The Acid-catalyzed Isomerization of the Adducts of Azodiacyls with Cyclopentadiene and 1,3-Cyclohexadiene

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Received December 2, 1971

The isomerization of the Diels–Alder adducts of azodiacyls with cyclopentadiene and 1,3-cyclohexadiene is powerfully catalyzed by strong protic acids and by Lewis acids. In adducts from *p*-substituted azodibenzoyls with cyclopentadiene the catalytic effect increases with electron release by the substituent.

L'isomérisation des produits d'addition de la réaction de Diels–Alder entre les azodiacyles et le cyclopentadiène et le cyclohexadiène-1,3 est très fortement catalysée par des acides protiques forts et par les acides de Lewis. Dans les produits d'addition entre les azodibenzoyles *p*-substitués et le cyclopentadiène, l'effet catalytique augmente avec l'effet donneur d'électrons du substituant.

Canadian Journal of Chemistry, **50**, 1568 (1972)

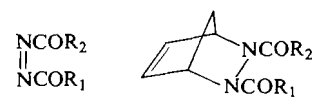
A number of reactions which proceed by [3,3] sigmatropic pathways are known to be catalyzed by Lewis acids (1–3) or by protic acids (2, 4–8). Many of these isomerizations involve allyl substituents in the Claisen (1), the dienol-benzene (6), or the dienone-phenol (7, 8) rearrangements. The catalyzed reactions are not all necessarily concerted (5).

Recently we have shown that the adducts **2** of azodiacyls **1** and cyclopentadiene undergo a [3,3] sigmatropic rearrangement to the racemic ($R_1 = R_2$) or isomeric ($R_1 \neq R_2$) *cis* bicyclic 1,3,4-oxadiazines **3** and **4** (9, 10). We now wish to report that this isomerization also is exceedingly sensitive to acid catalysis and to show how this catalysis can be utilized in studies of these and related isomerizations.

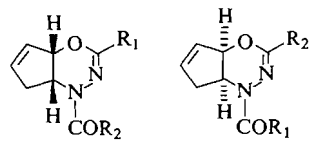
Qualitatively the effect could be simply demonstrated by adding traces of strong acids, *e.g.* hydrogen chloride or trifluoroacetic acid (TFA) to solutions of **2***a* in a wide range of solvents and evaporating the solutions to give the pure oxadiazine. In an inadvertent proof of the catalysis an attempt to purify a slightly colored sample of the very labile adduct **2***b* (10) in a pentane solution containing commercial activated charcoal led to the recovery of pure **3***b*;[1] the charcoal was found to give a p*H* of 2 to an aqueous suspension.

On a more quantitative basis (Table 1) the half-life of **2***a* which was 11 h in heptane at 62° was reduced to 1.3 s by the inclusion of 1.3×10^{-1} *M* TFA (1% v/v) or to 1.3 min by 1.3×10^{-2} *M* hydrogen chloride. Similarly 1.3×10^{-1} *M* TFA reduced the half-life of **2***b* in heptane at 52° from 22 min to 2.0 s. The isomerizations, which were all cleanly first order in adduct, were followed by u.v. spectrophotometry of dilute solutions (*ca.* 10^{-4} *M*), the slow thermal ones by the repeated scan technique (9), and the fast acid-catalyzed ones by following the development of the C=N chromophore of **3***a* at 290 nm and of **3***b* at 250 nm.

On a preparative scale the isomerization of **2***a* could be achieved under a wide range of conditions, at room temperature or by heating, in solutions containing TFA in excess or in amounts as little as 0.1 equiv. Typically a 2% solution of **2***a* in benzene could be isomerized



1 **2**



3 **4**

a $R_1 = R_2 = Ph$
b $R_1 = R_2 = CMe_3$
c $R_1 = R_2 = p\text{-}MeOC_6H_4$
d $R_1 = R_2 = p\text{-}O_2NC_6H_4$
e $R_1 = p\text{-}O_2NC_6H_4$; $R_2 = p\text{-}MeOC_6H_4$

[1]For racemic oxadiazines the simple notation for one enantiomer will be used.

