Transannular Interaction in 3-Heterobicyclo[3.3.0]octanes, Implications for the Mechanism of Biotin Action

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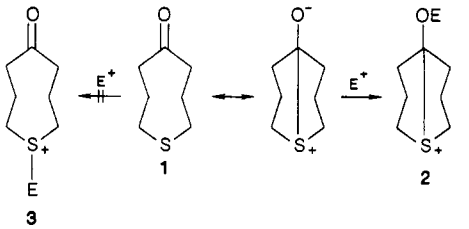
endo(*exo*)-7-(Tosyloxy)-3-thiabicyclo[3.3.0]octane and *endo*(*exo*)-7-(tosyloxy)-3-oxabicyclo[3.3.0]octane were synthesized from the corresponding 3-heterobicyclo[3.3.0]octan-7-ones. For *exo*-7-(tosyloxy)-3-thiabicyclo-[3.3.0]octane, solvolysis in methanol resulted in a retention/inversion ratio of 2.3. The entropy of activation was found to be ca. −39 J/mol K in 80% ethanol/water. The three other tosylates underwent substitution with exclusive inversion, entropies of activation ranging from −49 to −54 J/mol K. These results are interpreted in terms of a weak transannular sulfur–C_7 interaction. In *exo*-7-(tosyloxy)-3-thiabicyclo[3.3.0]octane, anchimerically assisted displacement of the tosyloxy group gives rise to the retention product. Attempts to observe the 5-methyl-1-thioniatricyclo[3.3.0.$0^{3,7}$]octane cation by low-temperature ^{1}H and ^{13}C NMR failed. Coordination to the ring heteroatom instead of ionization was found upon addition of antimony pentafluoride to 3-thiabicyclo[3.3.0]octan-7-one, *exo*-7-chloro-7-methyl- and *endo*-7-methoxy-7-methyl-3-thiabicyclo[3.3.0]octane, the *endo*-7-hydroxy-7-methyl derivative gave complex product mixtures. Alkylation of 3-thiabicyclo[3.3.0]octan-7-one with triethyloxonium tetrafluoroborate yielded exclusively the S-ethylated product. 1′,3′-*N*-Bis(phenylsulfonyl)biotin methyl ester was found to coordinate antimony pentafluoride to the ester carbonyl group. From the whole of the data it is concluded that sulfur transannular interaction cannot play a significant role in the mechanism of biotin action.

Introduction

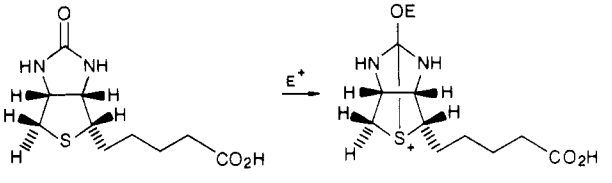
Transannular interactions in medium size ring compounds have been the subject of intensive and highly successful research activities, including both physical organic[1] and synthetic aspects.[2] Among many other results, a thorough understanding of the trajectory of nucleophilic attack on the electrophilic carbon atom of a carbonyl group was achieved, commonly referred to as the Bürgi–Dunitz principle.[3]

Astonishing reactivities can be observed due to transannular interactions. For example, when treated with an electrophile, 5-thiacyclooctanone (**1**, eq 1) almost exclu-



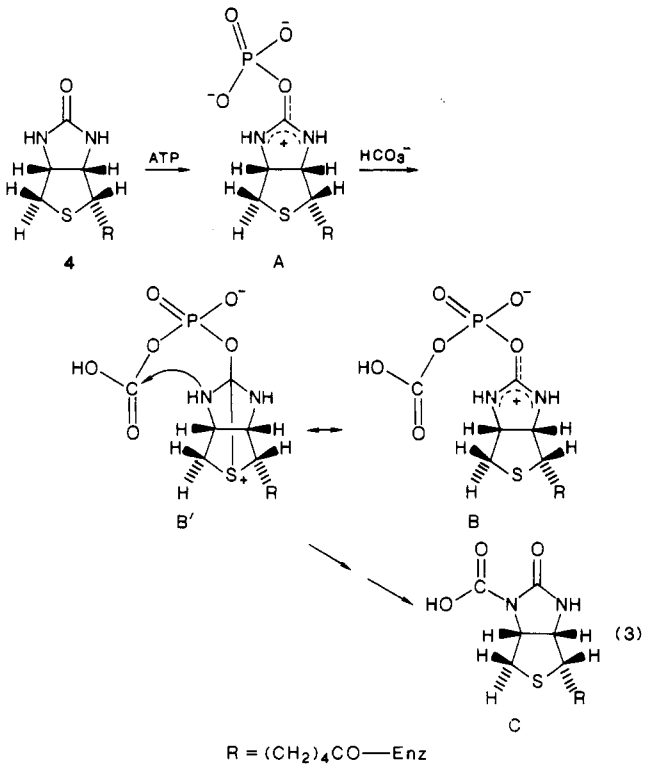
(1)

sively yields the bicyclic sulfonium salts **2** (eq 1) and not the S-addition products **3** (eq 1).[4] This observation led to the assumption that a similar sulfur–carbonyl interaction might be effective in the coenzyme biotin[5] (**4**, eq 2).



(2)

In fact it is believed that the first steps in the biochemical reaction of biotin, i.e. transfer of carbon dioxide, consist of phosphorylation at the urea oxygen followed by condensation with bicarbonate and intramolecular carboxylation at 1′-N[6] (eq 3). 1′-N-Carboxybiotin (C, eq 3), the actual carboxyl carrier, is finally obtained together with inorganic phosphate. Transannular sulfur–carbonyl interaction in the intermediate B′ (eq 3) would render 1′-N more nucleophilic, thus facilitating carboxylation on nitrogen (B, B′ → C, eq 3).



(3)

* Liebig Fellow of the Fonds der Chemischen Industrie, 1986–1988.

(1) (a) Huisgen, R. *Angew. Chem.* **1957**, *69*, 341. (b) Leonard, N. J. *Acc. Chem. Res.* **1979**, *12*, 423.

(2) For a review on preparative aspects of neighboring-group effects in organic sulfur compounds see: Gundermann, K. D. *Angew. Chem.* **1963**, *75*, 1194.

(3) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153.

(4) (a) Leonard, N. J.; Brown, T. L.; Milligan, T. W. *J. Am. Chem. Soc.* **1959**, *81*, 504. (b) Leonard, N. J.; Milligan, T. W.; Brown, T. L. *J. Am. Chem. Soc.* **1960**, *82*, 4075.

(5) Mildvan, A. S.; Scrutton, M. C.; Utter, M. F. *J. Biol. Chem.* **1966**, *241*, 3488.

(6) (a) Dugas, H.; Penney, C. *Bioorganic Chemistry*; Springer: New York, 1981. (b) Kluger, R.; Davis, P. P.; Adawadkar, P. D. *J. Am. Chem. Soc.* **1979**, *101*, 5995. Reference 6a also discusses alternative carboxylation mechanisms.

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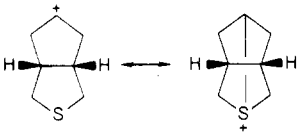
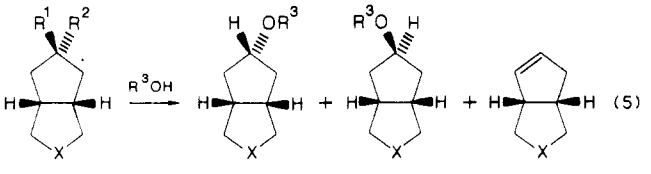
Various approaches have been taken to either prove or disprove this interesting assumption of a transannular S → C=O interaction in the cofactor biotin. Basicity measurements[7] and kinetic investigations of the N–H proton exchange[8] as well as structural elucidation of stable adducts formed by reacting electrophiles with biotin (4) and derivatives acylated at 1′-N[9] are reported in the literature. So far, none of them indicated significant sulfur–carbonyl interaction. Of course, biotin (4) is a urea derivative, and therefore the electrophilicity of its carbonyl carbon is greatly diminished compared to that of ketones such as 1 (eq 1).

