition (in mg) of mixture obtained by crystallization*		
	A	B	C
None	0	62	7
Acetic acid	56	12	4
(−)-Tartaric acid	16	10	45
(+)-Tartaric acid	17	4	25
(+)-Diethyltartarate	0	47	4
(+)-Alanine	13	29	2
(−)-Menthol	3	44	0
(+)-Menthone	20	0	14
(−)-Limonene	0	22	24
Triethylamine	0	38	34

* Sample results are shown. Repeated recrystallization experiments from pure acetone, and in the presence of (−)-limonene and triethylamine additives, failed to yield any significant amounts of the chiral crystalline form A.

The photochemical conversion of (6b) to (8b) occurs, in quantitative yields for the enantiomeric crystals of chiral A, as well as for the racemic materials B and C. Scheme 2 shows the postulated pathway for this reaction [correlation between the absolute configurations of the reactants and products has not been determined, and the enantiomeric reactants of (6b) which lead to either (+)-(8b) or (−)-(8b) are tentatively designated as (+)-(6b) or (−)-(6b), respectively]. This enantioselective photoconversion consists of two steps, the conrotatory ring closure of (6b) to the intermediate (7b), and the 1,5-hydrogen shift of (7b) to give the product (8b). The latter sigmatropic reaction occurs in the solid state in a suprafacial manner (Tanaka, Kakinoki & Toda, 1992). It is not clear which step is less stereoselective. The 'soft' chirality features of (6b), spontaneously resolved by crystallization, can thus be frozen by a photochemical
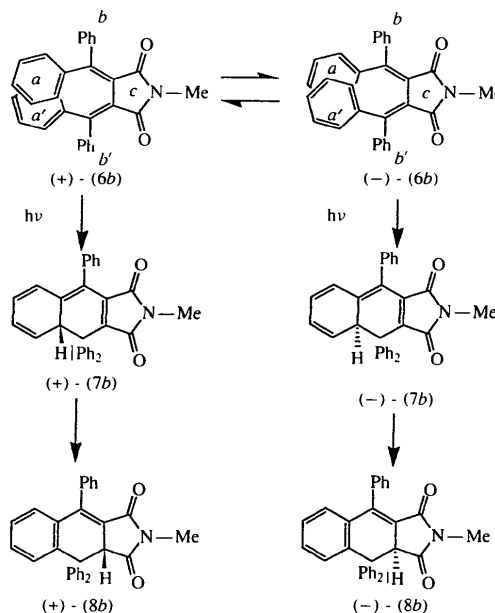
reaction in the solid state to give an optically active photocyclization product (8b). (6c–f) crystallized as racemic solids only, and irradiation of the latter gave the corresponding racemic photocyclization products (8c–f). It is interesting to note that similar photochemically induced reactions of (6) to (8) also occur in solution. For example, irradiation of (6f) in THF gives (8f) in 45% yield (Toda, Nakaoka, Yuwane & Todo, 1973).

The unique properties of system (6), and the simultaneous occurrence of chiral as well as racemic crystalline polymorphs of the (6b) derivative, led us to examine in more detail the molecular and crystal structures of the three crystal forms A, B and C.

The molecular structures are characterized by bond lengths and bond angles within the normal range. The structure of (6b) is characterized by an overall C_2 symmetry (Fig. 2). The latter is obeyed approximately in crystals A and C, where the molecules occupy general sites in the unit cell, and strictly in B where they are positioned on the crystallographic axes of twofold rotation. The molecular structure of (6b) varies only slightly from one crystal to another. In all three cases the observed conformation is characterized by a syn-disposition of the two diphenylmethylene fragments with respect to the central C(5)—C(21) bond of the imide ring. The phenyl rings a and a' (Scheme 2) are almost parallel to one another and overlap significantly; the dihedral angles between these rings are within the range 9–12° (Table 6). Favorable aryl–aryl π–π interactions between these rings contribute significantly to the stabilization of the observed molecular structure (Klebe & Diederich, 1993, and references therein; Burley & Petsko, 1986). They also compensate for the apparent deviation from planarity of, and a diminished electron delocalization in, the —C=C—C=O fragments. The torsion angles about the central =C—C= bonds, which reflect on the steric hindrance within the molecule, vary from 14° in B, through 14 and 20° in A, to 20 and 21° in C (Table 6). The degree of electron delocalization is thus expected to be smaller in C than in A and B. The
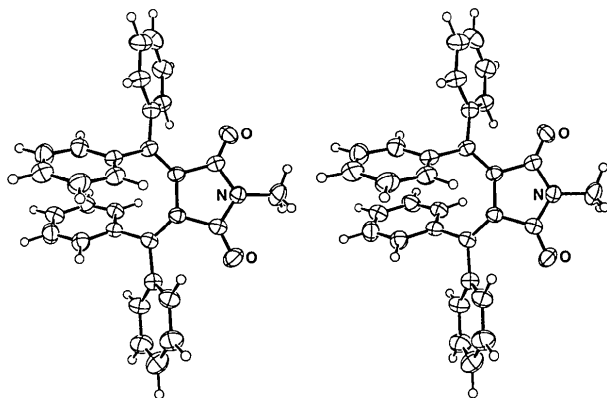

