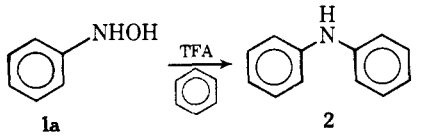
An Acid-Catalyzed Reaction of Arylhydroxylamines with Benzene. Selectivity of the Reaction Sites

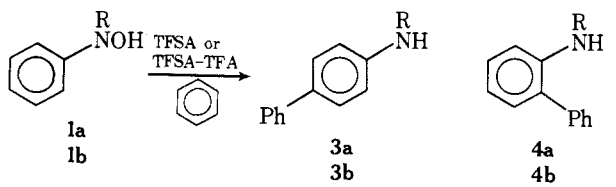
Sir:

We have previously described the reaction of arylhydroxylamines with benzene catalyzed by trifluoroacetic acid (TFA) which yields diphenylamines.[1] In this communication we wish to report the reaction of arylhydroxylamines with benzenes in which a carbon–carbon bond between the two aromatic rings is formed.



1a **2**

In this study, *N-tert*-butylphenylhydroxylamine (**1b**) was chosen because the steric bulk of the *N-tert*-butyl group would be expected to decrease the reactivity at the nitrogen atom. This assumption seems to be correct since the reaction of **1b** with benzene in TFA was slow and complex.[2] On the other hand, in trifluoromethanesulfonic acid (TFSA), the reaction proceeded very smoothly by attack on the benzene ring as well as the NOH group, to give aminobiphenyls, **3b** (49%) and **4b** (8%), and 4-trifluoromethanesulfonyloxy-*N-tert*-butylaniline (10%). This result prompted us to

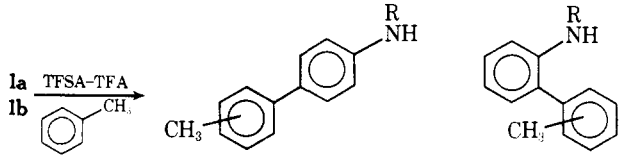


1a **1b** **3a** **3b** **4a** **4b**

a, R = H; b, R = *t*-Bu

examine the reaction of **1a** with benzene in the presence of the stronger acid, TFSA. The result is shown in Table I. In the presence of TFA, the major product was diphenylamine (**2**). The addition of TFSA changed the reaction site. In presence of more than 4 equiv of TFSA only 4-aminobiphenyl (**3a**, 48%) and 2-aminobiphenyl (**4a**, 23%) were obtained. Reaction at the nitrogen atom was suppressed. The presence or absence of TFSA, and not the polarity of the medium appears to be the controlling factor (compare runs **3** and **7** in Table I).[3]

The reaction of **1** with toluene in the presence of TFSA gave a mixture of methylaminobiphenyls (**5a,b** and **6a,b**). The reaction at the meta position of toluene appears to reflect the high reactivity of the attacking species.[4]