TABLE I. Uncatalyzed and acid-catalyzed isomerization of adducts of azodiacyls in heptane

Adduct	Temperature (°C)	Acid concentration (M)	Half-life (s)
2*a*	62	—	3.9×10^4
		1.3×10^{-1}*	1.3
		1.3×10^{-2}†	78
		2.8‡	5.4×10^3
2*b*	52	—	1.3×10^3
		1.3×10^{-1}*	2.0
7	62	—	1.6×10^9§
		1.3×10^{-1}*	5.1×10^4

*TFA.
†Hydrogen chloride.
‡Acetic acid.
§Estimated by comparison of catalyzed isomerization rates of 7 and **2***a*, see text.

by refluxing for 3 min with 0.1 equiv of TFA. In all cases evaporation of the solutions gave crystalline product containing a small amount of TFA derived material (weak i.r. absorption at 1780 cm^{-1}) but washing with dilute ammonia removed this to give the oxadiazine in high yield (>90%) and purity.

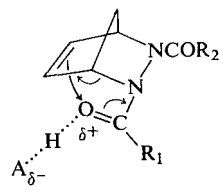
The conversion of **2***a* into **3***a* is in fact quantitative, all solution spectra of **2***a* in the presence of TFA eventually becoming superimposable on those of pure **3***a* with the same amount of TFA added. The changes in the spectra of **3***a* induced by TFA are very minor suggesting that protonation of **3***a* is negligible. Thus the u.v. absorption band of the PhC=N chromophore in heptane was unreduced in intensity by the addition of 1.3×10^{-1} M TFA and showed a hypsochromic shift of only 6 nm. Though complete protonation transfer to pyridine, quinoline, and other heterocyclic bases by TFA in hexane has been detected by u.v. spectroscopy (11), it is likely that with the much less basic heterocycle **3***a* only proton association can occur in saturated hydrocarbon solvents. The observed band shift in heptane may be due to this.

The generality of the catalysis was explored for other protic acids and for Lewis acids. The isomerization of **2***a* was followed by n.m.r. spectroscopy in the presence of *p*-toluenesulfonic acid (0.2 equiv), boron trifluoride etherate (0.2 equiv), and tin (IV) chloride (1.0 equiv). In each case the reaction was markedly accelerated and was essentially quantitative on work-up of the solutions. Acetic acid was, however, rather ineffective; a 17% (v/v, 2.8 M) solution of it in heptane at 62° isomerized **2***a* only seven times faster than the isomerization in pure heptane.

Aqueous hydrochloric acid also catalyzed the isomerization but first order kinetics were not observed on u.v. analysis, the oxadiazine being slowly hydrolyzed. Thus solutions of **2***a* and **3***a* in excess of 0.1 M aqueous ethanolic hydrochloric acid for 1 day at room temperature gave identical end products containing at least four components (t.l.c.) and showing strong absorption in the OH/NH region of the i.r. spectrum. The instability of the dihydro derivative of **3***a* to aqueous acid has already been discussed (9).

The nature of the complex between the acid and the substrate in the transition state in hydrocarbon solvents must be speculative. The site of complexation is probably the same as that of protonation in solvents where proton transfer is possible. In simple amides the evidence is now conclusive that protonation occurs on oxygen (12), but no comparable studies have been carried out on hydrazides.

