

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, PURDUE UNIVERSITY, LAFAYETTE, IND., AND LOUISIANA STATE UNIVERSITY, BATON ROUGE, LA.]

## Walden Inversion by Radicals. The Reaction of Phenyl Radicals with Disulfides<sup>1</sup>

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RECEIVED SEPTEMBER 3, 1963

The relative rate constants are reported at 60° for the reaction of phenyl radicals, generated from phenylazotriphenylmethane, with aliphatic disulfides. Two reactions occur: hydrogen abstraction (eq. 1) and attack at sulfur to yield a phenyl alkyl sulfide (eq. 2), and the rate constants are calculated for both processes. An excellent correlation is obtained in the log-log graph of the rates for the radical displacement on sulfur *vs.* the ionic S<sub>N</sub>2 displacement on either sulfur or carbon. The significance of this is enhanced by the fact that the S<sub>N</sub>2 reaction on sulfur is known to involve a Walden inversion mechanism. It is concluded, therefore, that the energetics of the radical displacement and the S<sub>N</sub>2 reaction are similar, and that the radical reaction involves a three-atoms-in-a-line, Walden inversion transition state. This would appear to be the only simple, unambiguous evidence in an organic system that radicals displace by a backside attack mechanism. Some discussion is also given of the hydrogen-donating abilities of the disulfides and of the mechanism of phenylation by PAT.

Over 30 years have passed since London, Eyring, Polanyi, and others presented theoretical arguments which suggested that the bimolecular displacement reaction by radicals (the SH<sub>2</sub> reaction) involves a backside displacement mechanism, with three-atoms-in-a-line in the transition state, similar to the Walden inversion mechanism for the S<sub>N</sub>2 reaction.<sup>3</sup> However, attempts to demonstrate this experimentally have met extreme difficulties, and no unambiguous proof had been obtained in an organic system.<sup>4</sup> We here present the first such proof; the model reaction is the attack by phenyl radicals from phenylazotriphenylmethane on the sulfur of aliphatic disulfides.

Previous attempts to determine the geometry of the transition state of the SH<sub>2</sub> reaction had involved study of the reaction of iodine atoms with alkyl iodides. The elegant work of Noyes and his students<sup>5</sup> had indicated a possibility that an SH<sub>2</sub> reaction occurs in this system by a Walden inversion mechanism. However, the rate pattern is completely wrong<sup>4</sup> for a Walden inversion (neopentyl reacts faster than methyl). Recently Benson<sup>6</sup> has obtained evidence that in the crucial case of *sec*-butyl iodide, where racemization of the optically active compound has been observed, a mechanism is involved in which iodine atoms attack the iodide rather than the carbon atom. There seems to be little question that most, if not all, alkyl iodides react with iodine atoms at iodide to generate an alkyl free radical, and the reaction, therefore, is not an SH<sub>2</sub> displacement at carbon.

We have previously discussed the reaction of radicals at the S-S bond of disulfides as a model for the SH<sub>2</sub> reaction.<sup>4,7,8</sup> The S-S bond is uniquely reactive toward radicals, and there seemed to be a good chance that attack at sulfur could compete with hydrogen abstraction reactions much better than in analogous carbon systems. The geometry of the SH<sub>2</sub> reaction

(1) Reactions of Radicals, Part 8. This work was supported in part by the Public Health Service Research Grant GM-09020 from the National Institutes of Health and by Grant AT(11-1)-1169 from the U. S. Atomic Energy Commission. Grateful acknowledgment is made to the donors of these funds.

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(3) The theoretical calculations are summarized in S. Glasstone, K. J. Laidler, and H. Eyring, "Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, pp. 87-91, 108, 110-112. Also see N. N. Semenov, "Some Problems in Chemical Kinetics and Reactivity," Pergamon Press, New York, N. Y., 1958, Appendix to Vol. 1.

(4) Experimental approaches are summarized in W. A. Pryor and T. L. Pickering, *J. Am. Chem. Soc.*, **84**, 2705 (1962).

(5) R. A. Herrmann and R. M. Noyes, *ibid.*, **78**, 5764 (1956); J. E. Bujake, M. W. T. Pratt, and R. M. Noyes, *ibid.*, **83**, 1547 (1961).

(6) S. W. Benson, *J. Chem. Phys.*, **38**, 1945 (1963).

(7) W. A. Pryor and P. K. Platt, *J. Am. Chem. Soc.*, **85**, 1496 (1963).