With this in mind it appeared worthwhile addressing the more fundamental question of whether transannular stabilization of positive charge can effectively occur in 3-thiabicyclo[3.3.0]octanes (eq 4). Here, no mesomeric



(4)

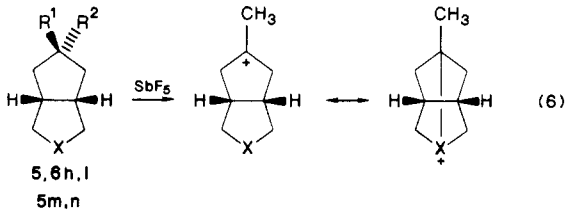
stabilization of a C-7 carbocation by adjacent heteroatoms can occur. Two general strategies were followed for the generation of a cationic center at C-7. Solvolyses of exo and endo tosylates were carried out, and the product distributions and activation parameters were determined (**5c,d**, eq 5). For the generation and NMR study of stable



(5)

5,6c,d (5: X = S; 6: X = O) **5,6e** (c: R^1 = H, R^2 = OTs) **5,6f** (d: R^1 = OTs, R^2 = H) **5,6g** (R^3 = Me, Et)

cations, the antimony pentafluoride promoted ionization of substrates bearing suitable leaving groups at C-7 was attempted (**5h,l,m,n**, eq 6). For comparison, the behavior



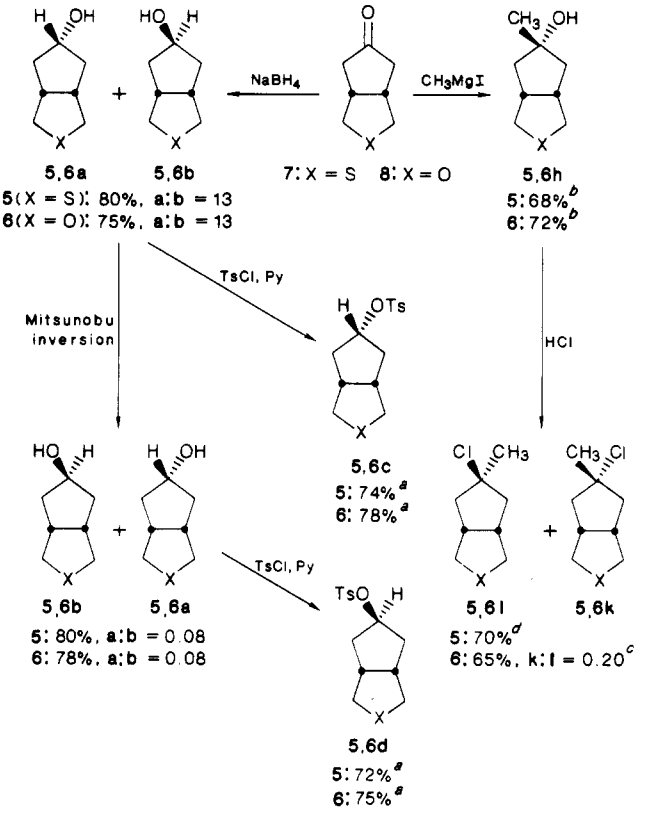
(6)

5,6h,l **5m,n**

5: X = S; 6: X = O; h: R^1 = CH_3, R^2 = OH; l: R^1 = Cl, R^2 = CH_3; m: R^1 = CH_3, R^2 = OCH_3; n: R^1 = R^2 = OCH_3

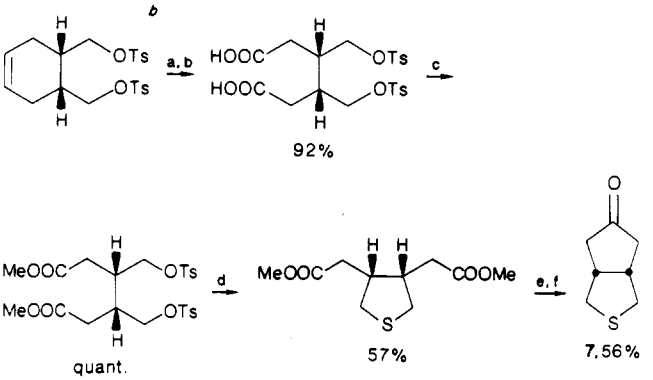
of the corresponding 3-oxabicyclo[3.3.0]octanes **6** (eq 5, 6) was studied as well. Furthermore, the reactivity of the ketones **7** and **8** toward antimony pentafluoride was investigated as well as that of 1′,3′-*N*-bis(phenylsulfonyl)-biotin methyl ester **9**. The latter one represents a biotin derivative with strongly reduced electron density in the urea moiety. Finally, the structure of the product resulting

Scheme I



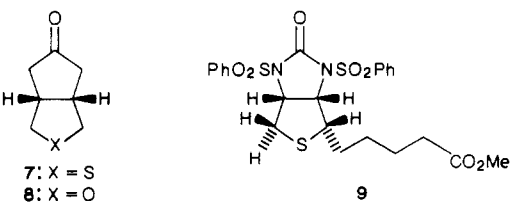
[a] Isomerically pure after crystallization (270-MHz ^{1}H NMR analysis. [b] No exo-alcohol formed (270-MHz ^{1}H NMR analysis). [c] The exo/endo mixture was used without separation. [d] No endo chloride formed (270-MHz ^{1}H NMR analysis).

Scheme II[a]



[a] (a) O_3; (b) HCO_3H; (c) CH_2N_2; (d) Na_2S; (e) NaH; (f) H^+/H_2O. [b] Reference 12.

from the alkylation of ketone **7** with triethyloxonium tetrafluoroborate was elucidated.



7: X = S
8: X = O

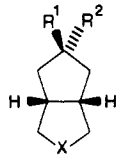
9

Results

(a) Syntheses. The synthesis of the endo/exo tosylates **5,6c,d**, the endo tertiary alcohols **5,6h**, and the exo chlorides **5,6l** is depicted in Scheme I. The starting ketone

(7) Bowen, C. E.; Rauscher, E.; Ingraham, L. L. *Arch. Biochem. Biophys.* **1968**, *125*, 865.
(8) (a) Perrin, C. L.; Dwyer, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 5163. (b) Fry, D. C.; Fox, T. L.; Lane, M. D.; Mildvan, A. S. *J. Am. Chem. Soc.* **1985**, *107*, 7659.
(9) Berkessel, A.; Breslow, R. *Bioorg. Chem.* **1986**, *14*, 249.

Table I. Solvolysis of the Tosylates 5,6c,d: Rates of Reaction, Activation Parameters,[a] and Product Distributions[d]



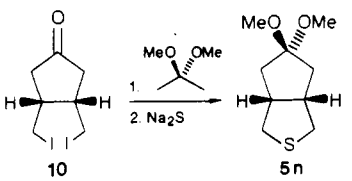
entry	tosylate	temperature,[b] °C	rate of solvolysis,[c] s^{-1}	$\Delta H^{\ddagger}$,[c] kJ mol^{-1} $\Delta S^{\ddagger}$,[c] J mol^{-1} K^{-1}	product distribution[e] endo (exo) methyl ether[f] 5,6e (5,6f)	product distribution[e] olefin 5,6g[f] (product balance[g])
1	5c: X = S, R^1 = H, R^2 = OTs	49.6	$5.53 \pm 0.15 \times 10^{-5}$			
		60.7	$1.75 \pm 0.07 \times 10^{-4}$	88.4 ± 0.3	0[h]	8
		70.5	$4.37 \pm 0.15 \times 10^{-4}$	-53.1 ± 1.2	(92)	(96)
2	5d: X = S, R^1 = OTs, R^2 = H	49.6	$9.38 \pm 0.09 \times 10^{-5}$			
		60.7	$3.02 \pm 0.08 \times 10^{-4}$	91.6 ± 0.3	28	7
		70.5	$7.95 \pm 0.14 \times 10^{-4}$	-39.2 ± 0.8	(65)	(99)
3	6c: X = O, R^1 = H, R^2 = OTs	49.6	$3.25 \pm 0.10 \times 10^{-5}$			
		60.7	$1.03 \pm 0.03 \times 10^{-4}$	92.0 ± 0.1	0[h]	15
		70.5	$2.37 \pm 0.03 \times 10^{-4}$	-49.5 ± 3.5	(85)	(93)
4	6d: X = O, R^1 = OTs, R^2 = H	49.6	$2.18 \pm 0.02 \times 10^{-5}$			
		60.7	$6.95 \pm 0.21 \times 10^{-5}$	92.0 ± 0.1	83	17
		70.5	$1.87 \pm 0.02 \times 10^{-4}$	-49.8 ± 0.5	(0[h])	(92)