Fig. 2. Stereoview of the molecular structure of (6b), as observed in crystal B, projected approximately on the plane of the imide ring. 50% probability ellipsoids are shown for the non-H atoms.

Table 6. Selected structural parameters of (6b) in the various crystals

Crystal	A	B	C
(a) Intramolecular nonbonding distances (Å)			
C(6)···C(29)	3.311 (13)	3.310 (3)	3.335 (5)
C(6)···C(30)	3.381 (13)	3.353 (3)	3.348 (5)
C(13)···C(22)	3.305 (12)	3.310	3.335 (3)
C(14)···C(22)	3.273 (14)	3.353	3.338 (5)
C(13)···C(29)	3.059 (13)	3.021 (3)	3.089 (4)
(b) Torsion angles (absolute values, °)			
C(6)—C(5)—C(21)—C(22)	38.8 (15)	34.7 (4)	43.2 (5)
C(4)—C(3)—C(5)—C(6)	19.6 (16)	13.7 (4)	20.2 (6)
O(20)—C(19)—C(21)—C(22)	14.3 (15)	13.7	20.9 (6)

(c) Dihedral angles between the mean planes of the ring fragments: the two overlapping phenyls a and a', the two other phenyl rings pointing outward, b and b', and the five-membered imide ring c (°)

a—a'	12.3 (3)	9.2 (1)	10.4 (1)
b—b'	31.1 (3)	42.6 (1)	24.9 (1)
c—a	43.2 (3)	52.2 (1)	45.2 (1)
c—a'	50.3 (3)	52.2	46.2 (1)
c—b	74.9 (3)	66.9 (1)	82.7 (1)
c—b'	74.1 (3)	66.9	73.2 (1)

optical properties correlate well, qualitatively, with these observations, crystals of A and B showing an orange color while crystals of C being yellow.

The distances of the C atoms of one ring from the plane of the other ring are within the ranges 3.07–3.67 in A, 2.99–3.38 in B, and 3.08–3.51 Å in C; the lower values are for the inner atoms (closer to the imide ring), while the higher values are for the outer (peripheral) ones. The corresponding median distances in the central part of the overlapping rings are near 3.3 Å in A and C and near 3.2 Å in B. Interconversion between the phenyls a and a' is thus sterically hindered in these structures. It has already been shown that the shortest possible carbon to phenyl ring distance for a perpendicular arrangement of two benzene rings is ca 4.1 Å [with a ring center-to-ring center distance near 5.0 Å (Klebe & Diederich, 1993)]. Such a long distance cannot be achieved in crystals A, B and C without a severe distortion of the molecular structure of (6b). Evidently, at room temperature the energy barrier for racemization of (6b) is considerably higher in the condensed crystalline phase than in solution. The above observations confirm, therefore, that (6b) is a chiral compound at least in the solid state, adopting either a left- or right-handed stable helical configuration. The other two phenyl substituents directed outwards appear to have the largest conformational freedom with respect to the central core of the molecule. Their twist angle about the =C—C(aryl) bond is thus most sensitive to crystal packing forces. Structural parameters which reflect most on the conformational variation of (6b) in the three crystal types are summarized in Table 6.