5

	o-	m-	p-	%
a, R = H	18	9	13	
b, R = *t*-Bu	18	11	17	

6

	mixture %
a, R = H	23
b, R = *t*-Bu	7

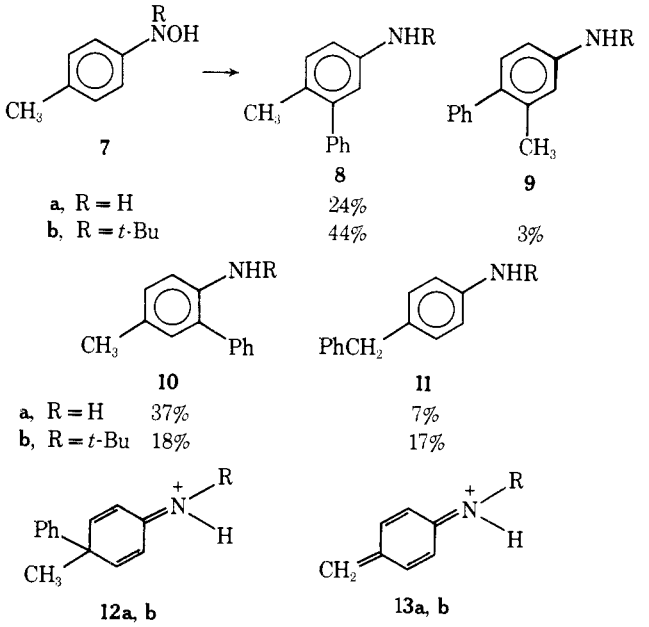
Reaction of *N-tert*-butyl-4-methylphenylhydroxylamine (**7b**) with benzene in TFSA–TFA gave an interesting mixture; the major product (**8b**, 44%) was formally produced by meta substitution. The occurrence of 4-(*N-tert*-butylamino)-2-methylbiphenyl (**9b**), however, suggests that the isomers are formed by the rearrangement of an intermediate cyclohexadienimmonium salt (**12b**). Nucleophilic attack

Table I. Reaction of Phenylhydroxylamine with Benzene

Run	Amounts of acids (mol)[a] CF_3CO_2H	CF_3SO_3H	Benzene (mol)[a]	Procedure	Product (%)[b] 2	3a	4a
1	4	0	3.5	*c, e, g*	41	3	3
2	10	0	9.0	*c, e, g*	56	9	8
3	25	0	22.0	*c, e, g*	46	12	11
4	25	0	22.0	*c, e*	12	5	5[h]
5	25	0.2	22.5	*c, e*	20	4	4
6	25	1.2	22.5	*c, f*	39	19	17
7	25	2.3	22.5	*c, f*	14	46	25
8	0	2.0	60.0	*d, f*	2	25	12
9	0	4.0	60.0	*d, f*	1	32	16
10	0	20.0	60.0	*d, f*	<1	48	23

[a] Moles per a mole of **1a**. [b] Based on VPC. [c] Phenylhydroxylamine (**1a**) was added to a stirred mixture of acids and benzene at 5°. [d] CF_3SO_3H was added dropwise to a mixture of **1a** and benzene at 5°. [e] For 12 hr. [f] For 30 min. [g] In the presence of a catalytic amount of ascorbic acid. [h] Azoxybenzene was the major product.

Scheme I



7 **8** **9**

	8	9
a, R = H	24%	
b, R = *t*-Bu	44%	3%

10 **11**

	10	11
a, R = H	37%	7%
b, R = *t*-Bu	18%	17%

12a, b **13a, b**

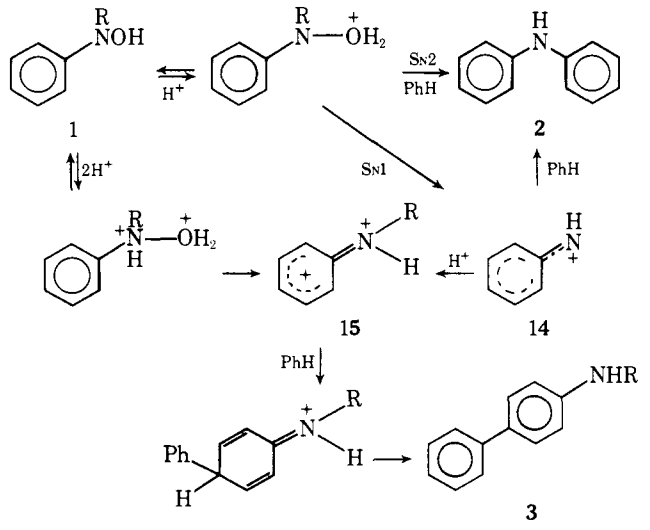
also occurs at the methyl carbon to give 4-(*N-tert*-butylamino)diphenylmethane (**11b**). Its formation is explained by the participation of the unsaturated compound (**13b**).[5] A similar result was obtained from the reaction of 4-methylphenylhydroxylamine (**7a**) with benzene.