(8) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 48-57, 63.

can be studied in disulfides just as well as in carbon compounds. As shown in Fig. 1, the geometry is similar in the two, since the two lone pairs on sulfur occupy the positions of the two hydrogen atoms in the carbon analog. Furthermore, and more convincingly, the analogy between the S<sub>N</sub>2 reactions at carbon and at sulfur is exact, and nucleophiles attack on the S-S bond from the backside in a Walden inversion mechanism.<sup>9</sup> In both these S<sub>N</sub>2 reactions, the neopentyl system is very unreactive.<sup>10</sup> This inertness of the neopentyl system can be used as an operational criterion for a backside attack mechanism just as inversion of an optically active species can be. In the S<sub>E</sub>2 reaction, where the mechanism involves frontside attack, the neopentyl and methyl systems react at about the same rate.<sup>11,12</sup> This rate criterion of mechanism is illustrated in the comparison of the first three of the reactions shown in Chart I.

CHART I		Ratio of rates for R = <i>t</i> -butyl to R = methyl
Reaction type	Reaction	
S <sub>N</sub> 2 (carbon)		10 <sup>-6</sup>
S <sub>N</sub> 2 (sulfur)		10 <sup>-5.2</sup>
S <sub>E</sub> 2 (carbon)		1
SH <sub>2</sub> (sulfur)		10 <sup>-2.1</sup>

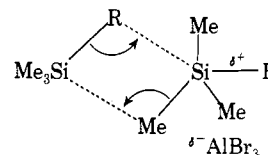
The fourth reaction shown in Chart I is the SH<sub>2</sub> reaction of phenyl radicals with disulfides. If the rate pattern for this reaction is compared with that the other three reactions, the geometry of the SH<sub>2</sub> reaction can be

(9) Data of A. Fava discussed in ref. 8.

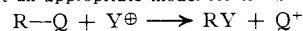
(10) Rate data for both S<sub>N</sub>2 reactions are taken from ref. 4 and 8.

(11) E. D. Hughes and H. C. Volger, *J. Chem. Soc.*, 2359 (1961).

(12) G. A. Russell and K. L. Nagpal (*Tetrahedron Letters*, 421 (1961)) have reported a disproportionation reaction of alkylsilanes which correlates with rates of S<sub>N</sub>2 reactions. The reaction is considered to be an S<sub>N</sub>2 reaction at silicon and S<sub>E</sub>2 at carbon and to involve the dimeric transition state



This reaction is not an appropriate model for the S<sub>E</sub>2 reaction



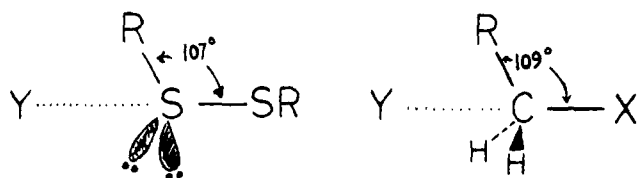
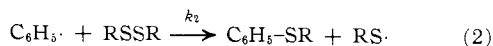
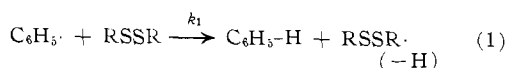


Figure 1.

deduced. As will be seen below, radicals are less selective than are ions, and the over-all spread of the rates is greatly compressed. However, the energetics of the SH2 reaction on sulfur parallels the energetics of the SN2 reactions, and the radical reaction can be concluded to involve a Walden inversion mechanism.

#### Data

Disulfides react with radicals in two ways: attack on hydrogen and attack on sulfur.<sup>4</sup> For the phenyl radical, these two reactions are



In the presence of  $\text{CCl}_4$ , reaction 3 also occurs. Using previously reported techniques,<sup>7,13</sup> values of  $k_1/k_3$  and  $k_2/k_3$  can be obtained, and Table I gives these data.

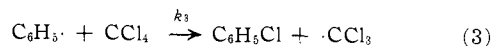


Figure 2 is a log-log graph of relative rates of reaction 2 vs. rates for the SN2 reactions<sup>10</sup> on carbon and sulfur. (The upper end of each bar is the point for the SN2 reaction on carbon, and the lower end is for the SN2 reaction on sulfur.) Despite the compression in the scale of the SH2 reaction, the log-log graph shows an excellent correlation. Since the logarithm of a rate constant is proportional to energy, we conclude that similar energetic requirements affect the stereochemistry of both the SH2 and the SN2 reactions. Therefore, the SH2 reaction involves a backside, three-atoms-in-a-line transition state.