Of particular interest with respect to the present discussion are the intramolecular distances between the potential reactive centers of the photocyclization reaction which occurs in the solid materials (see Scheme 2).

Indeed, in the observed conformation, these centers are in close proximity, facilitating the photoaddition reaction. The corresponding distances between the unsaturated carbon sites which join during the photochemical reaction, C6···C30 and C14···C22, are 3.38 and 3.27 Å in A, 3.35 Å in B, and 3.35 and 3.34 Å in C (Table 6). These match perfectly well the topochemical requirements of photoinduced organic reactions between unsaturated systems in the solid state (Thomas, Morsi & Desvergne, 1977).

The crystal structures A, B and C are illustrated in Figs. 3, 4 and 5, respectively. They represent three different crystalline polymorphs of (6b). Crystals of A are chiral, consisting of (6b) molecules in either a purely right-handed or a purely left-handed 'helical' configuration. Crystals B and C contain equal amounts of the two configurations, and are racemic. The three structure types are stabilized primarily by dispersion forces and directional C—H···O=C interactions. The shortest intermolecular C···O distances which characterize the latter are within the range 3.18–3.32 Å; the specific contacts in each crystal structure are detailed in the legends to Figs. 3–5. Such distances are comparable with mean C—H···O hydrogen bond lengths observed for chloroform, dichloromethane and ethynyl proton donors (Steiner, 1994), but are significantly shorter than the average for alkene hydrogen bonds (Desiraju, 1991). They thus represent relatively strong attractions which contribute to the high melting points of these crystals (Goldberg, Bernstein & Kosower, 1982; Goldberg, Bernstein, Kosower, Goldstein & Pazhenchevsky, 1983). Interconversions between the three crystalline forms A, B and C occur readily, as described above. It is important to note, however, that crystals of A, but not of B or C deteriorate with time. A consistent indication, that phase A is energetically less favorable than phases B or C, has been obtained from semiempirical estimates of crystal-packing energy, using the program OPEC (Gavezotti, 1989, 1990). The observations of this study
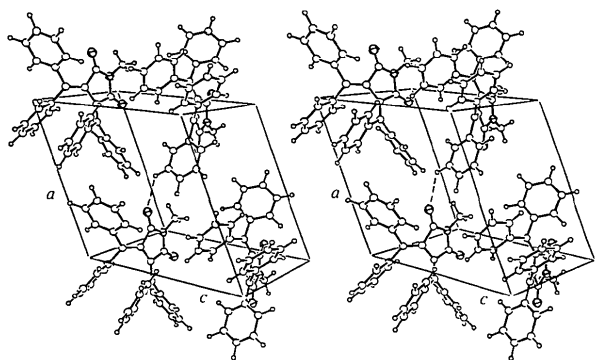
suggest that crystallization of the chiral A form is a kinetically controlled process, which is, not surprisingly, quite sensitive to crystallization conditions.

The process of crystallization often facilitates optical resolution of racemic samples, which under standard conditions isomerize rapidly in solution, if one of their resulting solids has a chiral structure. The prochiral molecular configuration of (6b) frozen in the solid state is used as a starting material in a stereoselective photochemical reaction to yield an optically resolved molecular product. The present example is thus of significant interest in the wider context of utilizing the crystalline medium for absolute asymmetric synthesis. A more thorough analysis of the experimental conditions is still required to optimize the yield of the chiral polymorph.
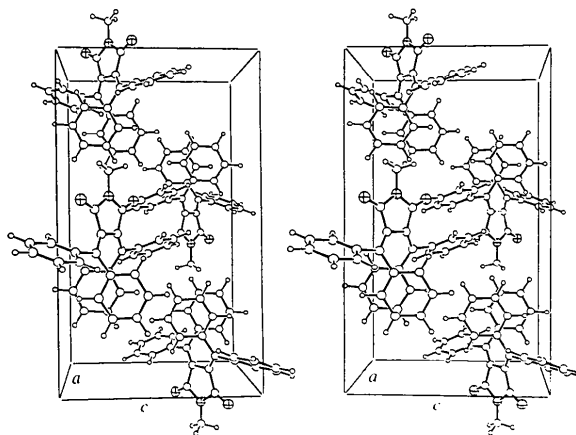

Fig. 4. Stereoview of the crystal structure of B. The shortest C=O···H—C intermolecular distances in this structure are: O4···C14 (at $x, 1 - y, z + \frac{1}{2}$) 3.296(3) Å and its symmetry equivalent.