If, by analogy with amides, complexation in hydrocarbon solvents occurs at oxygen, then for a concerted reaction the representation **5** might reasonably describe the geometry leading to the transition state for the product **3**; in **5** the electrophilic oxygen initiates attack by the olefinic π electrons. A similar picture pertains to complexation at nitrogen, the likelihood of this alternative depending on the pyramidal (sp^3) as opposed to the planar (sp^2) character of the N—C=O system, since if the former is dominant complexation, like protonation, would relieve repulsion between lone electron pairs.[2] The involvement of an open protonated structure, *e.g.* **6**, in a non-concerted pathway cannot be discounted. In the absence of species



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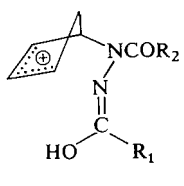

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[2]As a referee has suggested, even if the *N*-complexed (or protonated) species is less stable than its *O*-counterpart it might nevertheless provide the preferred isomerization path; the two species would of course be in rapid equilibrium.

TABLE 2. Effect of *p*-substituent on the ratio of TFA (1.3×10^{-3} *M*)-catalyzed to uncatalyzed isomerization in benzene at 70.0°

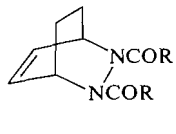
Adduct **2**	*p*-Substituent	Uncatalyzed half-life (min)	Catalyzed half-life (min)	Rate enhancement
d	NO_2	32.4	20.0	1.6
a	H	145	1.38	105
c	MeO	95	0.17	560

capable of diverting it, the ring closure of **6** might be highly stereospecific and lead to the observed high yields of *cis* oxadiazines.

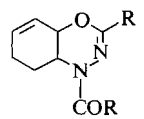
There are two predictable consequences of the invocation of **5**, or its *N*-complexed counterpart. The first is that in the case of two different symmetrical adducts under the same conditions that with the more basic amide group should be more susceptible to catalytic rate enhancement relative to the uncatalyzed (thermal) reaction. This is vividly borne out by the isomerization rates of **2***a*, *c*, and *d* in benzene at 70° (Table 2) in which the ratio of catalyzed (1.3×10^{-3} *M* TFA) to uncatalyzed rates increases with electron release from the aryl group.

The second consequence is that in the transformation of an unsymmetrical adduct ($R_1 \neq R_2$) to the mixture of isomeric oxadiazines, the isomer distribution for the thermal reaction must alter for the catalyzed reaction in the direction of the isomer derived through the transition state complexed at the more basic amide group. This is well illustrated utilizing again the substituent effects of the nitro and methoxy groups. In the absence of acid the yield from **2***e* of oxadiazine **4***e* was $40 \pm 5\%$ (10) but with 1.3×10^{-1} *M* TFA it was $85 \pm 5\%$, showing the predicted increase in participation of the anisamide group. A practical method is thus suggested of improving the yields of those oxadiazines which are minor products in the thermal isomerization of unsymmetrical adducts.

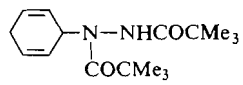
As part of a general study of the effect of the nature of the bridge on the stability of adducts of azodiacyls and cyclic 1,3-dienes we synthesized the [2.2.2]diazabicyclo derivatives **7**, m.p. 157–158°, and **8**, m.p. 126.5–127.5°, from cyclohexadiene in yields of 60 and 28% respectively. These adducts, unlike their cyclopentadiene counterparts, were completely stable at temperatures up to 150°. At 200° isomerization was complete in 1.5 h for **7** and 45 min for **8** (cf. likewise the greater stability of **2***a* than *b* (10)). The products **9**, m.p. 164.5–165.5°, and **10**, m.p. 66–67°, were identified as oxadiazines by their spectroscopic properties, in particular by the C=N chromophore in the u.v. spectrum at 294 nm for **9** and at 240 nm for **10**, and by the diagnostic (9, 10) splitting pattern of the *cis* tertiary hydrogens in the n.m.r. spectrum.[3]



7 R = Ph
8 R = CMe_3



9 R = Ph
10 R = CMe_3



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Rate values in solution could not therefore be obtained for **7** and **8** using the u.v. analytical technique described for the cyclopentadiene adducts, which isomerized readily in solution <90°. In view of the powerful catalytic effect of acids discussed above it seemed reasonable that isomerization rates for **7** and **8** might be brought within a range suitable for determination by u.v. spectrophotometry.