Substituted hydroxylamines with nucleophilic leaving groups,[6] such as *p*-methoxy and *p*-chloro at the para position, react with benzene under similar conditions to give terphenylamines,[7] which are the products from 4-biphenylhydroxylamine and benzene.[7]

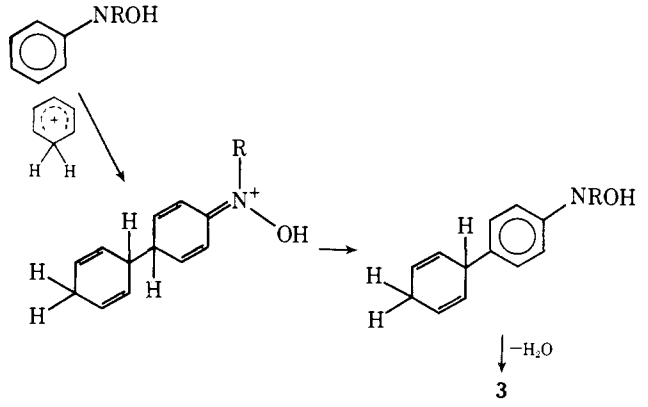
Concerning the possible reaction mechanism, we must consider the effect of acidity on the determination of reaction sites.

The proposed reaction pathways to diphenylamine (**2**) and aminobiphenyl (**3**) are shown in Scheme II.[8] Diphenylamine (**2**) can result from an acid-catalyzed SN2 (A2) type reaction on the nitrogen atom, from an acid catalyzed SN1 (A1) type reaction involving an anilenium ion (**14**),[9] or through an intermediate mechanism. A possible mechanism leading to aminobiphenyl (**3**) involves a protonated nitrenium ion (**15**), which can be formed from diprotonated phenylhydroxylamine or by protonation of the anilenium ion (**14**). This clearly explains the necessity of a strong acid. The recent observation of protonated nitrenium ions as sta-

Scheme II



Scheme III



ble species generated by anodic oxidation in a strongly acidic medium,[10] supports the participation of the intermediate ion in this reaction.

Another mechanism which may lead to aminobiphenyls should be considered (Scheme III). This involves an electrophilic attack of benzenium ion on phenylhydroxylamine, followed by aromatization and dehydration. However, this mechanism hardly explains the formation of **8** and **11** from 4-methylphenylhydroxylamine (**7**).

References and Notes

(1) K. Shudo and T. Okamoto, *Tetrahedron Lett.*, 1839 (1973).
(2) The products identified were **2** (12%), **3a** (6%), **4a** (2%), **3b** (5%), **4b** (1%), and azoxybenzene (5%). *N-tert*-Butyldiphenylamine could not be identified.
(3) Both **2** and **3** are stable under these reaction conditions.
(4) H. C. Brown and K. L. Nelson, *J. Am. Chem. Soc.*, **75**, 6295 (1953); L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, **1**, 35 (1963).
(5) It is possible to explain the formation of **8** by nucleophilic attack of benzene on **13**.
(6) G. A. Olah and J. Welch, *J. Am. Chem. Soc.*, **97**, 208 (1975).
(7) Products from these reactions are 4-aminobiphenyl, 4-amino-*p*-terphenyl, 4'-amino-*m*-terphenyl, and probably 4'-amino-*o*-terphenyl. Identification of the last compound has not been done yet.
(8) A simple discussion that SN2 reaction leads to **2** and SN1 reaction leads to **3** does not explain the role of the acids used, though the slow reaction of **1b** in the presence of TFA may suggest the importance of bimolecular mechanism in the TFA-catalyzed reaction which gives **2**. An alternative pathway, which cannot be eliminated, involves phenylhydroxylamine *O*-ester formed in the presence of TFSA. The ester solvolyzes to anilenium ion **14**, which reacts with benzene. Even in this case, protonation of **14** is very probable. The formation of azoxybenzene (run 4), which is suppressed by the presence of ascorbic acid, is explained by the homolytic cleavage of the N–O bond, probably the Loeffler–Freytag type homolysis of $PhNH_2^+$–OH. This and the reactions of para-substituted phenylhydroxylamines eliminate the homolytic process in the present reactions.
(9) P. G. Gassman, *Acc. Chem. Res.*, **3**, 26 (1970); P. G. Gassman, G. A. Campbell, and F. C. Fredrick, *J. Am. Chem. Soc.*, **94**, 3884 (1972).
(10) U. Svanholm and V. D. Parker, *J. Am. Chem. Soc.*, **96**, 1234 (1974); D. Serve, *ibid.*, **97**, 434 (1975).