[a] Ethanol/water, 8:2. [b] Accuracy ±0.1 °C. [c] Solvolyses were run in duplicate, numbers given are mean values and maximum aberrations of single measurements from the mean value. [d] Ca. 0.03–0.06 M tosylate in CD_3OD, 74 °C, 60–80% conversion. [e] Accuracy ca. ±3%, relative. [f] Mol %, relative. [g] Mol %, absolute. [h] Not detectable by 270-MHz ^1H NMR spectroscopy.

8 was prepared as described elsewhere,[10] ketone 7 was either obtained from its known ethylene ketal[11] or by the shorter and more convenient sequence outlined in Scheme II.

Although the stereochemistry at C-7 of the 3-heterobicyclo[3.3.0]octanes **5,6a–d,h,k,l** (Scheme I) is already clearly predictable from the synthetic sequence employed, it was exemplarily confirmed by NOE spectroscopy on compounds **5c,d**, **5,6h**, and **5l** (Scheme I). For example, endo alcohol **6h** showed a 1.5% NOE of the 6,8-H_{exo} signals upon irradiation of the methyl resonance, whereas irradiation of exo tosylate **5d** at the 7-H resonance resulted in a 8.9% NOE of the 6,8-H_{endo} signals.

The alcohols **5,6a,b** and **5h** (Scheme I) could be converted to the corresponding methyl ethers **5,6e,f** and **5m** (eq 5, 6) by treatment with sodium hydride/methyl iodide in good yields. Dimethyl ketal **5n** was obtained from the known diiodide **10**[10] as shown in eq 7. Sulfonylation of



10 5n (7)

biotin methyl ester[13] with benzenesulfonyl chloride/sodium hydride afforded the biotin derivative **9** in 68% yield.

(b) Solvolyses. The endo/exo tosylates **5,6c,d** (Scheme I) were solvolized in ethanol/water, 8:2 (v/v), at 49.6, 60.7, and 70.5 °C. The formation of toluenesulfonic acid was monitored by conductivity measurements. The rate constants obtained by pseudo-first-order analysis of the time vs conductivity profiles are given in Table I, together with the enthalpies and entropies of activation.

Furthermore, the endo/exo tosylates **5,6c,d** (Scheme I) were solvolized in methanol-d_4 in sealed NMR tubes at 74 °C. The identities of the solvolysis products were established by comparison of the 270-MHz ^1H NMR spectra with those of the authentic samples **5,6e,f** (eq 5). Resonances in the region δ 5.40–5.80 ppm were assigned to the elimination products **5,6g** (eq 5). The quantitative assessment of the reaction products rests upon multiple ^1H NMR integrations of the well-separated 7-H resonances and is also given in Table I. In all cases, product balances were better than 92%.

(c) Low-Temperature NMR Experiments. The 3-heterobicyclo[3.3.0]octanes **5,6h,l** and **5m** (Scheme I, eq 6) were reacted with equimolar amounts of antimony pentafluoride in liquid sulfur dioxide at −78 °C. The mixtures were then transferred into coaxial NMR tubes and sealed, the inner tube being charged with methylene-d_2 chloride/TMS as lock solvent and standard, respectively. NMR spectra were recorded at the temperatures stated in Table II, which also gives a summary of the ^{13}C NMR shift differences observed upon reacting the 3-heterobicyclo[3.3.0]octanes with the Lewis acid. The assignment of the C-2,4 and C-6,8 triplets rests upon selective irradiation of the corresponding ^1H resonances and observation of the C-7 ^{13}C signal. When the selective ^1H decoupling was done at the 6,8-H frequency, the triplet fine structure of the C-7 resonance vanished and the C-6,8 triplet also collapsed to a singlet.

Inspection of Table II clearly reveals that the substrates under scrutiny yielded neither carbocationic products (^{13}C NMR resonances typically found in the range 300–350 ppm[14a,b]) nor bridged oxonium or sulfonium ions. In the latter case, downfield shifts of comparable magnitude should result for the ^{13}C NMR resonances of C-2,4 and

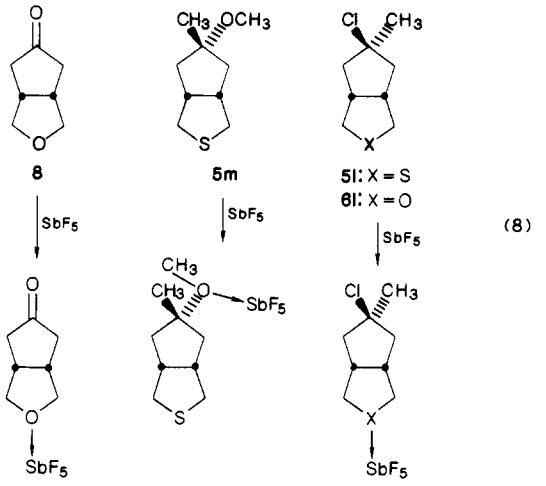
(10) Baraldi, P. G.; Pollini, G. P.; Simoni, D.; Barco, A.; Benetti, S. *Tetrahedron* **1984**, *40*, 761.
(11) Baraldi, P. G.; Barco, A.; Benetti, S.; Gandolfi, C. A.; Pollini, G. P.; Polo, E.; Simoni, D. *Gazz. Chim. Ital.* **1984**, *114*, 177.
(12) (a) Ladbury, J. E.; Turner, E. E. *J. Chem. Soc.* **1954**, 3885. (b) The reported yield can be raised to 73% employing 5 equiv of tosyl chloride and lowering the reaction temperature to −28 °C.
(13) Knappe, J.; Ringelmann, E.; Lynen, F. *Biochem. Z.* **1961**, *335*, 168.
(14) (a) Olah, G. *Angew. Chem.* **1973**, *85*, 183. (b) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972. (c) Olah, G. A.; Donovan, D. J.; Lin, H. C.; Mayr, H.; Andreozzi, P.; Klopman, G. *J. Org. Chem.* **1978**, *43*, 2268.
(15) Exclusive binding to the carbonyl oxygen should result in a downfield shift of the carbonyl resonance of ca. 20–30 ppm: Hartmann, J. S.; Stilbs, P.; Forsén, J. *Tetrahedron Lett.* **1975**, 3497.