Refluxing of **7** in benzene containing 1.3×10^{-1} *M* TFA for 20 h indeed gave an 88% yield of **9**, along with small amounts of NH/OH containing material (i.r. spectrum), presumably arising by a solvolytic process. When the acid-catalyzed (1.3×10^{-1} *M*) reaction was followed

[3]The properties of the dihydro derivative of **9**, and of its precursor **7** and its dihydro derivative, were the same as those described (13, 14) for samples obtained by independent synthesis.

by repeated scan u.v. spectrophotometry at 62° in heptane the first order rate plot gave, as expected, a straight line fit only for the early stages. From the initial slope a rate constant of isomerization of 1.35×10^{-5} s^{-1} was obtained, corresponding to a half-life of 14.3 h. This value is greater than that for the adduct **2***a* by a factor of 3.9×10^4, representing a $\Delta\Delta G^{\ddagger}$ of 7.0 kcal mol^{-1} between the two adducts.

If the isomerizations for the [2.2.1] and the [2.2.2] ring systems are mechanistically analogous in both the catalyzed and the uncatalyzed case, so that the only energy differences in the $\Delta G^{\ddagger}$ terms arise from the differences in the bridge size, then the $\Delta\Delta G^{\ddagger}$ value is also applicable to the uncatalyzed reaction. On this basis the uncatalyzed rate constant for **7** in heptane at 62° has an estimated value of 4.4×10^{-10} s^{-1}, corresponding to a half-life of about 50 years.

Solvolytic pathways appeared to predominate when the isomerization of **8** was attempted in the presence of TFA in refluxing heptane. No **10** could be detected among the several products though it was in fact shown to be stable to the reaction conditions. Boron trifluoride etherate was more successful. A 1.6×10^{-3} *M* solution of it in heptane caused a 50% conversion of **8** to **10** after reflux for 15 min. Longer reflux times or higher catalyst concentrations led to the accumulation of by-products.

The synthesis of both cyclohexadiene adducts **7** and **8** was accompanied by the formation of much NH containing material which in the case of the azodibenzoyl reaction was not examined further. The azodipivaloyl reaction gave, as well as **8**, its dihydro derivative dipivaloylhydrazine, isolated in 40% yield from the total reaction product by water extraction (and probably arising by oxidation of cyclohexadiene to benzene), as well as a second 1:1 product of the azo compound and the diene. The latter was separated from **8** in 14% yield by silica gel chromatography, and was shown to be the product **11** of the "ene reaction" of the azo compound with the diene; this pathway is known to be the main one in the reaction of the diene with diethyl azodicarboxylate (15). The identity of **11** follows from the symmetrical pattern of the four vinyl protons and the presence of one N—H exchangeable with D_2O in its n.m.r. spectrum, and from the appearance only of end absorption in its u.v. spectrum.

Experimental

The following spectrometers were used: for i.r., a Beckman IR 10; for u.v., a Coleman EPS-3T Hitachi with a cell compartment heated by a constant temperature circulating pump; for n.m.r., a Varian T60 or HA100.

Microanalyses were done by The Baron Consulting Co., P.O. Box 663, Orange, Conn., U.S.A.

Solvents were purified and dried by conventional means. Anhydrous magnesium sulfate was used as drying agents for solutions in organic solvents. Melting points are uncorrected.

Compounds 1–4

All the azo compounds **1**, the adducts **2**, and their isomers **3** and **4** have been described or referred to earlier (10).

