Differences Among the Mechanisms of Reaction of Phenylhydroxylamine with Various Carbonyl Compounds

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ABSTRACT: In order to obtain a better knowledge of the special behavior of phenylhydroxylamine as a nucleophile, the mechanism of its reaction with 2,6-dichlorobenzaldehyde, norcamphor, and cyclohexanone, and also the hydrophobic effect on its reaction with 2,6-dichlorobenzaldehyde and benzaldehyde, was studied. The results led us to assume that the planar molecule of phenylhydroxylamine should be placed parallel to the planar molecule of benzaldehyde in order to permit the attack of the lone electron pair of the nitrogen on the carbonyl group, forming, together with a hydrogen bond between the hydroxyl group and the carbonylic oxygen atom, a packed preassociation complex. This mechanism is not observed in the case of norcamphor or 2,6-dichlorobenzaldehyde due to the steric hindrances produced by the lack of planarity of these molecules. © 2000 John Wiley & Sons, Inc. Int J Chem Kinet 32: 453–459, 2000

INTRODUCTION

It has been suggested that the reaction of nitrogen nucleophiles with carbonyl compounds exhibits different types of pH-rate profiles [1]. These profiles show one or two negative breaks corresponding to a change in the rate-determining step of the reaction, from nucleophile attack on the carbonyl group, forming an addition intermediate by a concerted or a stepwise mechanism, to dehydration of this intermediate.

However, it has been demonstrated that the reactions of furfurals and benzaldehydes with phenylhydroxylamine have a pH-rate profile without a negative break, indicating that only one step is rate-determining over the entire pH range 1 to 12 [2,3]. This rate-determining step is the dehydration of an addition intermediate formed from the reactants. Amines of basicity similar to that of phenylhydroxylamine exhibit a profile with one negative break in moderate acid regions, indicating a change in the rate-determining step of the reaction from the attack of the phenylhydroxylamine on the carbonyl group, giving an addition intermediate, to the dehydration of this intermediate to products. This special behavior of phenylhydroxylamine is interpreted [2] as the existence of a very fast step of attack, of phenylhydroxylamine on the aldehydes, by a preassociation mechanism in which an "encounter complex" is formed that has certain steric requirements.

This work was carried out in order to obtain more information about this special behavior of phenylhy-

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droxylamine and the different mechanism of attack on the carbonyl group (1) by the study of its reaction with norcamphor, used as substrate for the examination of the steric requirements of certain organic reactions [4,5], 2,6-dichlorobenzaldehyde, where the steric interaction with the two *ortho*-substituents forces the aldehyde group out of a coplanar conformation with the aromatic ring [6], and cyclohexanone, an aliphatic ketone that does not exert steric constraints on the reaction; and (2) by analyzing the hydrophobic effect, produced for the addition of LiCl, in order to obtain information on the nature of the reaction transition states of the different mechanisms of attack of the nucleophile on the carbonyl compounds [7–9].

EXPERIMENTAL

Materials

The organic reagents employed were commercially available products and were either redistilled or recrystallized. Solutions of various nucleophile reagents were purified by recrystallization from ethanol-water and the solutions were prepared just before use. Phenylhydroxylamine was prepared according to the method of Smissman and Corbert [10] and was purified by recrystallization from benzene-light petroleum (b.p. 40–60°C). Inorganic chemicals and carboxylic acids used in buffers were of reagent grade and were used without further purification.

