$C_6H_4CO_2(CH_2)_6CH_3$, 5462-02-2; 2,4-$Cl_2C_6H_3CO_2(CH_2)_6CH_3$, 86954-32-7; O_2N-*p*-$C_6H_4CO_2(CH_2)_6CH_3$, 14309-44-5; $(CH_3)_3CCO_2CH_2Ph$, 2094-69-1; $EtO_2C(CH_2)_4CO_2Et$, 141-28-6; $H_3CCH{=}CO_2(CH_2)_6CH_3$, 16930-99-7; (+)-$PhCO_2CH(CH_3)(CH_2)_5CH_3$, 34881-29-3; DEAD, 1972-28-7; cyclopentyl *p*-methoxybenzoate, 5421-01-2; 1-oxa-2-cyclotridecanone, 947-05-7; cyclopentanol, 96-41-3; (−)-2-octanol, 6169-06-8.

Temperature Dependence of the Kinetic Isotope Effect in the Homolytic Abstraction of Benzylic Hydrogen by Bromine

Richard D. Gilliom,* R. Michael Brewer,[1] and Karen R. Miller[1]

Department of Chemistry, Southwestern at Memphis, Memphis, Tennessee 38112

Received March 29, 1983

The competitive bromination of hydrocarbons with bromine, as well as with *N*-bromosuccinimide, has been widely studied.[2-5] The intramolecular kinetic isotope effects of bromination of deuterium-substituted toluene has been reported at two temperatures.[6] In view of the importance of the temperature dependence of the primary kinetic hydrogen isotope effect as a mechanistic criterion, recently summarized by Kwart,[7] it is surprising that no such complete study has been reported for bromination. We present such a study at this time.

Results and Discussion

Reactivities of bromine to toluene and to deuteriotoluene each relative to 4-chlorotoluene in benzene solution were determined at 0, 10, 25, 40, and 60 °C. Values of the isotope effect were obtained from these reactivities. Results are reported in Table I.

The reacted toluenes accounted for at least 80% of the bromine added. This loss of bromine is explained by the entrainment of bromine with the nitrogen flow used to remove HBr as it is formed. No attempt was made to return unreacted bromine to the reaction flask nor was any attempt made to analyze for the amount lost. The relative rate of deuteriotoluene to 4-chlorotoluene reported in Table I for 40 °C includes three values determined with use of toluene-α,α,α-d_3. These three runs afforded $k_D/k_c = 0.215 \pm 0.004$, while four determinations using toluene-d_8 gave $k_D/k_c = 0.208 \pm 0.066$. As these values were indistinguishable, they were combined and all other reported values were determined with use toluene-d_8.

The kinetic isotope effects, k_H/k_D, were determined from the selectivities and are reported in Table I and are in satisfactory agreement with the bromine value of 4.6 at 77 °C reported by Wiberg and Slaugh and of 3.6 at 110 °C for *N*-bromosuccinimide bromination.[6] This data gives a good fit to the Arrhenius relation (eq 1, $S = 0.059$, $r^2 = 0.969$) which affords the activation parameters $E_D{}^* - E_H{}^* = 2.5$ ($S = 0.22$) kcal/mol and $A_H{}^*/A_D{}^* = 0.188$ ($\ln A_H{}^*/A_D{}^* = -1.669$, $S = 0.374$). The interpretation of these

$$\ln (k_H/k_D) = \ln (A_H{}^*/A_D{}^*) + (E_D - E_H)/RT \qquad (1)$$

values may be based upon the criteria given by Bell[9] and more recently by Kwart.[7] The k_H/k_D value, 7.2, at 25 °C is in the range of Kwart's criteria for a linear H-transfer transition state, while the values of $E_D{}^* - E_H{}^*$ and $A_H{}^*/A_D{}^*$ are both in the ranges anticipated for a linear H-transfer transition state that involves quantum mechanical tunneling and are well outside the criteria for a nonlinear transition state. Indeed it appears that the observation reported earlier of a linear transition state with tunneling for benzylic H abstraction with *tert*-butoxy radical[10] is reproduced for benzylic bromination. Kwart has reported a nonlinear transition state for the *tert*-butoxy abstraction of allylic hydrogen.[11]