2,3-Dibenzoyl-2,3-diazabicyclo[2.2.2]oct-5-ene (7)

A solution of azodibenzoyl (1.19 g, 5 mmol) and 1,3-cyclohexadiene (Aldrich Chemical Co., 1.2 g, 15 mmol) in carbon tetrachloride (20 ml) was kept in the dark at room temperature for 20 h. Removal of some crystalline material (NH absorption in its i.r. spectrum) and concentration of the faintly orange filtrate gave slightly impure **7** (60%). Three crystallizations from ethanol and drying at 80° for 20 h gave prisms, m.p. 157–158° (lit. (14) m.p. 151–152°); $\nu(CCl_4)$ 1697, 1659 cm^{-1} (C=O); λ_{max} (EtOH) 220 (ε 14 500), 255 nm (ε 7850); $\tau(CDCl_3)$ 2.2–2.8 (10 phenyl H), 3.5 (2 vinyl H, broad), 4.6 and 5.2 (2 *tert* H, both broad[4]), 7.7 (2 methylene H, broad), 8.5, 8.7 p.p.m. (2 methylene H, doublet).

Hydrogenation of **7** was carried out in ethanol using di-imide generated by reaction of hydrazine with hydrogen peroxide. A solution of **7** (0.318 g, 1 mmol) in ethanol (15 ml) containing 95% hydrazine (1.2 ml) was brought to about 50° and 50% hydrogen peroxide (1.2 ml) in ethanol (6 ml) was added dropwise with vigorous stirring at a rate so as to maintain the temperature below the boiling point. The solution was finally stirred for 1/2 h and evaporated and the residue twice crystallized from aqueous ethanol giving 2,3-dibenzoyl-2,3-diazabicyclo[2.2.2]octane (80%) as needles, m.p. 174–176° (lit. (14) m.p. 171.5–172.5°); ν(Nujol) 1668 and 1632 cm^{-1} (C=O); λ_{max} (EtOH) (ε 15 700), 250 nm (ε 7580); $\tau(CDCl_3)$ 2.2–2.9 (10 phenyl H), 5.1 and 5.9 (2 *tert* H, both broad), 7.4–8.7 p.p.m. (8 methylene H).

cis-1-Benzoyl-4a,7,8,8a-tetrahydro-3-phenyl-1H-4,1,2-benzoxadiazine (9)

The adduct **7** was kept at 200° in a sealed evacuated tube for 1.5 h. The slightly colored melt crystallized on cooling and had an i.r. spectrum identical with that of analytical oxadiazine obtained as needles, m.p. 164.5–165.5°, from ethanol; $\nu(CCl_4)$ 1660 and 1650 (C=O, C=N, not necessarily respectively) 1091 cm^{-1} (C—O—C); λ_{max} (EtOH) 294 nm (ε 16 900); $\tau(CDCl_3$, 100 MHz) 2.1–2.9 (10 phenyl H), 3.7–4.1 (2 vinyl H, overlapping with complex splitting), 5.13 (C_{8a}—H, two triplets, $J_{8a,4a} = J_{8a,8A} = 3.6$ Hz, $J_{8a,8B} = 12$ Hz), 5.42 (H_{4a}, triplet containing $J = 3.6$ and another comparable splitting), 7.6 (C-7 methylene H_2, complex), 7.9, 8.3 p.p.m. (C-8 methylene AB system, $J_{AB} = 12$ Hz).

[4]They coalesce at higher temperatures. A fuller account of the properties and stability of 2,3-diazabicyclo[2.2.*n*] adducts from azodibenzoyl will be discussed in a forthcoming publication.

Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.16; H, 5.66; N, 8.34.

Hydrogenation with di-imide, as described for 7, gave *cis*-1-benzoyl-4*a*,5,6,7,8,8*a*-hexahydro-3-phenyl-1*H*-4,1,2-benzoxadiazine (82%), m.p. 162.5–163.5° (lit. (13) m.p. 163–164°) on crystallization from ethanol; $\nu(CCl_4)$ 1636, 1625 (C=O, C=N), 1094 cm^{-1} (C—O—C); λ_{max} (EtOH) 220 (ε 16 500), 291 nm (ε 15 800); $\tau(CDCl_3)$ 2.0–2.8 (10 phenyl H), 5.15 and 5.50 (2 *tert* H, both complex), 7.5–8.6 p.p.m. (8 methylene H).