Kinetic Procedure

The reactions between norcamphor and nucleophile reagents at 25°C were followed on a Varian DMS 80 spectrophotometer by monitoring the formation of the nitrone (λ = 255 nm), semicarbazone (λ = 255 nm), phenylhydrazone (λ = 320 nm), and methyloxime (λ = 243 nm) in 20% aqueous ethanol at ionic strength 0.5 (KCl). A sufficient excess of nucleophile reagent was employed to ensure pseudo-first-order kinetic behavior, except in the case of reactions between carbonyl compounds and phenylhydroxylamine, where excess of the carbonyl compound was used. The reactions between 2,6-dichlorobenzaldehyde and benzaldehyde with phenylhydroxylamine were carried out in 40% aqueous ethanol, ionic strength 0.5 (KCl). The other reactions were carried out in 20% aqueous ethanol. First-order rate constants (k_{obs}) were calculated by computer, where the reactions were followed for three half-lives ($t_{1/2}$). Statistical uncertainty on these values never exceeded 5%. Second-order rate constants were calculated by dividing the first-order rate constants by the concentration of the free amine, $k_2 = \{k_{obs}/[\text{amine}]1\}$. For the reaction using excess of the carbonyl compound (reaction of phenylhydroxylamine with norcamphor, 2,6-dichlorobenzaldehyde and cyclohexanone), the second-order rate constants were calculated by the equation $k_2 = k_{obs}/[\text{carbonyl compound}]$. *fc*, where $fc = K_a/(K_a + H^+)$, (K_a = acid constant of phenylhydroxylamine). Third-order rate constants (k_1, k_{H^+}, k_{OH^-}) were obtained from the slopes of plots of second-order rate constants against the concentration of catalytic species.

pKa Determination

The pK_a of phenylhydroxylamine was determined following the spectrophotometric method of Albert and Sergeant [11]. The pH-meter was standardized following the method of Bates [12]. In 20% aqueous ethanol at ionic strength 0.5 (KCl), the value of pK_a was 1.96, and in 40% aqueous ethanol at ionic strength 0.5 (KCl), the value of pK_a was 1.87.

Equilibrium Constants for the Addition Intermediate Formation

The equilibrium constants, K_{ad}, for the addition intermediate formation from norcamphor and various amines were determined spectrophotometrically [13]. These equilibrium constants were determined by measuring the decrease in absorbance at 285 nm of a solution of norcamphor (0.033 M) in the presence of varying concentrations of amines. The pH was maintained between pH 8.5 and 9.5 with 0.01 M of the buffer (phosphate or borate), and ionic strength was adjusted to 0.5 with KCl. At this pH, dehydration of the addition intermediate was relatively slow, so that the observed absorbance could be extrapolated to zero time to determine the initial rapid decrease in ketone absorbance caused by addition intermediate formation. The calculated values of the fraction of ketone converted to addition intermediate (I) were based on an assumed absorbance of zero for the addition compound at 285 nm. We took into consideration the measurements in triplicate for each concentration of different amines, using the equation $K_{ad} = \{([C{=}O]_t - [C{=}O]_1) / [C{=}O]_1\} \times [\text{nucleophile}]$, where $[C{=}O]_t$ is the initial carbonyl absorbance and $[C{=}O]_1$ is the free carbonyl absorbance.

RESULTS AND DISCUSSION

Kinetics Analysis

The pH dependences of the apparent second-order rate constants ($k_2$ap) for the reaction of norcamphor, 2,6-

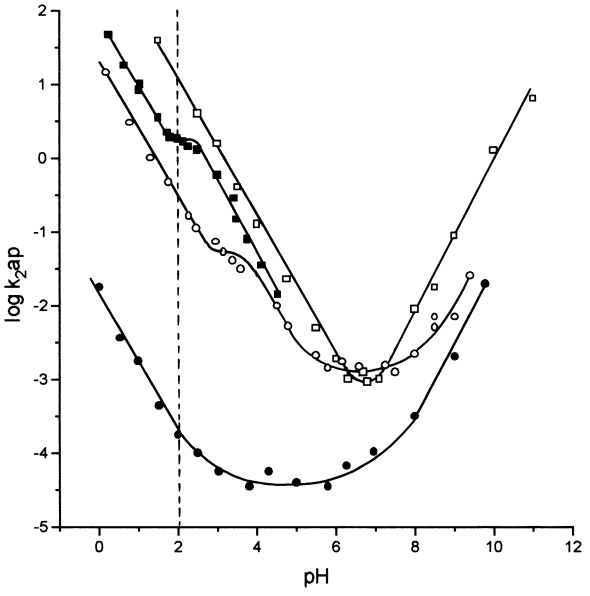
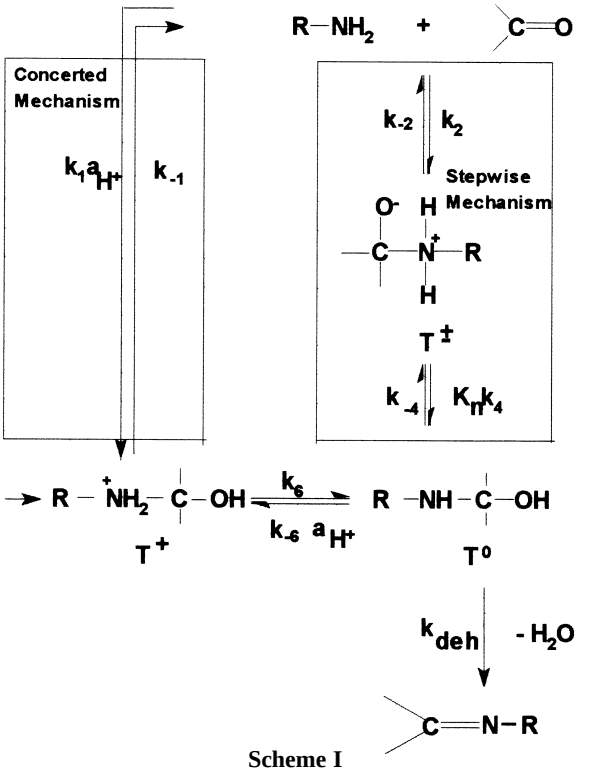