Table II. ^{13}C NMR Resonances of Compounds 5l,m, 6h,l, 7, and 8 Before and After Reaction with Electrophiles[a]

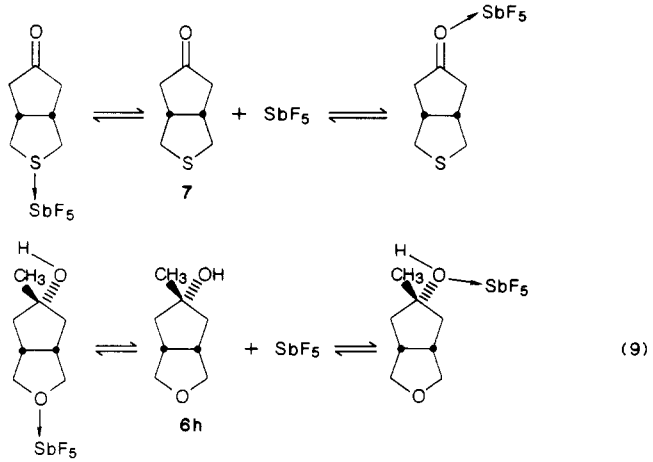
entry	1	2	3	4	5	6	7
substrate	7	7[b]	8	5l	5m	6h	6l
electrophile	SbF_5	$Et_3O^+BF_4^-$	SbF_5	SbF_5	SbF_5	SbF_5	SbF_5
solvent	SO_2	CD_3CN	SO_2	SO_2	SO_2	SO_2	SO_2
temperature, °C	−60	ambient	−60	−60	−60	−60	−60
δ,[a] ppm							
C-1,5	44.86	45.44	39.60	47.61	46.02	43.49	44.78
	(44.79)	(43.82)	(40.79)	(47.83)	(47.27)	(42.91)	(43.89)
C-2,4	36.63	37.33	72.61	40.78	40.99	76.10	73.70
	(41.36)	(46.43)	(84.57)	(44.34)	(43.69)	(79.73)	(81.74)
C-6,8	42.08	43.52	42.02	51.74	45.02	48.80	51.25
	(41.98)	(42.57)	(42.32)	(50.61)	(44.48)	(47.56)	(50.87)
C-7	221.37	218.10	223.46	84.26	87.39	83.70	85.85
	(224.28)	(215.01)	(225.06)	(82.92)	(94.62)	(94.59)	(83.88)
OCH_3					50.80		
					(53.63)		
CH_3				30.71	23.78	26.81	30.43
				(30.74)	(23.04)	(22.90)	(30.47)

[a] δ values after complexation are given in brackets, δ(TMS) = 0 ppm. [b] $\delta(CH_3) = 10.19$, $\delta(CH_2) = 37.09$ ppm.

C-7.[14c] Instead, the Δδ patterns observed indicate that ketone 8, methyl ether **5m**, and the exo chlorides **5,6l** simply formed the Lewis acid–base adducts shown in eq 8. In the cases of the bifunctional Lewis bases **7** and **6h**,



the shift pattern together with the relative broadness of the C-7 and C-2,4 resonances indicated that the Lewis acid was equilibrating between the ring heteroatom and the oxygen attached to C-7 (eq 9). When the endo alcohol



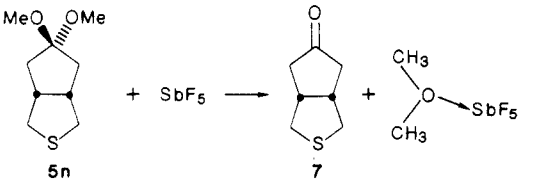
5h was reacted with antimony pentafluoride at −78 °C, rapid decomposition to a complex product mixture was observed by ^{13}C NMR spectroscopy. The reaction of the dimethyl ketal **5n** with 1 equiv of antimony pentafluoride in liquid sulfur dioxide was followed by ^1H NMR spectroscopy. After an initial period of continuous changes,

Table III. C=O Stretching Frequencies[a] of 5-Thiacyclooctanone[b] and Bicyclic Ketones 7 and 8 in Various Solvents

entry	solvent	5-thiacyclo-octanone (1)[b]	3-thiabicyclo-[3.3.0]octan-7-one (7)	3-oxabicyclo-[3.3.0]octan-7-one (8)
1	cyclohexane	1713, 1696	1754	1752
2	chloroform	1696, 1686	1741	1739
4	2,2,2-trifluoro-ethanol		1731	1735

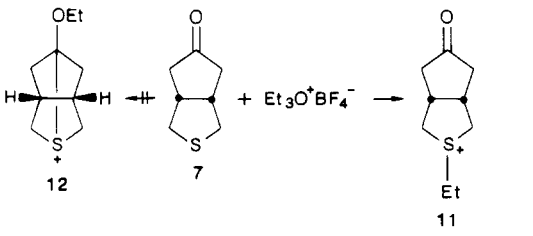
[a] In cm^{-1}. [b] Literature ref 4.

the set of resonances of the thiaketone **7** remained, together with a 6H singlet, attributable to dimethyl ether coordinated to antimony pentafluoride[16] (eq 10). The



reaction of the biotin derivative **9** with antimony pentafluoride was followed by ^1H NMR, too. At −60 °C in liquid sulfur dioxide, the shift pattern indicated coordination of the Lewis acid to the ester carbonyl group (cf. Experimental Section). Thus the bis(sulfonamide) **9** does not serve as a suitable model compound.

(d) Miscellaneous. Treatment of the thiaketone **7** with triethyloxonium tetrafluoroborate in methylene chloride at ambient temperature resulted in the rapid and quantitative formation of a crystalline product. This material could unambiguously be shown to be the sulfonium ion **11** and not the tricyclic product **12** (eq 11). It is sufficient



to mention here that its carbonyl stretching frequency in the IR (1734 cm^{-1}) is virtually the same as that of the starting ketone **7** (Table III).

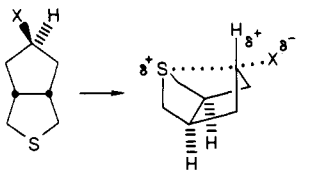
(16) Fratiello, A.; Kubo, R.; Liu, D.; Vidulich, G. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1415.

Discussion

It is apparent from the outcome of the attempted ionizations of the bicyclo[3.3.0]octanes **5,6h,l**, **5m**, **7**, **8** (eq 8, 9) and **5n** (eq 10) that the tendency of the substrates to form a cationic center at C-7 is not significantly enhanced by the heteroatom in the 3-position. Especially the reactivity of 3-thiabicyclo[3.3.0]octan-7-one (**7**, eq 9, 11) is in striking contrast to its monocyclic analogue **1** (eq 1).[4] Whereas the sulfur–carbonyl interaction in the latter one is already manifested by the occurence of two C=O bands in the IR spectrum (Table III), ketone **7** shows no such band splitting (Table III). Furthermore, the monocyclic ketone **1** is known to add electrophiles almost exclusively to the carbonyl oxygen, forming stable bicyclic sulfonium ions (eq 1). Bicyclooctanone **7**, however, shows no such tendency, as exemplified by its reaction with antimony pentafluoride (eq 9) and the structure of its ethylation product **11** (eq 11). Formation of a tricyclic cation as an unstable intermediate may be invoked in the decomposition reaction of the endo alcohol **5h**; however, no unequivocal experimental evidence is available so far.

In summary it appears that transannular interaction with the 7-position in 3-heterobicyclo[3.3.0]octanes is much too weak to allow for the formation of *stable tricyclic cations* of the type depicted in eq 4 or 6.

Nevertheless sulfur—but not oxygen—in the 3-position of 3-heterobicyclo[3.3.0]octanes is able to interact with a developing positive charge at C-7, yielding a cationic species of type **13** (eq 12) as a *kinetically important intermediate*. This assumption of a partial charge delo-



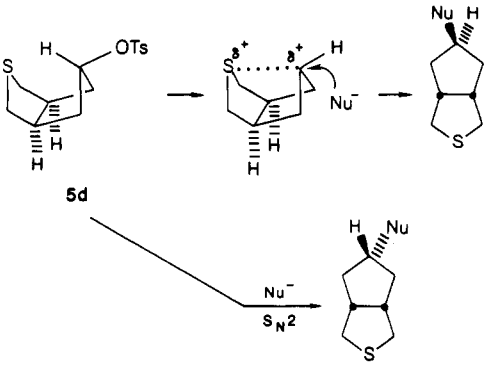
(12)

13

calization to the sulfur atom was first derived from the observation that endo alcohol **5h**, although a typical S_N1 substrate, nevertheless gives exclusively the exo chloride **5l** upon treatment with hydrogen chloride (Scheme I). In contrast, its oxygen analogue **6h** affords both endo and exo chloride (**6k,l**, Scheme I) in a ratio expected from the relative ease of attack on the two faces of the intermediate C-7 carbocation (exo/endo = 5:1, Scheme I).