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Oxygen Binding to Iron Porphyrins

Sir:

The current literature abounds with simple synthetic models of myoglobin and hemoglobin,[1-5] all of which are capable of binding oxygen reversibly. In addition to reversible binding, however, a good model must be inert towards oxidation and reproduce the thermodynamic constants of the biological systems. We report here the first such comparison of a synthetic ferrous porphyrin model with myoglobin, the results of which help to delineate the role of the aproprotein in oxymyoglobin.

Using the "picket fence" porphyrin model, Fe($\alpha,\alpha,\alpha,\alpha$-TpivPP)(1-MeIm),[4,6] we have determined the enthalpy and entropy of oxygen binding in the solid state. The porosity of the crystals of this material allows the full equilibration of the solid with oxygen without the difficulties of most solution studies: the eventual irreversible oxidation of the compound and the complex equilibria with axial base. The solid-gas approach has the further advantage of a known molecular geometry as determined from x-ray diffraction data.[7] A simple manometric adsorption apparatus[8] in conjunction with an electronic manometer[9] was used in all experiments. The temperature of the apparatus was controlled to ±0.1°C, while connected to a vacuum line, which could be evacuated to a pressure of 10^{-6} Torr. Volumes were calibrated by expanding nitrogen from an outside gas bulb of known volume and pressure into the evacuated apparatus.

Isotherms were determined by desorption of a fully saturated[10] sample of Fe($\alpha,\alpha,\alpha,\alpha$-TpivPP)(1-MeIm)·$O_2$ into an evacuated volume. Each isotherm consists of at least six points, each point representing the extrapolation to equilibrium of 4 hr of data.[11] These isotherms followed the Langmuir equation at low pressures (less than 15 Torr), indicating that the iron binding sites are noninteracting in the crystal lattice. A typical plot of $\theta/(1-\theta)$ vs. p_{O_2}, where θ is the fraction of saturation at equilibrium, is shown in Figure 1 for the data collected at 25.0°. The thermodynamic enthalpy and entropy of reaction with oxygen were derived from a weighted least-squares fit to a van't Hoff plot ranging over 50°.[12] The calculated constants are $\Delta H° = -15.6 \pm 0.2$ kcal/mol and $\Delta S° = -38 \pm 1$ cal deg^{-1} mol^{-1} (standard state of 1 atm). The interpolated $K_{eq}^{20°}$ is 2400 atm^{-1} or equivalently, $p_{1/2}^{20°} = 0.31$ Torr. It should be noted that some deviation from the Langmuir isotherm was observed at high pressures at 0°; this is attributable to a strong physical adsorption of oxygen on the porphyrin rather than to the binding at the iron atom: the metal free ligand, $\alpha,\alpha,\alpha,\alpha$-$H_2$TpivPP, physically adsorbs oxygen with an equilibrium binding constant of roughly 2 atm^{-1} at 0°. It should also be noted that in contrast to solution models, our solid samples are remarkably inert to oxidation. For example, one sample has been cycled between O_2 and vacuum more than 200 times with no observable irreversible oxidation.

A comparison of our thermodynamic constants with those of a selection of myoglobins and of the model of Chang and Traylor[3] is made in Table I. It is clear that the "picket fence" is a good model for myoglobin in this respect. The close similarity of the model to the biological sys-