*2,3-Dipivaloyl-2,3-diazabicyclo[2.2.2]oct-5-ene (**8**)*

A solution of azodipivaloyl (7.6 g, 38 mmol) and 1,3-cyclohexadiene (6.0 g, 75 mmol) in carbon tetrachloride (75 ml) was refluxed in the dark under nitrogen for 3 days. The red–brown solution was evaporated and the residual gum was triturated with hexane to give an off-white solid (9.0 g) containing three major and one minor product (t.l.c. on silica gel). Extraction of the solid with water gave from the extracts 1,2-dipivaloylhydrazine (3.0 g, 40%), which was purified by sublimation and identified by m.p. and mixed m.p., and by its i.r. and n.m.r. spectrum.

The water insoluble fraction was chromatographed in portions on silica gel using as eluant a mixture of ether: benzene: petroleum ether: ethyl acetate in the proportions 1:2:10:10. The first and main fraction was the *adduct* **8** (3.0 g total, 28%) which was crystallized from aqueous acetone as long needles, m.p. 126.5–127.5°; $\nu(CCl_4)$ 1712, 1642 cm^{-1} (C=O); u.v. end absorption only (EtOH or *iso*-octane); $\tau(CDCl_3)$ 3.57 (2 vinyl H, triplet, $J = 4.0$ Hz), 4.97 (2 *tert* H, broad singlet), 7.67–8.17 (4 methylene H, complex), 8.73 p.p.m. (18 *tert*-butyl H, singlet).

Anal. Calcd. for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.27; H, 9.64; N, 10.06.

Further elution gave the "ene" product *1,2-dipivaloyl-1-(2,5-cyclohexadienyl)hydrazine* (**11**) (1.50 g total, 14%), an analytical sample of which was prepared by recrystallization from aqueous acetone and then vacuum sublimation as fine prisms, m.p. 159–160°; $\nu(CCl_4)$ 3405 (NH, broad), 1715, 1657 cm^{-1} (C=O); u.v. end absorption only (EtOH); $\tau(CDCl_3$, 100 MHz) 2.99 (1 NH, broad singlet, exchangeable with NaOD), 3.97 (C_2—H and C_6—H, broad unsymmetrical doublet, $J = 10$ Hz, A_2 portion of A_2B_2), 4.19 (C_1—H, center portion only visible, but chemically shifted downfield from $C_{2,6}$—H as a broad multiplet in benzene-d_6), 4.37 (C_3—H and C_5—H, B_2 portion), 7.33 (C-4 methylene H_2, complex, at least 10 lines), 8.76, 8.80 p.p.m. (9 *tert* butyl H each, sharp singlets).

Anal. Found: C, 68.98; H, 9.33; N, 10.51.

*cis-1-Pivaloyl-4a,7,8,8a-tetrahydro-3-tert-butyl-1H-4,1,2-benzoxadiazine (**10**)*

The adduct **8** was heated in a sealed evacuated tube at 200° for 45 min. The *oxadiazine* **10** crystallized on cooling and had m.p. 64.5–66° directly. Recrystallization from aqueous acetone raised this to 66–67°; $\nu(CCl_4)$ 1650 cm^{-1} (C=O, C=N); λ_{max} (EtOH) 240 nm (ε 12 000); $\tau(CDCl_3$, 100 MHz) 3.97 (C_5—H, two triplets, $J_{5,6} = 9.5$, $J_{5,4a} = 3.3$ Hz), 4.12 (C_6—H, complex), 5.44 (C_{8a}—H, two triplets, $J_{8a,4a} = J_{8a,8A} = 3.6$, $J_{8a,8B} = 12$ Hz), 5.73 (C_{4a}—H, broadened triplet containing $J = 3.3$ and 3.6 Hz), 7.7 (C-7 methylene H_2, complex), 8.3 (C-8 methylene H_2, complex), 8.64 and 8.80 p.p.m. (9 *tert* butyl H each, sharp singlets).