Table I. Relative Rates of and Isotope Effect for Bromine Atom Abstraction from Toluene

T, °C	no. expts	$K_H/k_c{}^a$	no. expts	k_D/k_c	k_H/k_D
0	3	1.01 ± 0.01 [b]	3	0.109 ± 0.012	9.27
10	3	1.04 ± 0.03	4	0.117 ± 0.012	8.89
25	3	1.20 ± 0.04	4	0.161 ± 0.010	7.19
40	3	1.31 ± 0.04	7	0.211 ± 0.043	6.21
60	6	1.59 ± 0.10	5	0.348 ± 0.072	4.57

[a] k_H is rate constant for toluene, k_c for 4-chlorotoluene, and k_D for deuterated toluene. [b] Experimental error represents average deviation of the number of experiments shown. Each experiment represents at least triplicate analysis.

The "polar effect" in homolytic benzylic hydrogen abstraction reactions as observed by good Hammett-type ρ–σ plots for the relative reactivities of meta- and para-substituted toluenes has generally been interpreted in two ways. Zavitsas[12] has suggested that the order of reactivity of toluenes with a number of abstracting radicals simply parallels their benzylic C–H bond strengths without the need of postulating charge separation in the transition state. This arguement requires that all ρ values be negative for abstraction from toluenes. The finding of positive ρ values obtained with use of alkyl radicals as the abstracting species, summarized by Henderson,[13] casts doubt on the Zavitsas' interpretation although the validity of the results have been questioned[14] due to the apparent incursion of side reactions. The second interpretation has been summarized by Pryor[15] and employs polar resonance structures to stabilize the transition state. This interpretation suggests that the sign of ρ is determined by the electronegativity of the abstracting radical. The results reported in Table I for the reactivity of toluene relative to that of 4-chlorotoluene call both of these interpretations into question. Certainly the observation that 4-chlorotoluene is less reactive than toluene is consistent with the reported[5] negative value of ρ for bromination. The data in Table I give an Arrhenius relationship (eq 2, $S = 0.036$, $r^2 = 0.972$) with the Arrhenius parameter $E_{Tol}{}^* - E_{4\text{-ClTol}}{}^* = 1.38$ kcal/mol ($S = 0.13$). This result corresponds to a "two-

$$\ln (k_{Tol}/k_{4\text{-ClTol}}) = [2.51(S = 0.23) - 692.4(S = 67.7)]/T \qquad (2)$$

point isokinetic relationship"[16] and an isokinetic temper-

---

[1] NSF-URP Participant.

[2] Walling, C.; Rieger, A. L.; Tanner, D. D. *J. Am. Chem. Soc.* **1963**, *85*, 3129.

[3] Russell, G. A.; De Boer, C. *J. Am. Chem. Soc.* **1963**, *85*, 3136.

[4] Russell, G. A.; Desmond, K. M. *J. Am. Chem. Soc.* **1963**, *85*, 3139.

[5] Pearson, R. E.; Martin, J. C. *J. Am. Chem. Soc.* **1963**, *85*, 3142.

[6] Wiberg, K. B.; Slaugh, L. H. *J. Am. Chem. Soc.* **1958**, *80*, 3033.

[7] Kwart, H. *Acc. Chem. Res.* **1982**, *15*, 401.

[8] Gilliom, R. D.; Ward, B. F. *J. Am. Chem. Soc.* **1965**, *87*, 3944.

[9] Bell, R. P. "The Tunnel Effect in Chemistry"; Chapman and Hall: New York, 1980.

[10] Larson, G. F.; Gilliom, R. D. *J. Am. Chem. Soc.* **1975**, *97*, 3444.