Some comment is required on why the scale of the relative rates of the SH2 reaction is compressed relative to that of the SN2 reaction. Steric interaction mechanisms occur in greater variety than do polar interactions; therefore, two transition states must be very similar for steric effects to lead to a quantitative relation between the two reactions. For example,<sup>14a</sup> the steric effects of R groups on the rates of hydrolysis of *o*-substituted benzamides are correlated excellently by Taft's  $E_s$  values,<sup>14b</sup> which are derived from hydrolysis rates of *o*-substituted benzoates. However, the hydrolysis of thiolacetates is not correlated by  $E_s$ . Taft<sup>14a</sup> has explained this as follows: "Because of the specific nature of steric factors, it seems likely that the quantitative utility of steric substituent parameters will be quite limited." Exact correlations of steric factors are less expected than of polar factors, and, when found, are even more significant. Therefore, there seems little doubt that, although the SH2 reaction has a compressed reactivity scale, the transition state for the SN2 and the SH2 reactions of these disulfides are extremely similar.

The relative rates for abstraction of hydrogens from these disulfides,  $k_1/k_3$ , also provide interesting information. The  $\alpha$ -hydrogens of the disulfides are compar-

(13) G. A. Russell and R. F. Bridger, *Tetrahedron Letters*, 737 (1963). We are grateful to Dr. Russell for a preprint of his complete article which is in press.

(14) (a) R. W. Taft, Jr., *J. Am. Chem. Soc.*, **74**, 3120 (1952); (b) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," ed. by M. S. Newman, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 598.

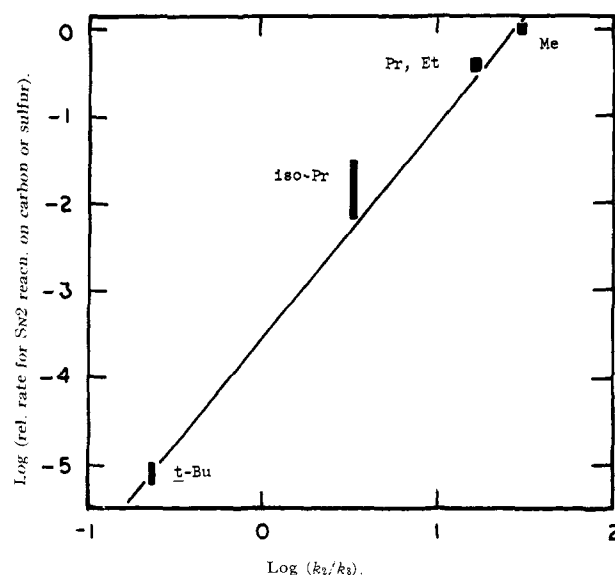


Fig. 2.—Log-log graph of relative rates for SN2 reactions on carbon (upper end of bar) and sulfur (lower end of bar) vs.  $k_2/k_3$ .

able in activity to benzylic hydrogens;  $\beta$ -hydrogens are much less labile. If primary hydrogens are compared, primary  $\alpha$ -hydrogens are 6.8 times more reactive than are primary  $\beta$ -hydrogens. Solving the simultaneous equations for the reactivity of each type of hydrogen in these disulfides gives a reactivity series for primary:second:tertiary  $\alpha$ -hydrogens of 1:3.2:9.1. Russell and Bridger<sup>13</sup> find the reactivity for benzylic hydrogens to be 1°:2°:3°:1:4.6:9.7, and for aliphatic hydrogens to be 1:8.4:40. Thus, hydrogens  $\alpha$  to a sulfur atom are comparable to benzylic hydrogens both in absolute reactivity and in sensitivity to substitution effects. It is interesting that despite these highly labile hydrogens, most disulfides are attacked on sulfur to a larger extent than they are on hydrogen.