Figure 1 pH dependence of the logarithms of second-order rate constants for nitrone formation in 20% aqueous-ethanol from phenylhydroxylamine and norcamphor (○), cyclohexanone (●), and 40% aqueous-ethanol from phenylhydroxylamine and 2,6-dichlorobenzaldehyde (■), benzaldehyde (□), at 25°C and ionic strength 0.5 mol dm^{-3}.

dichlorobenzaldehyde, cyclohexanone, and benzaldehyde with phenylhydroxylamine are shown in Figure 1. All the rate constants were extrapolated to zero buffer concentration.

The pH-rate profiles of the reaction of phenylhydroxylamine with norcamphor and 2,6-dichlorobenzaldehyde show a negative break corresponding to a change in the rate-determining step from the dehydration of the addition intermediate formed in a rapid preequilibrium (k_{deh}) to the concerted oxonium-ion catalyzed attack of the nucleophile on the carbonyl compounds at low pH (k_1). The pH-independent region corresponds to a solvent-catalyzed intramolecular proton transfer in a zwitterionic addition intermediate ($T^{\pm}$) to give the neutral addition intermediate T^0 ($K_n k_4$, where $K_n = k_2/k_2$). This kind of profile was classified as "A" by Sayer et al [1]. See Scheme I.



Scheme I

The curves in Figure 1 for the reactions between phenylhydroxylamine and norcamphor and 2,6-dichlorobenzaldehyde were calculated employing Eq. (1) together with the rate constants in Table I. The fit between the experimental data and the theoretical curve is acceptable. Eq. (1) is obtained from the steady-state treatment of the mechanism in Scheme I:

$$k_2\text{ap} = k_{ad} \cdot K_{ad}k_{deh}/\{k_{ad} + K_{ad}k_{deh}\} \qquad (1)$$

where k_{ad} and k_{deh} correspond to the product formation in the region of rate-determining addition intermediate formation [Eq. (2)] and dehydration [Eq. (3)], respec-

Table I Rate Constants for Nitrone Formation from Phenylhydroxylamine with 2,6-Dichlorobenzaldehyde, Benzaldehyde, Norcamphor, and Cyclohexanone[a]

	Norcamphor	2,6-Dichlorobenzaldehyde	Cyclohexanone	Benzaldehyde
k_1, $M^{-2}\ s^{-1}$	2.1×10^1	1.00×10^2		
$K_n k_4$, $M^{-1}\ s^{-1}$	5.6×10^{-2}	1.58×10^0		
$K_{ad}\ k_{H^+}$, $M^{-1}\ s^{-1}$	2.1×10^2	5.62×10^2	1.78×10^{-2}	1.26×10^3
$K_{ad}\ k_0$, s^{-1}	1.78×10^{-3}		4.47×10^{-5}	1.58×10^{-3}
$K_{ad}\ k_{OH^-}$, $M^{-1}\ s^{-1}$	9.99×10^2		3.16×10^2	7.12×10^3