More detailed information could finally be obtained from the solvolysis of the tosylates **5,6c,d** (Scheme I). Inspection of Table I (entries 3,4) reveals that *endo*-3-oxabicyclic tosylate **6c** and its exo isomer **6d** solvolyze at almost identical rates, the endo tosylate **6c** being slightly faster ($k_{6c}/k_{6d} \approx 1.5$). Activation parameters are in the typical range of S_N2 reactions. Furthermore, substitution products are formed with exclusive inversion at C-7 (Table I, entries 3, 4).

A similar behavior is observed in the case of *endo*-3-thiatosylate **5c** (Table I, entry 1). Its exo isomer **5d**, however, yields the substitution product in a *retention/inversion ratio of 2.3* (Table I, entry 2) and solvolyzes somewhat faster than the endo tosylate **5c** ($k_{5d}/k_{5c} \approx 1.7$). The remarkable stereochemical outcome of the solvolysis of exo tosylate **5d** can easily be explained by assuming anchimeric assistance of the sulfur atom in the displacement of the tosyloxy group (eq 13). Obviously, the positive charge can only partially be on sulfur. Formation of a tricyclic sulfonium ion with three equally strong S–C bonds should give rise to products resulting from attack of the nucleophile on the 2,4-positions at least to some extent. Furthermore, the entropy of activation of the solvolysis



5d (13)

of exo tosylate **5d** is significantly higher compared to **5c** and **6c,d** (Table I), but still far away from the typical S_N1 range (ca. 0–40 J/mol K[17]). Consequently, the formation of inversion product in the solvolysis of exo tosylate **5d** is best explained by competing S_N2 reactivity.

Conclusion

A carbocationic center at C-7 of a 3-thia- but not of a 3-oxabicyclo[3.3.0]octane is weakly stabilized by the heteroatom in the 3-position. The formation of a stable tricyclic sulfonium ion appears to be unfavorable. Force field calculations on the parent hydrocarbons *cis*-bicyclo[3.3.0]octane and tricyclo[3.3.0.$0^{3,7}$]octane revealed that 3,7-bridging in the bicycle results in a rise in strain energy of ca. 30–35 kcal/mol.[18] On the other hand, 1,5-bridging in cyclooctane leading to *cis*-bicyclo[3.3.0]octane does not result in a significant increase in strain energy (0–3 kcal/mol).[18] Clearly, the results obtained for the hydrocarbons cannot quantitatively be applied to the heterocycles discussed here. Nevertheless, the increase in strain energy associated with 3,7-bridging in *cis*-bicyclo[3.3.0]-octane may well explain the observed weakness of transannular 3,7-interaction.

Due to the high electron density of a urea moiety compared to a ketone, transannular S → C=O interaction in biotin (**4**, eq 2) appears extremely unlikely. This result is in agreement with earlier conclusions drawn from the kinetics of H/D exchange in biotin,[8] basicity measurements,[7] and structural elucidation of adducts formed from biotin derivatives with various Lewis acids.[9]

Experimental Section

General Procedures. Melting points are uncorrected. Elemental analyses were carried out by Schwarzkopf analytical labs, New York, NY, or by Analytische Laboratorien Malissa and Reuter, Engelskirchen, West Germany. IR spectra were recorded on a Perkin-Elmer 257 instrument. ^1H NMR spectra were measured at 270 MHz on a Bruker WH-270 spectrometer or at 300 MHz on a Bruker AM-300 spectrometer. ^{13}C NMR spectra were taken at 67.9 MHz on a Bruker WH-270 instrument or at 75.5 MHz on a Bruker AM-300 instrument. Low-temperature spectra in liquid sulfur dioxide were recorded with use of coaxial NMR tubes, the inner tube being charged with CD_2Cl_2/TMS as lock solvent/reference. Triethyl oxonium tetrafluoroborate was freshly prepared prior to use.[19] Satisfactory analytical data (^1H NMR, IR, elemental analyses) were obtained for compounds **5a–f,h,l–n** and **6a–f,h,k,l** and are available as Supplementary Material.

Syntheses. Dimethyl *meso*-3,4-Bis[(tosyloxy)methyl]-hexanedioate. *CAUTION*: Operations on the isolated hydroperoxide should always be carried out behind a safety shield. The

(17) Schaleger, L. L.; Long, F. A. *Adv. Phys. Org. Chem.* **1963**, *1*, 1.
(18) Engler, E. M.; Andose, J. D.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8005.
(19) Meerwein, H. *Organic Syntheses*; Wiley: New York, 1973; Collect. *Vol.* V, p 1080.

ozonolysis/oxidative workup should not be carried out on larger scale. A solution of 5.00 g (11.1 mmol) of *meso*-4,5-bis[(tosyloxy)methyl]cyclohexene[12] in 250 mL of a 2:1 methylene chloride/methanol mixture was placed into a 500-mL round-bottomed flask. Ozone was bubbled through the solution at −90 °C until the blue color of excess ozone persisted. Excess ozone was removed by stripping with nitrogen, and the solvent was removed in vacuo. The remaining colorless oil was taken up in a mixture of 9.60 mL of formic acid and 1.65 mL of 30% hydrogen peroxide. The flask was immersed into a water bath and kept at 20 °C for 14 h. *CAUTION*: It is essential to maintain the temperature of the reaction mixture at ca. 20 °C by keeping it in the relatively large 500-mL flask. A smaller surface/volume ratio may lead to uncontrolled overheating of the solution with concomitant formation of untractable tarry material. The mixture was then cooled to 4 °C; the crystalline product was filtered off and briefly washed with formic acid. Drying at 30 °C, 0.1 Torr, afforded 5.26 g (10.2 mmol, 92%) of the diacid as colorless crystals, sufficiently pure for further reactions. An analytically pure sample was obtained by recrystallization from acetonitrile, mp 133–135 °C dec: ^{1}H NMR (DMSO-d_6) δ 2.01–2.33 (m, 6 H, CH_2CO_2, CH), 2.43 (s, 6 H, CH_3), 3.85–4.04 (m, 4 H, CH_2OSO_2), 7.48 (d, J = 8.3 Hz, 2 H, aryl H), 7.74 (d, J = 8.3 Hz, 2 H, aryl H); IR (KBr) $\tilde{\nu}$ 3060, 2930, 2870, 1700, 1595, 1485, 1435, 1355, 1280, 1240, 1205, 1185, 1175, 1090, 945, 920, 900, 830, 815, 790, 700, 655 cm^{-1}. Anal. Calcd for $C_{22}H_{26}O_{10}S_2$ (514.57): C, 51.35; H, 5.09. Found: C, 51.56; H, 5.22.

Five grams (9.72 mmol) of the crude diacid were suspended in 20 mL of ether, and a solution of diazomethane in ether was added at ca. 20 °C until the yellow color persisted. Solvent was then removed in vacuo, affording 5.27 g (quant) of dimethyl *meso*-3,4-bis[(tosyloxy)methyl]hexandioate as colorless crystals, sufficiently pure for further reactions. An analytically pure sample of the diester was obtained by recrystallization from ethyl acetate/chloroform, mp 122–123 °C dec: ^{1}H NMR ($CDCl_3$) δ 2.26–2.42 (m, 6 H, CH_2CO_2, CH), 2.46 (s, 6 H, CH_3), 3.60 (s, 6 H, OCH_3), 3.94–4.08 (m, 4 H, CH_2OSO_2), 7.36 (d, J = 8.4 Hz, 2 H, aryl H), 7.75 (d, J = 8.4 Hz, 2 H, aryl H); IR (KBr) $\tilde{\nu}$ 3060, 2990, 2965, 2930, 1730, 1595, 1435, 1365, 1350, 1265, 1210, 1190, 1170, 1160, 1090, 985, 935, 905, 820, 790, 705, 660 cm^{-1}. Anal. Calcd for $C_{24}H_{30}O_{10}S_2$ (542.62): C, 53.12; H, 5.57. Found: C, 53.02; H, 5.47.