Fig. 3. Stereoview of the crystal structure of A. A short C=O···H—C intermolecular contact, O(20)···C(25) (at $1 - x, y - \frac{1}{2}, 1 - z$) 3.25(1) Å, is indicated by a dashed line. Neighboring molecules displaced by b are also involved in a strong interaction: O4···C16 (at $x, y - 1, z$) 3.18(1) Å.
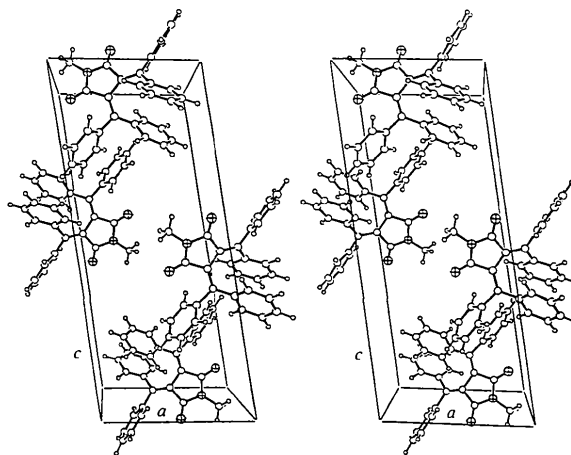

Fig. 5. Stereoview of the crystal structure of C. The shortest C=O···H—C intermolecular distances are between molecules displaced by a, and between molecules related by inversion at (0,0,0.5): O4···C33 (at $x + 1, y, z$) 3.290(6), O4···C34 (at $x + 1, y, z$) 3.270(5) and O20···C14 (at $-x, -y, 1 - z$) 3.319(5) Å.

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Structure of 5-(3,4,5-Trimethoxyphenyl)-2-iodomethyltetrahydrofuran: A Precursor of Acetylcholinesterase Inhibitors with Platelet-Activating Factor Antagonistic Activity

BY LAURENCE LE TEXIER, EDITH FAVRE AND JEAN-JACQUES GODFROID

Laboratoire de Pharmacochimie Moléculaire, Unité de Recherche Chimie et Pharmacologie, Université Paris 7 Denis Diderot, 2 Place Jussieu, 75251 Paris CEDEX 05, France

AND SABINE HALUT-DESPORTES

Laboratoire de Chemie des Métaux de Transition, UA No. 419, Université Paris 6 Pierre et Marie Curie, 4 Place Jussieu, 75252 Paris CEDEX 05, France

Abstract

The trans configuration of an iodomethyltetrahydrofuran derivative (2) has been determined as part of a structure–activity relationships study of acetylcholinesterase inhibitors with correlated platelet-activating factor antagonistic activity. Synthesis of tetrahydrofurfuryloxypyridinium bromide via the key intermediate (2) is described. $C_{14}H_{19}IO_4$, $M_r = 378.2$, monoclinic, space group $P2_1/n$, $a = 7.686\,(1)$, $b = 8.113\,(2)$, $c = 24.249\,(6)$ Å, $\beta = 99.96\,(2)°$, $V = 1489\,(1)$ Å^3, $Z = 4$, $D_x = 1.69\,\mathrm{Mg\,m^{-3}}$, $T = 293\,\mathrm{K}$, $F(000) = 752$, $\mu(\mathrm{Mo}\,K\alpha) = 21.3\,\mathrm{cm^{-1}}$, $R = 0.034$ for 2494 independent reflexions with $I > 3\sigma(I)$.

Introduction

The structure of iodomethyltetrahydrofuran (2) (Fig. 1) was determined as part of the investigation into structure–activity relationships in 2,5-disubstituted tetrahydrofuran derivatives with dual activity, i.e. acetylcholinesterase inhibition combined with platelet-activating factor antagonistic activity in the same molecule (Le Texier et al., 1995). The final aim is to find potent drugs as palliative treatment of Alzheimer's disease.

Alzheimer's disease (AD) is a progressive dementia which results in severe memory loss and cognitive decline. Memory impairments in AD result from a deficit