[a] 25°C, ionic strength 0.5 (KCl), 20% ethanol v/v; except for reaction between phenylhydroxylamine with 2,6-dichlorobenzaldehyde and benzaldehyde, which is 40% ethanol v/v.

tively. K_{ad} is the equilibrium constant for neutral addition intermediate formation:

$$k_{ad} = k_1 a_{H^+} + K_n k_4 \quad (2)$$

where k_1 is the rate constant for the concerted acid-catalyzed attack as the slow step, and $K_n k_4$ corresponds to the solvent intramolecular proton transfer, and

$$k_{deh} = k_{obs}/[C{=}O] \cdot fc = k_{H^+}[H^+] + k_0 + k_{OH^-}[OH^-] \quad (3)$$

where $fc = K_a/K_a + [H]^+$ and [C═O] is the concentration of the carbonyl compound. k_{H^+} and k_{OH^-} are the rate constants corresponding to the oxonium-ion and hydroxide-ion catalyzed dehydration. k_0 is the rate constant of the uncatalyzed dehydration.

Bronsted Correlation

For the reaction of norcamphor with phenylhydroxylamine, semicarbazide, methoxylamine, phenylhydrazine, hydroxylamine, and *N*-methylhydroxylamine (Table II), the Bronsted-type correlation (Figure 2) between the oxonium-ion catalytic rate constants for the attack step (k_1) and the pK'_a of different amines ($pK'_a = pK_a$ measured under the same conditions as our experiments) exhibits a good linearity with $\beta = 0.385$ and the correlation coefficient $r = 0.964$. The point corresponding to the reaction between phenylhydroxylamine and norcamphor fits reasonably with the Bronsted line, suggesting that the acid-catalyzed "concerted mechanism" of attack of amines on the carbonyl compounds, which is well known [14], must also be the mechanism of the reaction of phenylhydroxylamine with norcamphor. This behavior is different from that of the reaction between phenylhydroxylamine and the benzaldehydes [2].

Table II Kinetic and Equilibrium Constants for Additional Intermediate Formation from Nitrogen Nucleophiles and Norcamphor at 25°C[a]

Amine	$pK^{a\prime}$	log k_1	K_{ad}, M^{-1}
Phenylhydroxylamine	1.96[c]	1.32	
Semicarbazide	3.65[d]	1.75	0.064 ± 0.006
Methoxylamine	4.70[e]	2.00	0.049 ± 0.007
Phenylhydrazine	5.25[f]	2.67	
N-methylhydroxylamine	5.96[d]	2.75	0.068 ± 0.007
Hydroxylamine[b]	5.97[d]	2.82	0.58 ± 0.07

[a] Ionic strength 0.5 (KCl) and 20% ethanol v/v.
[b] Ref. 20.
[c] Ref. 2.
[d] Ref. 21.
[e] Ref. 22.
[f] Ref. 23.

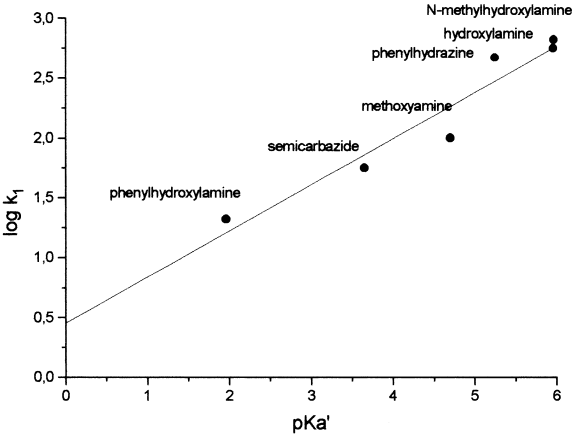


Figure 2 Bronsted plot for oxonium ion-catalyzed attack step for reaction between norcamphor and different nitrogen nucleophiles.