[11] Kwart, H.; Brechbiel, M.; Miles, W.; Kwart, L. D. *J. Org. Chem.* **1982**, *47*, 4524.

[12] Zavitsas, A. A.; Pinto, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 7390.

[13] Henderson, R. W. *J. Am. Chem. Soc.* **1975**, *97*, 213.

[14] Zavitsas, A. A.; Hanna, G. M. *J. Org. Chem.* **1975**, *40*, 3782.

[15] Pryor, Wm. A.; Davis, Wm. H.; Stanley, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 4754.

[16] Leffler, J. E.; Grunwald, E. "Rates and Equilibria of Organic Reactions"; Wiley: New York, 1963.

0022-3263/83/1948-3600$01.50/0 © 1983 American Chemical Society

ature of 275.9 K. While these results are tentative, they certainly suggest that the sign of ρ as a mechanistic criterion is suspect. At temperatures below 276 K, 4-chlorotoluene is expected to be more reactive than toluene to bromine-atom abstraction. This corresponds to a change in the sign of ρ. All of our attempts to determine the relative reactivity at temperatures below 0 °C failed because of inhomogeneity of the reaction mixture.

The warning given by Kwart about giving mechanistic significance to the value of a primary isotope effect obtained at a single temperature and the value of applying his "full" criterion based upon the temperature dependence of the kinetic isotope effect has recently been reviewed.[7] The results presented here suggest a similar warning about giving significance to the sign and magnitude of the value of ρ obtained at a single temperature is also pertinent.

Experimental Section

Toluene-α,α,α-d_3 was obtained as at least 99% isotopically pure from Merck Sharp and Dohme Isotopes. Toluene-d_8 was obtained as 99+% isotopically pure from Aldrich Chemical Co. Both were used as supplied.

A flask containing a benzene solution of toluene, 4-chlorotoluene, and chlorobenzene, each ca. 1 M, was placed in a constant-temperature bath for 20 min and nitrogen was bubbled through the solution to degas it. A benzene solution of 0.67 M bromine was then added by using a pressure-equalizing addition funnel, and the solution was irradiated with a 275-W Sylvania sunlamp, placed externally, until all bromine was consumed as shown by the KI test. The total toluene to bromine molar ratio was 10:3. The rate of addition of bromine was adjusted so that the reacting solution remained nearly colorless. Evolved hydrogen bromide was continuously entrained by bubbling nitrogen through the solution, through a water-cooled condenser and into a sodium hydroxide trap. This procedure has been shown to minimize or eliminate the reaction of the aralkyl radical with HBr.[5] Gas chromatographic analysis was carried out as previously described.[8]

Registry No. Deuterium, 7782-39-0; hydrogen, 1333-74-0; toluene, 108-88-3; 4-chlorotoluene, 106-43-4.

Efficient Synthesis of 2-Methyl-4-Hydroxy-2*H*-1,2-Benzothiazine 1,1-Dioxides

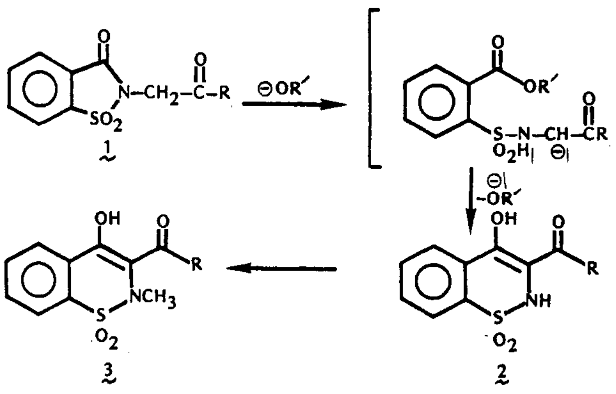
Paul D. Weeks,* Fredric J. Vinick, Ralph Breitenbach, and Stanley Jung