Anal. Calcd. for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.11; H, 9.25; N, 9.98.

*TFA-Catalyzed Isomerization of **2a** to **3a** on a Preparative Scale*

TFA (4.9 μl, 0.1 equiv) was added to a refluxing solution of **2***a* (200 mg, 0.66 mmol) in benzene and the refluxing was maintained for 3 min. The solution was evaporated, the residue was triturated with two drops of methanol to induce crystallization, dilute aqueous ammonia was added, and the precipitate (180 mg, 90%) was collected. Its i.r. spectrum was superimposable on that of analytically pure **3***a*.

*Effect of Aqueous Acid on **2a** and **3a***

Solutions of the adduct **2***a* or its isomer **3***a* (152 mg, 0.5 mmol) in 77% aqueous ethanol containing 0.10 *M* hydrochloric acid reacted completely in about 1 day at room temperature. Evaporation gave gummy solid residues which were identical in all respects, having superimposable i.r. and u.v. spectra and containing four components (t.l.c.).

The effect of the same solvent medium on a very dilute solution (*ca.* 10^{-4} *M*) of adduct was monitored at 35° by following the increase in absorbance at 290 nm (see below for details of kinetic experiments), which reached a maximum after 55 min and then began to fall. An estimate of the initial slope of a first order rate plot gave a half-life of 20 min.

*Isomerization of **2a** by Other Catalysts*

In the following the isomerization of the adduct **2***a* was followed by n.m.r. spectroscopy (probe temperature 35°).

(a) p-Toluenesulfonic acid: 19 mg (0.2 equiv) was added to a solution of the adduct (152 mg, 0.5 mmol) in dimethylsulfoxide-d_6 (1 ml). Reaction was complete in about 8 h.

(b) Boron trifluoride etherate: 14.2 mg (0.2 equiv) in chloroform-*d* (0.25 ml) was added to a solution of the adduct (152 mg, 0.5 mmol) in chloroform-*d* (0.25 ml). Reaction was complete before the spectrum could be run.

(c) Tin(IV) chloride: 26 mg (1 equiv) in methylene chloride (0.5 ml) was added to a solution of the adduct (76 mg, 0.25 mmol) in methylene chloride (0.5 ml). The reaction was monitored in the region of absorption of the CH_2 group and was complete in about 4 min. Lesser amounts of catalyst caused incomplete isomerization.

In the work-up for reactions *a* and *b* the solutions from the n.m.r. tube were evaporated to dryness in a stream of nitrogen and dilute aqueous ammonia was added. The oxadiazine crystallized and was filtered off. The i.r. spectrum was identical with that of analytically pure material.

In reaction *c*, dilute aqueous ammonia was added and the methylene chloride extracts were dried and evaporated. The residue was slightly gummy and had a weak absorption in the NH region of its i.r. spectrum, but one crystallization from aqueous methanol gave pure oxadiazine.

*TFA-Catalyzed Isomerization of **2e** to **3e** and **4e***

A solution of **2***e* (0.2 g, 0.69 mmol) in benzene (50 ml) containing TFA (1.3×10^{-1} *M*) was refluxed for 2 min and then evaporated. Integration of the methoxy signals in the n.m.r. spectrum at 100 MHz (10) showed the presence of $85 \pm 5\%$ of **4***e*, before and after work-up with dilute aqueous ammonia.

*TFA-Catalyzed Isomerization of **7** to **9***

A solution of 7 (80 mg, 0.25 mmol) in benzene (30 ml)

containing TFA (1%, 1.3×10^{-1} *M*) was refluxed for 20 h and then evaporated to dryness in a stream of nitrogen. An excess of dilute aqueous ammonia was added and the crystalline residue (70 mg, 88%) filtered off. Its spectrum was the same as that of pure **9**, and it had m.p. and mixed m.p. 163.5–164.5° after crystallization from aqueous ethanol. The balance of the reaction product was found in the ammoniacal filtrate by evaporation to dryness and extraction of the residue with methylene chloride which gave a gummy solid with i.r. absorption in the OH/NH and C=O regions.