Examining Figure 1 and considering a perpendicular line to pH = 2 that intercepts the profiles of the reaction of phenylhydroxylamine with norcamphor, benzaldehyde, 2,6-dichlorobenzaldehyde, and cyclohexanone, it is apparent that the interceptions correspond to different rate-determining steps: the oxonium-ion concerted catalyzed attack of the phenylhydroxylamine on norcamphor, the uncatalyzed attack ($K_n k_4$) of phenylhydroxylamine in its reaction with 2,6-dichlorobenzaldehyde, and to the oxonium-ion catalyzed dehydration in the reaction of phenylhydroxylamine with benzaldehyde and cyclohexanone. The second-order rate constants are $k_2 = 0.25$, 1.78, 14.12, and 1.78×10^{-4} $M^{-1}s^{-1}$ for norcamphor, 2,6-dichlorobenzaldehyde, benzaldehyde, and cyclohexanone, respectively.

Profiles and Rate-Limiting Steps

It is interesting to note that in the case of the reaction of phenylhydroxylamine with cyclohexanone, the rate-pH profile is of type D, similar to that of its reaction with benzaldehyde. In both cases, the reaction does not follow the expected behavior (profile A) according to that proposed by Sayer [1]. In Figure 1, it may be observed that the rate constant of the oxonium-ion catalyzed dehydration step of the reaction of phenylhydroxylamine with cyclohexanone is slower than the rate constant of the uncatalyzed attack of phenylhydroxylamine on the norcamphor, and, surprisingly, it is approximately 7×10^4 times slower than the oxonium-ion catalyzed dehydration step of its reaction

Table III Second-Order Rate Constants for Nitrone Formation from Phenylhydroxylamine with 2,6-Dichlorobenzaldehyde and Benzaldehyde in Water and in LiCl Solution[a]

	k_2 M^{-1} s^{-1} (H_2O)	k_2 M^{-1} s^{-1} (LiCl)	k_2 H_2O/k_2 LiCl
2,6-Dichlorobenzaldehyde			
pH = 1.0	8.91	1.15	7.75
pH = 2.25	1.41	0.25	5.64
pH = 3.25	0.19	0.14	1.36
Benzaldehyde			
pH = 3.25	0.82	0.55	1.48

[a] [LiCl] = 5 M, 20% ethanol v/v, [C═O] = 1×10^{-3}.

with benzaldehyde. As the attack of phenylhydroxylamine on cyclohexanone should be faster than it is on norcamphor, due to the steric requirements in this latter compound, it is clear that the rate constant of the uncatalyzed attack of phenylhydroxylamine on cyclohexanone should be faster than the dehydration step of the same reaction over the whole pH range studied. This is not the case of the reaction of phenylhydroxylamine with benzaldehyde, where the rate constant of its oxonium-ion catalyzed dehydration step is faster than the rate constant of uncatalyzed and oxonium-ion catalyzed attack of similar nitrogen bases on the same carbonyl compound, as was demonstrated previously [2].

The reactions of phenylhydroxylamine with norcamphor and 2,6-dichlorobenzaldehyde show a profile of type A, as do the profiles of benzaldehyde and its derivatives in its reactions with phenylhydrazine [15] and with semicarbazide [16].

Hydrophobic Effect

The hydrophobic effect is "the tendency of nonpolar species to aggregate in water solution so as to decrease the hydrocarbon-water interfacial area" [7]. Compounds such as LiCl increase the hydrophobic effect and therefore decrease the solubility of hydrocarbons in water [17]. The effect on the kinetics of the reactions with the increase or decrease of the hydrophobic effect provides, in some cases, insights into the nature of the reaction transition state.