TABLE I

REACTION OF PHENYL RADICALS FROM PHENYL-AZOTRIPHENYLMETHANE (PAT) WITH DISULFIDES IN THE PRESENCE OF CARBON TETRACHLORIDE AT 60°

R in RSSR	$k_1/k_3^a$	$k_2/k_3^b$	% of attack which occurs on sulfur <sup>c</sup>
Methyl	0.57	31.0	98.2
Ethyl	1.3	17.4	93
Propyl	1.8	16	90
Isopropyl	1.9	3.3 <sup>d</sup>	64
<i>t</i> -Butyl	0.25	0.23 <sup>e</sup>	49

<sup>a</sup>  $k_1/k_3 = (\% \text{ attack on hydrogen}) / (\% \text{ attack on sulfur})$ .  
<sup>b</sup>  $k_2/k_3 = (\text{C}_6\text{H}_5\text{SR formed}) / (\text{C}_6\text{H}_5\text{Cl formed}) / (\text{RSSR})_0$ .  
<sup>c</sup> From ref. 7. <sup>d</sup> Measured over a 15-fold variation in  $(\text{CCl}_4) / (\text{RSSR})$  from 0.3 to 4.5. <sup>e</sup> Over a 25-fold variation in  $(\text{CCl}_4) / (\text{RSSR})$  from 0.4 to 10.0.

This work was part of a larger project in which we intended to generate phenyl radicals from phenylazotriphenylmethane (PAT) and measure the relative reactivity of hydrogens in a range of compounds. However, Russell and Bridger<sup>13</sup> have just published very extensive data of this sort, and we have discontinued our work. Before we learned of Russell and Bridger's work, we had measured the relative rate of abstraction of a hydrogen from toluene and acetone relative to reaction 3. We obtain 0.31 and 0.16, in agreement with 0.27 and 0.17 obtained by Russell and Bridger. We have also confirmed an unexpected feature of their work: In runs in pure  $\text{CCl}_4$ , appreciable amounts of benzene are formed. At very low concentrations of PAT, about 3% benzene is formed. This

apparently is the result of a cage reaction. Garst and Cole<sup>15</sup> have shown that 3% of the phenyl radicals from PAT are not scavengeable and, therefore, disappear in either a cage or a molecular process. At higher concentrations of PAT, more benzene is formed, but the sum of the yields of benzene and chlorobenzene decreases. An attractive hypothesis which explains these facts is that free phenyl radicals react with PAT in two ways: one produces benzene and the other traps phenyl radicals. The interesting thing is how efficient PAT is as a radical scavenger: 0.2 M PAT traps about 30% of the phenyl radicals in pure CCl<sub>4</sub>. It is clear, therefore, why Eliel, *et al.*,<sup>16</sup> found that the yield of

(15) J. F. Garst and R. S. Cole, *Tetrahedron Letters*, 679 (1963).

biphenyl decreases as the PAT concentration is increased in homolytic substitution in benzene. This results from the fact that PAT is a radical scavenger, rather than from the fact that biphenyl is produced in a geminate process.<sup>17</sup> The addition of phenyl radicals to PAT might be expected to be fast since it produces a stabilized radical with structure reminiscent of that of diphenylpicrylhydrazyl.

**Acknowledgment.**—Discussion with Prof. J. E. Leffler is appreciated.

(16) E. L. Eliel, M. Eberhardt, O. Simamura, and M. Meyerson, *ibid.*, 749 (1962).

(17) Also see D. H. Hey, M. J. Perkins, and G. H. Williams, *ibid.*, 445 (1963).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE JOHNS HOPKINS UNIVERSITY, BALTIMORE, MD.]

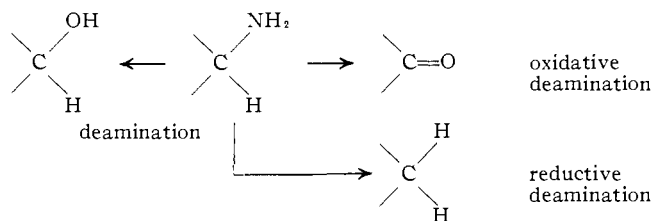
## A Direct Method for Reductive Deamination of Aliphatic Amines<sup>1</sup>