Attempted Isomerization of **8** *to* **10** *with Acid Catalysts*

(a) Trifluoroacetic Acid

A sample of **8** was refluxed in heptane containing 1.3×10^{-1} *M* TFA for 15 min and evaporated. The residue was taken up in carbon tetrachloride and extracted with aqueous ammonia. The organic layer was dried and shown by t.l.c. on silica gel to contain at least four products, none of which was **8** or **10**.

Control experiment: A sample of **10** was recovered essentially pure when refluxed as above for 20 min.

(b) Boron Trifluoride Etherate

The adduct (0.318 g, 1.14 mmol) was refluxed for 15 min in heptane (45 ml) containing 1.6×10^{-3} *M* boron trifluoride etherate and the clear solution was evaporated under reduced pressure. The n.m.r. analysis of the residue in carbon tetrachloride showed it to be an equimolar mixture of **8** and **10**; silica gel t.l.c. showed a trace of a third substance. Column chromatography on silica gel using ether:benzene:petroleum ether:ethyl acetate in the proportions 1:2:20:20 as eluant gave the oxadiazine (163 mg, 51%) as the first material eluted, identified by n.m.r. and i.r. spectroscopy.

Refluxing with a more concentrated (1.8×10^{-2} *M*) solution of TFA for 30 min caused complete reaction of **8**, but the oxadiazine was then contaminated with two N—H containing products.

Kinetic Determinations by Ultraviolet Spectrophotometry

Dilute solutions in the range 10^{-4}–10^{-5} *M* were used in 10 mm quartz cells (Hellma Canada Ltd.) with Teflon stoppers. These gave an excellent fit, allowing no evaporation losses over periods of several days, even within 10° of the solvent boiling point.

The purely thermal reactions in heptane and the reaction in heptane containing acetic acid were carried out by the repeated scan technique used in earlier work (9). The thermal reactions in benzene were followed by measuring the increase in absorbance with time at a suitable fixed wavelength, 325 nm for **2***a*, 335 nm for **2***c*, and 340 nm for **2***d*.

All the TFA-catalyzed reactions on the compounds **2***a–d* were also followed at a fixed wavelength using an external recorder (Beckman Ten-Inch Linear) running at a suitable high speed. An average of at least three runs was used in each case. The solutions in the cell were all brought to the required temperature and the TFA introduced using a 10 or 50 μl syringe as appropriate. For reactions whose half-lives were greater than a few seconds the cell was stoppered, shaken manually, and immediately returned to the compartment. For the very fast reactions the cell compartment lid was replaced by a styrofoam cover fitted with an electrical contact and a hole directly above the sample cell. Through this and through one of two holes in the Teflon stopper of the cell passed a stainless steel stirrer; the other hole permitted passage of the syringe needle. Immediately after injection of the TFA the solution was stirred with two strokes of the stirrer which was then held above the light path while the absorbance change was being recorded.

In the hydrogen chloride-catalyzed reaction the heptane was saturated with the gas and the solution standardized by titration. The required amount was then introduced with the microsyringe.

All the reactions, catalyzed or uncatalyzed, gave excellent first order kinetics throughout.

The isomerization of **7** in heptane at 62° in the presence of 1.3×10^{-1} *M* TFA was also followed by the repeated scan technique. The curves passed through an isobestic point at 263 nm for the first 5 h but then drifted away from this point. A pure sample of the oxadiazine **9** was used to obtain a value for A_∞, the final absorbance which would have been observed in a quantitative isomerization. The initial slope of the plot of $\ln (A_\infty - A_t)$ against t gave the rate constant for the isomerization.

We wish to thank the National Research Council of Canada for financial assistance.

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