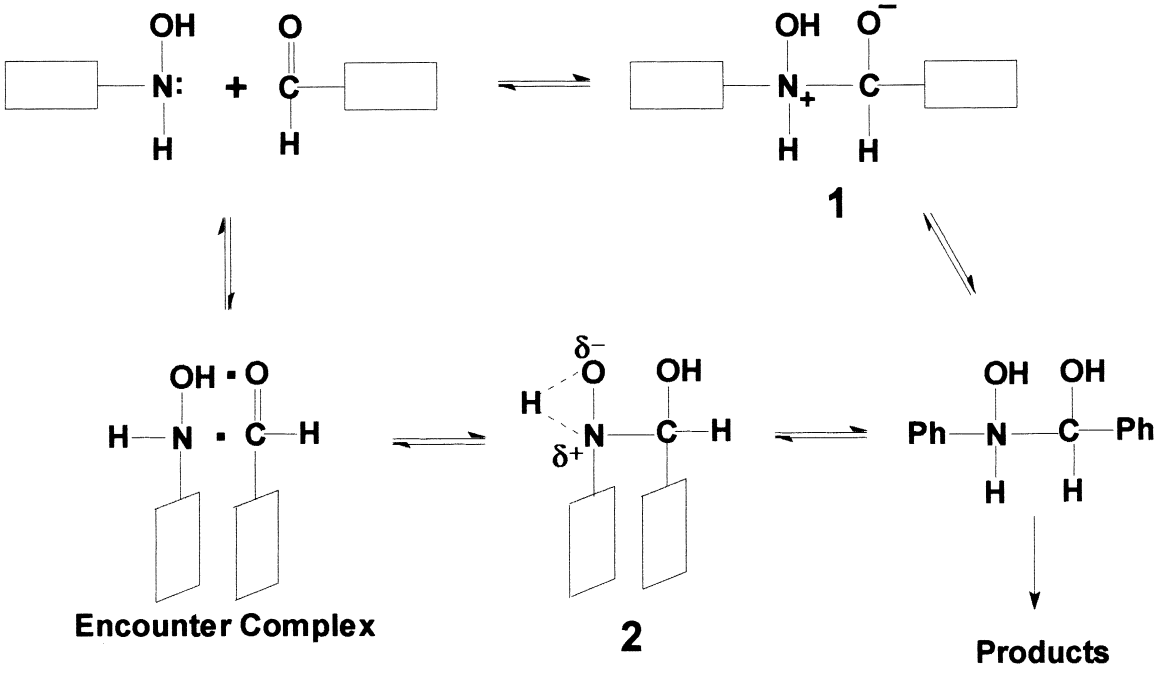
The reactions of phenylhydroxylamine with benzaldehyde and 2,6-dichlorobenzaldehyde in 5 M LiCl solution were studied. The results are given in Table III.

It may be observed that the reaction of phenylhydroxylamine with 2,6-dichlorobenzaldehyde exhibits different behavior for the three regions corresponding to different rate-determining steps. At pH = 1, the rate of the reaction is approximately 8 times slower; at pH = 2.25, it is 6 times slower; and at pH = 3.25 it is only 1.4 times slower in the solution with LiCl in comparison to the solution without LiCl.

This fact shows that the increase in the hydrophobic effect augments the energy of the transition states of the attack steps more than the energy of the dehydration step. So, it is clear that the transition state of the uncatalyzed and concerted acid-catalyzed attack of phenylhydroxylamine on 2,6-dichlorobenzaldehyde involve a significant charge formation and consequently require more energy for its formation. (See Scheme II—the transition state should be similar to intermediate 1.) In the reaction of phenylhydroxylamine with benzaldehyde at pH = 3.25, the rate of the reaction of the dehydration step is slower in LiCl solution by approximately 1.5 times, which agrees with the dehydration step of the reaction between phenylhydroxylamine and 2,6-dichlorobenzaldehyde.

In Figure 1, it may be observed that the rate constant of the dehydration step of the reaction of phenylhydroxylamine with benzaldehyde is approximately 7 times larger than that of its uncatalyzed attack on the 2,6-dichlorobenzaldehyde. Considering the decrease of the rate of this last step in 5 M LiCl solution (6 times), we can consider that the attack of phenylhydroxylamine on benzaldehyde, which also under these conditions is faster than the dehydration step, should be at least 42 times greater. The best explanation for this fact is the assumption that the planar molecule of phenylhydroxylamine is placed parallel to the planar molecule of benzaldehyde in order to permit the nitrogen nucleophile attack on the carbonyl group along the orbital π^* [18,19] as indicated in Scheme II.