***cis*-3,4-Bis(carbomethoxymethyl)tetrahydrothiophene.** A 500-mL round bottomed three-necked flask, equipped with a magnetic stirrer, two addition funnels, and nitrogen inlet and outlet, was charged with 50 mL of dimethylformamide. The addition funnels were charged with a solution of 15.0 g (27.6 mmol) of dimethyl *meso*-3,4-bis[(tosyloxy)methyl]hexandioate in 150 mL of dimethylformamide and a solution of 2.37 g (30.4 mmol) of sodium sulfide (freshly recrystallized from ethanol) in 150 mL of dimethylformamide, respectively. The two solutions were added simultaneously at ca. 20 °C within 1 h. The reaction mixture was then allowed to stir at ca. 20 °C for an additional 3 h. The solvent was removed at 40 °C, 0.1 Torr, water (200 mL) was added to the remaining semisolid mass, and the mixture was extracted with methylene chloride (3 × 100 mL). The combined organic layers were washed with water (100 mL), dried over anhydrous magnesium sulfate, and rotaevaporated. The residual yellow oil was subjected to Kugelrohr distillation (150 °C, 0.1 Torr), affording 3.66 g (15.7 mmol, 57%) of *cis*-3,4-bis(carbomethoxymethyl)-tetrahydrothiophene as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.28–2.47 (m, 4 H, CH_2CO_2), 2.57 (dd, J = 10.5 Hz, J = 5.9 Hz, 2 H, 2,5-H_{anti}), 2.69–2.73 (m, 2 H, 3,4-H), 3.04 (dd, J = 10.5 Hz, J = 6.0 Hz, 2 H, 2,5-H_{syn}), 3.70 (s, 6 H, OCH_3); IR (film) $\tilde{\nu}$ 3000, 2955, 2870, 1735, 1435, 1375, 1310, 1270, 1245, 1195, 1165, 1110, 995, 885, 840, 700 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4S$ (232.30): C, 51.71; H, 6.94. Found: C, 51.81; H, 6.88.

3-Thiabicyclo[3.3.0]octan-7-one (7): ^{1}H NMR ($CDCl_3$) δ 2.26 (dd, J = 19.2 Hz, J = 5.3 Hz, 2 H, 6,8-H_{endo}), 2.43–2.57 (m, 2 H, 6,8-H_{exo}), 2.68 (dd, J = 10.8 Hz, J = 4.0 Hz, 2,4-H_{endo}), 2.99–3.22 (m, 4 H, 2,4-H_{exo}, 1,5-H); IR (film) $\tilde{\nu}$ 2940, 2865, 1735, 1450, 1400, 1240, 1165, 1140, 955, 700 cm^{-1}. Anal. Calcd for $C_7H_{10}OS$ (142.22) (7): C, 59.12; H, 7.09. Found: C, 58.93; H, 7.04.

From *cis*-3,4-Bis(carbomethoxymethyl)tetrahydrothiophene: Sodium hydride (1.82 g, 60% suspension in mineral oil, 45.6 mmol) was placed into a 250-mL round-bottomed flask equipped with a reflux condenser and was briefly washed with absolute THF under nitrogen. A solution of 10.6 g (45.6 mmol) of *cis*-3,4-bis(carbomethoxymethyl)tetrahydrothiophene in 80 mL of absolute THF was added, and the mixture was refluxed with stirring for 12 h. The mixture was allowed to cool to ca. 20 °C. The solvent was removed, 80 mL of 20% hydrochloric acid was carefully added, and refluxing was continued until the evolution of carbon dioxide had ceased (ca. 2 h). The mixture was then diluted with water and extracted with ether (3 × 50 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (50 mL). The organic layer was dried over anhydrous magnesium sulfate and rotaevaporated. The remaining yellow oil was subjected to Kugelrohr distillation (90 °C, 0.05 Torr), affording 3.63 g (25.5 mmol, 56%) of 3-thiabicyclo-[3.3.0]octan-7-one (7) as a colorless oil.

From Its Ethylene Ketal.[11] Two grams (10.7 mmol) of the ethylene ketal of the ketone 7[11] were dissolved in 25 mL of a 3:1 acetic acid/water mixture and kept at ca. 20 °C for 6 h. Solid potassium carbonate was then added until the evolution of carbon dioxide had ceased. The mixture was extracted with ether (5 × 25 mL), and the combined organic phases were dried over anhydrous magnesium sulfate and rotaevaporated. The remaining yellowish oil was submitted to Kugelrohr distillation (90 °C, 0.05 Torr), affforded 1.25 g (8.79 mmol, 82%) of the ketone 7 as a colorless oil.

Sodium Borohydride Reduction of Ketones 7, 8. Ca. 13 mmol of the ketone was dissolved in 10 mL of absolute ethanol, and ca. 7 mmol of sodium borohydride was added at ca. 20 °C. After completion of the addition, the reaction mixture was stirred for an additional 2 h. The solvent was then removed in vacuo, the semisolid residue was taken up in 30 mL of water, and the aqueous suspension was extracted with methylene chloride (5 × 15 mL). The combined organic phases were dried over anhydrous potassium carbonate and rotaevaporated. The residual oil was purified by Kugelrohr destillation (**5a** 130 °C, 0.1 Torr, mp 40–40.5 °C; **6a** 70 °C, 0.1 Torr). See Scheme I for yields (exo/endo ratios by ^{1}H NMR spectroscopy from the crude products).

Mitsunobu Inversion[20] of Endo Alcohols 5, 6a. A solution of 4.85 mmol of the alcohol and 1.27 g (4.85 mmol) of triphenylphosphine in 6 mL of absolute ether was added dropwise to a solution of 845 mg (4.85 mmol) of ethyl azodicarboxylate and 593 mg (4.85 mmol) of benzoic acid at ca. 20 °C. The resulting yellow mixture was stirred at ca. 20 °C for 14 h. The solvent was then removed in vacuo, and the residual semisolid mass was subjected to silical gel chromatography (adsorbent/substrate ratio 30:1, eluting with ether). The purified benzoate (ca. 90% yield) was taken up in 10 mL of methanol, and a solution of 1.00 g of potassium hydroxide in 5 mL of water was added. The solution was kept at ca. 40 °C for 15 h. Water (50 mL) was added, and the mixture was extracted with methylene chloride (5 × 30 mL). The combined extracts were dried over anhydrous potassium carbonate and rotaevaporated. The residual oil was purified by Kugelrohr distillation (**5b** 130 °C, 0.05 Torr, mp 50–51 °C; **6b** 120 °C, 0.1 Torr). See Scheme I for yields (exo/endo ratios by ^{1}H NMR spectroscopy from the crude products).

Tosylation of Alcohols 5a,b and 6a,b. A solution of 477 mg (2.50 mmol) of *p*-toluenesulfonyl chloride in 5 mL of pyridine was cooled to 4 °C, and 2.00 mmol of the alcohol was added. The reaction mixture was kept at 4 °C for 72 h. It was then poured into a mixture of 20 g of ice and 10 mL of concentrated hydrochloric acid; the resulting suspension was extracted with chloroforme (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, and the solvent was removed in vacuo. Recrystallization from hexane/ethyl acetate (**5c, 6c,d**) or pentane/ethyl acetate (**5d**) yielded the isomerically pure tosylates **5c,d** and **6c,d** (mp **5c** 53–54 °C, **5d** 52.5–53 °C, **6c** 57.5–58 °C, **6d** 66 °C). See Scheme I for yields.

Endo Alcohols 5,6h. A solution of 5.00 mmol of methylmagnesium iodide in 15 mL of absolute ether was prepared in a flame-dried 50-mL three-necked flask, equipped with an addition funnel and a reflux condenser under nitrogen in the usual way from 121 mg (5.00 mmol) of magnesium turnings and 710 mg (312 μL, 5.00 mmol) of methyl iodide. A solution of 4.00 mmol of the ketone 7 or 8 in 10 mL of absolute ether was added dropwise at

(20) Mitsunobu, O. *Synthesis* **1981**, 1.