Pfizer Inc., Central Research, Groton, Connecticut 06340

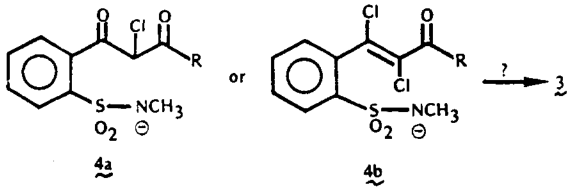
Received April 6, 1983

2-Methyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides (**3**) represent an important new class of antiinflammatory agents, which includes the drug piroxicam (**3**, R = 2-aminopyridyl).[1] Most previously reported syntheses of these valuable compounds proceed via the alkoxide-catalyzed rearrangement of a saccharin derivative (**1**) to afford a 4-hydroxy-1,2-benzothiazine (**2**),[2] which is then N-alkylated to afford the desired 2-methyl derivative, as shown in Scheme I.

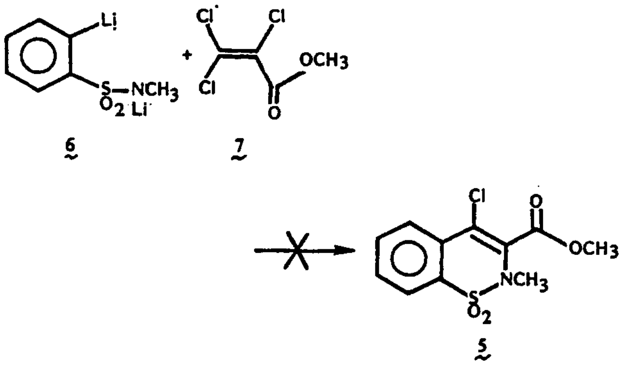
Scheme I



We wished to design a more efficient synthesis of compounds of type **3** and postulated that the closure of a derivative such as **4a** or **4b** might lead directly to the desired 2-methyl derivative.



Our initial attempts toward this end were directed toward the synthesis of **5**, potentially accessible through the reaction of the dianion **6**[3] with the readily available trichloroacrylate derivative **7**. It was presumed that the desired reaction would proceed via intermediate **4b** (R = OCH_3).



Unfortunately, only complex, intractable mixtures were obtained under a variety of experimental conditions. Returning to intermediate **4a** as an attractive precursor to benzothiazines **3**, we then investigated a Darzen's-like condensation of *N*-methylsaccharin (**8**) with chloroacetate **9**.[4] We report here the successful synthesis of **3** utilizing this pathway.

Results and Discussion

When readily available *N*-methylsaccharin (**8**) was combined with chloroacetate **9**[4] in the presence of 1 equiv of NaH in THF, vigorous gas evolution was noted. Surprisingly, upon quenching with dilute acid, only the starting materials **8** and **9** were recovered. However, when 2 equiv of metal hydride (NaH or KH) were employed and

---

(1) For a recent review on Benzothiazine Pharmacology, see: Lombardino, J. G.; Wiseman, E. H. *Trends Pharmacol. Sci.* **1981**, *2*, 132. Piroxicam literature has been reviewed by: Wiseman, E. H.; Lombardino, J. G., In "Chronicles of Drug Discovery"; Bindra, J. S., Lednicer, D., Eds.; Wiley: New York, 1981.

(2) For recent reviews on the chemistry of these systems, see: Catsoulacos, P.; Camoatsis, C. *J. Heterocycl. Chem.* **1979**, *16*, 1503. Lombardino, J. G.; Kuhla, D. E. *Adv. Heterocycl. Chem.* **1981**, *28*, 73. For a recent discussion on the alkoxide rearrangement 1 → 2 see: Schapira, C. B.; Perillo, I. A.; Lamdan, S. *J. Heterocycl. Chem.* **1980**, *17*, 1281.

(3) Watanabe, H.; Gay, R. L.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 900.

(4) The transformations discussed herein were carried out with both the methyl and methoxyethyl esters of 9; identical results (see Experimental Section for details) were observed in all cases.

0022-3263/83/1948-3601$01.50/0