The two benzene rings can pack, forming the previously suggested preassociation complex that then will evolve to the intermediate 2 (indicated in Scheme II, structure 2) by a similar transition state with little charge formation, thus being favored, or at least unaffected, by the hydrophobic effect. Similar behavior was observed in the case of the benzoin condensation [7]. This situation cannot occur with the 2,6-dichlorobenzaldehyde due to the fact that the planarity be-



Scheme II

tween the benzene ring and the carbonyl group is broken by the presence of the chloro atoms. In the case of the norcamphor, it is clear that steric hindrances of the molecule make the formation of this complex impossible.

CONCLUSIONS

1. Phenylhydroxylamine shows special behavior as a nucleophile in its reaction with benzaldehyde and some other aromatic carbonyl compounds, due to the formation of a preassociation complex that evolve by a transition state with no or little charge formation, being enough more stable than the corresponding charged transition state of its reaction with 2,6-dichlorobenzaldehyde.
2. This proposal is confirmed by two facts: (1) the differences of the profiles of the rate constants versus pH; (2) the increase of the hydrophobic effect by 5 M LiCl that decreases the rate constant of the uncatalyzed attack of phenylhydroxylamine on 2,6-dichlorobenzaldehyde as rate-determining step, while not affecting or increasing the same rate-determining step of its reaction with benzaldehyde.
3. This special behavior of phenylhydroxylamine in its reaction of attack on benzaldehyde can be explained considering that both planar molecules can form a packed preassociation complex that evolves by a transition state, where the hydrophobic parts predominate. This cannot occur in the case of 2,6-dichlorobenzaldehyde and norcamphor because of steric hindrances.

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BIBLIOGRAPHY

1. Sayer, S. M.; Pinsky, B.; Schonbrunn, A.; Washtien, W. J Am Chem Soc 1974, 96, 7999.
2. Brighente, I. M. C.; Budal, R.; Yunes, R. A. J Chem Soc Perkin II 1991, 11, 1861.
3. Fett, R.; Simionato, E. L.; Yunes, R. A. J Phys Org Chem 1990, 3, 620.
4. Brown, H. C.; Kishnamurthy, S. J Am Chem Soc 1972, 94, 7159.
5. Lambert, J. B.; Holcomb, A. G. J Am Chem Soc 1971, 93, 3952.
6. Bell, C. L.; Danyluk, S. S.; Shaefer, T. Can J Chem 1969, 47, 3529.

7. Breslow, R. Acc Chem Res 1991, 24, 159.
8. Breslow, R.; Groves, K.; Mayer, M. U. Pure Appl Chem 1998, 70, 1933.
9. Gajewski, J. J. Acc Chem Res 1997, 30, 219.
10. Smissman, E. E.; Corbett, M. D. J Org Chem 1972, 37, 1847.
11. Albert, A.; Serjeant, E. P. The Determination of Ionization Constants, 2nd ed.; Chapman and Hall: London, 1971.
12. Bates, R. G. Determination of pH Theory and Practice, 2nd ed.; Wiley: New York, 1973.
13. Sayer, J. M.; Jencks, W. P. J Am Chem Soc 1969, 91, 6353.
14. Rosemberg, S.; Silver, S. M.; Sayer, J. M.; Jencks, W. P. J Am Chem Soc 1974, 96, 7986.
15. Bastos, M. P.; do Amaral, L. J Org Chem 1979, 44, 980.
16. Wolfenden, R.; Jencks, W. P. J Am Chem Soc 1961, 83, 27.
17. Long, F. A.; McDevit, W. F. Chem Rev 1952, 52, 119.
18. Burgi, H. B.; Dunitz, J. D. Acc Chem Res 1983, 16, 153.
19. Kayser, M. M.; Morand, P. Tetrahedron Lett 1979, 695.
20. Brighente, I. M. C.; Vottero, L. R.; Terezani, A. J.; Yunes, R. A. J Org Phys Chem 1991, 4, 107.
21. Smith, R. M.; Martell, A. E.; Montekaitis, R. J. Critical Stability Constants of Metal Complexes; NIST Database: 1994.
22. Lamaty, G.; Roque, J. P.; Natat, A.; Silou, T. Tetrahedron 1986, 42, 2667.
23. do Amaral, L.; Sandstron, W. A.; Cordes, E. H. J Am Chem Soc, 1966, 88, 2225.