0 °C, and the resulting suspension was refluxed for 1 h. Water (10 mL) was then added with ice cooling, followed by a saturated aqueous solution of ammonium chloride until two clear layers had formed. The organic layer was separated, and the aqueous phase was extracted with ether (3 × 15 mL). The combined organic phases were washed with saturated aqueous sodium bisulfite (1 × 30 mL) and sodium bicarbonate (1 × 30 mL) and dried over anhydrous sodium sulfate. Rotaevaporation of the solvent furnished the crude alcohols **5,6h** as yellowish oils, which were purified by sublimation (**5h**, 60 °C, 0.1 Torr, mp 50 °C) and Kugelrohr distillation (**6h**, 95 °C, 0.2 Torr), respectively. See Scheme I for yields.

Chlorination of Endo Alcohols 5,6h. Ca. 6–7 mmol of the alcohol were dissolved in 50 mL of ether. The solution was cooled to 0 °C, and hydrogen chloride was slowly passed through for 1 h. The solution was then rotaevaporated, and the liquid residue was chromatographed on silica gel (adsorbent/substrate ratio 100:1, eluting with methylene chloride). Final purification was achieved by means of Kugelrohr distillation at 60 °C, 0.1 Torr. See Scheme I for yields and exo/endo ratios (determined from the crude product mixtures by ^{1}H NMR spectroscopy).

Methylation of Alcohols 5,6a,b and 5h. A 50-mL round-bottomed flask was flushed with nitrogen and charged with 72.3 mg (1.80 mmol) of a 60% suspension of sodium hydride in mineral oil. The suspension was briefly washed with absolute THF. A solution of 1.50 mmol of the alcohol in 15 mL of absolute THF was then injected, and the mixture was stirred at ca. 20 °C until the evolution of hydrogen had ceased. Methyl iodide was then added (112 μL, 226 mg, 1.80 mmol), and the mixture was stirred for 20 h. Solvent was removed in vacuo, and the semisolid residue was taken up in 20 mL of water and 20 mL of ether. The aqueous phase was extracted with another 20 mL of ether, and the combined organic layers were dried over anhydrous magnesium sulfate. The solution was rotaevaporated, and the liquid residue was subjected to silica gel chromatography (adsorbent/substrate ratio 100:1, eluting with ether). Final purification was achieved by Kugelrohr distillation at 50–80 °C, 0.1 Torr, affording 80–90% of the methyl ethers **5e,f,m** and **6e,f** as colorless oils.

7,7-Dimethoxy-3-thiabicyclo[3.3.0]octane (5n). A solution of 2.00 g (5.49 mmol) of *cis*-3,4-bis(iodomethyl)cyclopentanone[10] in 10 mL of 2,2-dimethoxypropane was placed into a 50-mL flask. Absolute methanol (0.2 mL) and *p*-toluenesulfonic acid (80 mg) were added, and the mixture was stirred under exclusion of light for 15 h. Triethylamine (1.00 mL) was then added, followed by 10 mL of benzene and 10 mL of water. The organic phase was separated, dried over anhydrous magnesium sulfate, and rotaevaporated. The remaining yellow oil was dissolved in 10 mL of absolute ethanol and added dropwise to a solution of 2.20 g (28.2 mmol) of sodium sulfide (freshly recrystallized from absolute ethanol) in 30 mL of absolute ethanol. After completion of the addition the solution was refluxed under nitrogen for 3 h. The solvent was then rotaevaporated, 30 mL water were added, and the mixture was extracted with ether (5 × 30 mL). The combined ether phases were dried over anhydrous magnesium sulfate and rotaevaporated. The remaining yellow oil was chromatographed on silica gel (50 g), eluting with hexane/ether 3:1. Final purification was achieved by Kugelrohr distillation at 80 °C, 0.1 Torr, affording 211 mg (20%) of the dimethyl ketal **5n** as a colorless oil.

1′,3′-*N*-Bis(phenylsulfonyl)biotin Methyl Ester (9). A 50-mL round-bottom flask was flushed with nitrogen and charged with 528 mg (11.0 mmol) of a 50% suspension of sodium hydride in mineral oil. The suspension was briefly washed with absolute THF, and a solution of 2.73 g (1.97 mL, 15.4 mmol) of benzenesulfonyl chloride in 15 mL of absolute THF was injected; 850 mg (3.29 mmol) of biotin methyl ester[13] was added, and the mixture stirred under nitrogen at 60 °C for 10 h. Solids were removed by centrifugation, and the solution was rotaevaporated. The residue was taken up in 10 mL of ethyl acetate and centrifuged again. The product was then precipitated from the solution by addition of 60 mL of hexane. Final purification was achieved by recrystallization from methanol/ethyl acetate, affording 1.20 g (68%) of a colorless powder, mp 173 °C: IR (KBr) $\tilde{\nu}$ 3070, 3020, 2955, 2870, 1735, 1590, 1450, 1375, 1360, 1315, 1230, 1215, 1175, 1145, 1115, 1085, 995, 885, 820, 815, 750, 730, 695, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08–1.72 (m, 6 H, 6,7,8-H), 2.28 (t, J = 6.9 Hz, 2 H, 9-H), 3.13 (dd, J = 13.2 Hz, J = 5.8 Hz, 1 H, 5-H_{endo}), 3.36 (dd, J = 13.2 Hz, J = 6.5 Hz, 1 H, 5-H_{exo}), 3.41–3.51 (m, 1 H, 2-H), 3.68 (s, 3 H, OCH_3), 4.62–4.76 (m, 2 H, 3,4-H), 7.47–8.00 (m, 10 H, aryl H); ^{13}C NMR ($CDCl_3$) δ 24.07 (t, C-6), 27.37 (t, C-7), 27.50 (t, C-8), 33.65 (t, C-9), 35.68 (t, C-5), 51.28 (q, C-11), 52.18 (d, C-2), 60.93 (d, C-4), 63.34 (d, C-3), 128.13 (d, aryl C), 129.19 (d, aryl C), 134.49 (d, aryl C), 137.64 (s, aryl C), 137.81 (s, aryl C), 149.89 (s, C-2′), 173.80 (s, C-10). Anal. Calcd for $C_{23}H_{26}N_2O_7S_3$ (538.65) (**9**): C, 51.29; H, 4.89; N, 5.20. Found: C, 51.34; H, 5.01; N, 5.17.

Kinetic Measurements. Conductance measurements were done in an air-tight thermostated cell, equipped with a stirrer and platinated platinum electrodes, the cell constant being ca. 1. Temperature accuracy was at least ±0.1 °C. To start a kinetic run, 250 μL of a ca. 30 mM stock solution of the corresponding tosylate in absolute THF was injected into the thermostated cell charged with 8 mL of an 8:2 ethanol–water mixture (v/v). Readings were taken with a LF 521 instrument, manufactured by Wissenschaftlich-Technische Werkstätten, Weilheim, West Germany. Solvolyses were followed by taking at least 20 readings approximately equally spaced in conductance over at least 3 half-lives. The raw conductance data were then fitted to the first-order rate equation, employing a standard least-squares computer program. In all cases correlation coefficients were better than 99.95%, mostly being 99.98–100%. No indications for processes other than pseudo-first-order could be obtained from the ln [c] vs time profiles.

Complexation of Compounds 5l,m, 6h,l, 7, 8, and 9 with Antimony Pentafluoride. Ca. 87 mg (ca. 0.4 mmol) of antimony pentafluoride was placed into a flame-dried Schlenck tube under nitrogen and dissolved in ca. 2 mL of liquid sulfur dioxide at −78 °C. A solution of an equimolar amount of the substrate in ca. 2 mL of liquid sulfur dioxide was added at −78 °C with shaking. The mixture was then transferred into a coaxial NMR tube and sealed. ^{13}C NMR spectral data of the complexes and of the uncomplexed substrates **5l,m**, **6h,l**, **7**, and **8** are given in Table II. Complexation of biotin derivative **9**: ^{1}H NMR (SO_2, −60 °C) [**9** + SbF_5] δ 2.82–3.73 (m, 6,7,8-H), 4.38–4.59 (m, 2 H, 9-H), 4.68–4.78 (m, 2 H, 5-H), 4.92–5.03 (m, 1 H, 2-H), 5.82 (s, 3 H, OCH_3), 6.22–6.30 (m, 2 H, 3,4-H), 8.95–9.40 (m, 10 H, aryl H); [**9**] δ 2.60–3.15 (m, 6 H, 6,7,8-H), 3.69 (t, J = 7.0 Hz, 2 H, 9-H), 4.55–4.72 (m, 2 H, 5-H), 4.79–4.93 (m, 1 H, 2-H), 5.00 (s, 3 H, OCH_3), 6.13–6.25 (m, 2 H, 3,4-H), 8.92–9.33 (m, 10 H, aryl H).