BY ALEX NICKON<sup>2</sup> AND ADA S. HILL

RECEIVED OCTOBER 19, 1963

Treatment of a primary amine sulfonamide with hydroxylamine-O-sulfonic acid in alkaline solution provides a direct method for reductive deamination (R-NH<sub>2</sub> → R-H) in the aliphatic series. Amino groups on primary, secondary, and tertiary aliphatic carbons can be replaced and these include benzylic, as well as ring and bridgehead carbons. The yields vary widely, but are usually high when corrected for unchanged sulfonamide. The conversion of β-naphthylamine to naphthalene indicates the method is also applicable to aromatic amines. Oxidative deamination to form a ketone (or an aldehyde) is a minor side reaction when the amino carbon carries one (or two) hydrogens. Side reactions predominated in the case of 9-aminofluorene *p*-toluenesulfonamide. Under typical experimental conditions in alkaline aqueous ethanol, the benzenesulfonamide of optically active 2-phenyl-2-butylamine gave 2-phenylbutane, with partial retention of configuration. A mechanism for the reductive deamination is proposed that involves N-amination of the sulfonamide and loss of a sulfonic acid to give a monosubstituted diimide (RN=NH), which loses nitrogen. Under the experimental conditions hydroxylamine-O-sulfonic acid converted benzenesulfonic acid to benzenesulfonamide, which was identified as a product in one of the runs with benzylamine benzenesulfonamide.

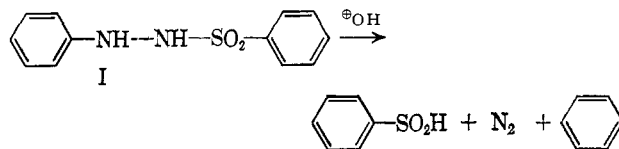
The removal or replacement of a primary amino group attached to carbon can be accomplished many ways. Such processes are usually referred to as "deaminations" even though they can lead to a variety of products and can be brought about directly or indirectly by numerous reagents. For clarity in discussion we shall restrict the term *deamination* to an amine transformation that gives a product of the same oxidation level.<sup>3</sup> *Oxidative deamination* and *reductive deamination* can then refer to transformations of an amine to products of higher and lower oxidation levels, respectively. Deamination is exemplified by the nitrous acid treatment of a primary amine to produce



(among other things) an alcohol. The mechanism of this well known reaction continues to attract much research attention.<sup>4</sup> Oxidative deamination is illustrated by the conversion of an amine to a carbonyl compound. This over-all change can sometimes be brought about in the laboratory directly by the use of oxidizing agents<sup>5</sup> and is of biological importance in

connection with oxidations and transaminations of amino acids.<sup>6</sup> Reductive deamination involves net replacement of an amino group by hydrogen. Procedures that accomplish this change for aromatic primary amines are well known,<sup>7</sup> but in the aliphatic series no direct method has been available. In a preliminary note we recently described such a method,<sup>8</sup> and the present paper reports the details of that study.<sup>9</sup>

Our approach originated from a report by Escales that alkaline treatment of benzenesulfonphenylhydrazide (I) yielded benzenesulfonic acid, nitrogen, and benzene.<sup>10</sup> Later, McFayden and Stevens treated a series of benzenesulfonarylhazides II (Ph = phenyl, Ar = aryl) with sodium carbonate and obtained



the corresponding aromatic aldehydes along with nitrogen and benzenesulfonic acid.<sup>11</sup> To account for

(6) J. S. Fruton and S. Simmonds, "General Biochemistry," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 750-766.

(7) N. Kornblum, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 262.

(8) A. Nickon and A. Sinz, *J. Am. Chem. Soc.*, **82**, 753 (1960).

(9) Another direct method has since been reported and involves treatment with difluoramine [C. L. Bumgardner, K. J. Martin, and J. P. Freeman, *ibid.*, **85**, 97 (1963)].

(10) R. Escales, *Chem. Ber.*, **18**, 893 (1885).

(11) J. S. McFayden and T. S. Stevens, *J. Chem. Soc.*, 584 (1936). Their reaction has proved useful for the synthesis of aromatic aldehydes, and an important modification has been described by M. S. Newman and E. G. Calfish, Jr. [*J. Am. Chem. Soc.*, **80**, 862 (1958)]. These last workers found that solid surfaces such as powdered soft glass catalyze the reaction markedly and can lead to successful conversions where others have reported failures [C. Niemann and J. T. Hays, *ibid.*, **65**, 482 (1943)].

(1) Abstracted from the Ph.D. Dissertation of Ada Sinz Hill (nee Ada Sinz), The Johns Hopkins University, 1960.

(2) Alfred P. Sloan Foundation Fellow.

(3) Oxidation levels are used in the sense suggested by R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, London, 1955, p. 4.

(4) J. H. Ridd, *Quart. Rev. (London)*, **15**, 418 (1961).

(5) L. Hellerman and A. G. Sanders, *J. Am. Chem. Soc.*, **49**, 1742 (1927).