Ethylation of Ketone 7 with Triethyloxonium Tetrafluoroborate.[19] Under exclusion of moisture, 30.6 mg (0.161 mmol) of triethyloxonium tetrafluoroborate[19] was dissolved in 0.5 mL of absolute methylene chloride. A solution of 24.1 mg (0.170 mmol) of the ketone **7** in 0.7 mL of absolute methylene chloride was added, and the mixture was kept at ca. 20 °C. After ca. 5 min, a crystalline material started to precipitate. The supernatant was pipetted off after 4 h, and the precipitation was recrystallized from methylene chloride/acetonitrile, affording 35.0 mg (80%) of colorless plates, mp 152–153 °C: IR (KBr) $\tilde{\nu}$ 1734 (CO) cm^{-1}; ^{1}H NMR (CD_3CN) δ 1.39 (t, J = 7.4 Hz, 3 H, CH_3CH_2S), 2.25 (dd, J = 19.1 Hz, J = 4.4 Hz, 2 H, 6,8-H_{endo}), 2.57 (dd, J = 19.1 Hz, J = 7.2 Hz, 2 H, 6,8-H_{exo}), 3.22 (q, J = 7.4 Hz, 2 H, CH_3CH_2S), 3.31–3.49 (m, 4 H, 1,5-H, 2,4-H_{endo}), 3.66 (dd, J = 13.2 Hz, J = 5.0 Hz, 2 H, 2,4-H_{exo}). See Table II for ^{13}C NMR data of ketone **7** and sulfonium salt **11**. Anal. Calcd for $C_9H_{15}BF_4OS$ (258.08) (**11**): C, 41.89; H, 5.86. Found: C, 42.16; H, 6.01.

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Registry No. **5a**, 118597-92-5; **5b**, 118710-76-2; **5b** (benzoate), 118597-94-7; **5c**, 118597-96-9; **5d**, 118710-78-4; **5e**, 118598-02-0; **5e** (deuterio), 118598-10-0; **5f**, 118710-81-9; **5f** (deuterio), 118710-83-1; **5g**, 118598-09-7; **5h**, 118597-98-1; **5l**, 118598-00-8; **5l**·SbF_5, 118598-14-4; **5m**, 118598-03-1; **5m**·SbF_5, 118598-15-5; **5n**, 118598-05-3; **6a**, 118597-93-6; **6b**, 118710-77-3; **6b** (benzoate), 118597-95-8; **6c**, 118597-97-0; **6d**, 118710-79-5; **6e**, 118598-04-2; **6e** (deuterio), 118598-11-1; **6f**, 118710-82-0; **6f** (deuterio),

118710-84-2; **6g**, 50305-99-2; **6h**, 118597-99-2; **6h**·SbF_5, 118598-16-6; **6k**, 118598-01-9; **6l**, 118710-80-8; **6l**·SbF_5, 118598-17-7; **7**, 118597-91-4; **7**·SbF_5, 118598-12-2; **7** (ethylene ketal), 89408-41-3; **8**, 56000-23-8; **8**·SbF_5, 118598-13-3; **9**, 118598-06-4; **9**·SbF_5, 118598-18-8; **10**, 89408-39-9; **11**, 118598-08-6; *meso*-4,5-bis((tosyloxy)methyl)cyclohexene, 32970-96-0; *meso*-3,4-bis((tosyloxy)-methyl)hexanedioic acid, 118597-88-9; dimethyl *meso*-3,4-bis-((tosyloxy)methyl)hexanedioate, 118597-89-0; *cis*-3,4-bis((carbomethoxy)methyl)tetrahydrothiophene, 118597-90-3; biotin methyl ester, 608-16-2.

Supplementary Material Available: Analytical data (^1H NMR, IR, and elemental analyses, melting points, conditions of Kugelrohr distillation) of compounds **5a-f,h,l,n** and **6a-f,h,k,l** (5 pages). Ordering information is given on any current masthead page.

Oxidative Aromatic Nitration with Charge-Transfer Complexes of Arenes and Nitrosonium Salts

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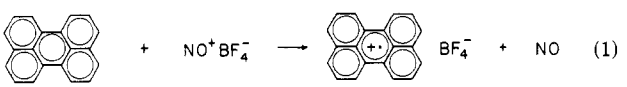
Brightly colored solutions are obtained immediately upon the exposure of various arenes (ArH) to nitrosonium (NO^+) salts. The colors arise from the charge-transfer transitions of 1:1 complexes [ArH,NO^+] that are reversibly formed as persistent intermediates. However the yellow-red charge-transfer (CT) colors are readily bleached by dioxygen, and the corresponding nitroarenes ($ArNO_2$) can be isolated in excellent yields from acetonitrile solutions. Such an oxidative aromatic nitration of aromatic donors proceeds via the initial autooxidation of the charge-transfer complex. The collapse of the resulting radical ion pair [$ArH^{\bullet+}$, NO_2] to the σ-adduct, followed by the loss of proton, affords $ArNO_2$. Direct evidence for electron transfer in the initial step when anthracene is treated with $NO^+PF_6^-$ stems for the isolation of (a) the anthracene ion radical salt [$(ArH)_2^{\bullet+}PF_6^-$] along with nitric oxide in dichloromethane solution and (b) the formation of 9-nitroanthracene (admixed with anthraquinone) in the more polar acetonitrile. The aromatic products (and isomer distribution) from oxidative aromatic nitration are highly reminiscent of those from electrophilic aromatic nitration. The possibility of common reactive intermediates in these two distinctive pathways for aromatic nitration is discussed.

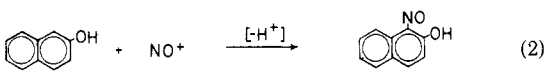
Introduction

Nitrosonium salts can serve effectively either as oxidants or as electrophiles toward different aromatic substrates. Thus the electron-rich polynuclear arenes suffer electron transfer with $NO^+BF_4^-$ to afford stable arene cation radicals, e.g.[1-3]



(1)

Other activated aromatic compounds such as phenols, anilines, and indoles undergo nuclear substitution with nitrosonium species,[4] e.g.



(2)

that are usually generated in situ from the treatment of nitrites with acid. It is less well-known, but nonetheless experimentally established,[5,6] that NO^+ forms intensely colored charge-transfer complexes with a wide variety of common arenes (ArH), i.e.

$$ArH + NO^+ \rightleftharpoons [ArH,NO^+] \quad (3)$$

For example, benzene, toluene, xylenes, and mesitylene generate yellow to orange vivid hues when added to colorless solutions of $NO^+PF_6^-$ in acetonitrile. Analogously, the more electron-rich durene, pentamethylbenzene, hexamethylbenzene, and naphthalene afford dark red solutions when exposed to NO^+. According to Mulliken,[7] such colors originate from the charge-transfer transitions ($h\nu_{CT}$) of the reversibly formed 1:1 electron donor-acceptor or EDA complexes, i.e.[8]

$$[ArH,NO^+] \xrightarrow{h\nu_{CT}} [ArH^+,NO] \quad (4)$$

These charge-transfer colors are sufficiently persistent to allow single crystals of various arene CT complexes with NO^+ to be isolated for structural elucidation by X-ray crystallography.[9] We were thus surprised to find that the brightly colored solutions were bleached when exposed to (dry) air—the rate of which showed a tendency for marked acceleration with increasing numbers of methyl substituents on the benzene donor. Such a trend in arene reactivity is diagnostic of oxidation and indeed reminiscent of the oxidative coupling and iodination of arenes with $NO^+BF_4^-$ that was recently reported by Radner.[10] In a

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