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A Computational Study of the Structure and Synthesis of Formazans

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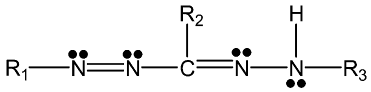
We report the results of a density functional theory (DFT) study of the structure and synthesis of a formazan molecule, 1,3,5-triphenylformazan. Three conformational minima of this formazan are identified, with the global minimum having an internal H-bond as part of a pseudo-six-membered ring. At the 6-31G(d) B3LYP level of theory the transition state for tautomerization and exchange of the hydrogen ion lies 4 kcal mol^{-1} above the global minimum. This barrier height is unchanged by the incorporation of solvent models. An extensive investigation of the potential energy surface for the synthesis of 1,3,5-triphenylformazan from benzaldehyde *N*-phenylhydrazone and benzenediazonium ion is reported. The results support the mechanism whose first step is the addition of the diazonium onto the central carbon atom of the phenylhydrazone. However, the transition states for both this addition and addition to the amino nitrogen atom lie on intrinsic reaction paths which connect to a minimum of the phenylhydrazone which is not its global minimum. The substitution of a methyl group for the hydrogen on the amino nitrogen of the hydrazone raises the energy of the initial intermediate by 10 kcal mol^{-1}, preventing formazan formation. The increase in energy of the intermediate corresponds with an increase in energy (relative to that of the unmethylated case) necessary to place the benzaldehyde *N*-methyl-*N*-phenylhydrazone into the right conformation for reaction. The inclusion of a solvent model of ethanol made negligible difference to the computed geometric structures, but significant changes in energies relative to those of the reactants. However, adding self-consistent reaction field (SCRF) solvation energies to the gas-phase free energies gave relative values that were similar to those obtained by full inclusion of solvent effects (SCRF) in the optimization and vibrational frequency computations.

I. Introduction

Formazans are compounds which contain the following characteristic structure:



$$R_1{-}\ddot{N}{=}\ddot{N}{-}\underset{}{\overset{R_2}{C}}{=}\ddot{N}{-}\overset{H}{\underset{\cdot\cdot}{N}}{-}R_3$$

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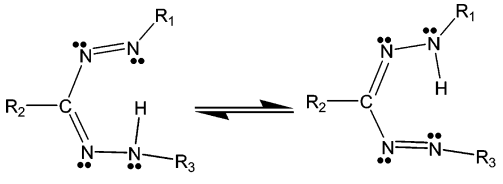
where R_2 varies and R_1 and R_3 are typically aromatic groups. These compounds began to be widely studied in the 1940s and 1950s because of the uniqueness of the reactions that involve them, as well as their suspected biochemical usefulness. Closely related molecules have been developed which will penetrate various plant and animal tissues, react with enzymes to produce formazans, and produce a strongly colored stain. This effect has been extensively investigated, including the especially dark staining of tumor cells in mice, with the hopes that formazans might be useful in chemotherapy or cancer diagnosis. Modest antibacterial properties have also been reported.[1]

An example of the utility of formazans is provided by monosaccharides such as glucose which, after conversion into phenylhydrazones, react to produce red formazans. However, only aldose phenylhydrazones form formazans, while ketose phenylhydrazones do not, distinguishing between aldoses and ketoses.[2] A related process has also been carried out to gain structural information about certain polysaccharides.[3]

Little research on formazans has been reported recently. In 1972, the products of the reaction of formazans with oxygen were reported.[4] Formazans were found to form colored complexes with ruthenium and osmium in 1981.[5] In 1998, the cytotoxicity of several biologically active compounds was evaluated using formazans to test cell survival.[6] In 1998 Buemi et al.[7] published a computational study of many possible conformations of the unsubstituted formazan and 3-nitroformazan.

The following diagram better represents the three-dimensional structure of the formazans:



1a **1a′**

Early experiments by von Pechmann[8] showed that the two structures shown cannot be experimentally distinguished. This observation was described by von Pechmann as tautomerism, with the hydrogen atom moving between the two nitrogen atoms. The indistinguishability of the two structures was confirmed by Hunter and Roberts[9] in 1941, with the reinterpretation that the two structures are mesomeric forms, with formazans having no precisely located double bonds.

Tiers, Plovan, and Searles[10] showed via NMR spectroscopy [on 1,5-di(4-methylphenyl)-3-(4-methoxyphenyl)formazan] that either **1a** and **1a′** comprise a resonance hybrid structure or tautomerization between them occurs with a rate constant of at

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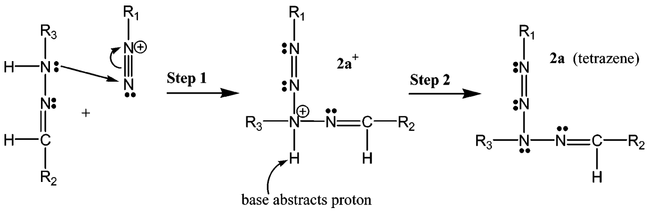
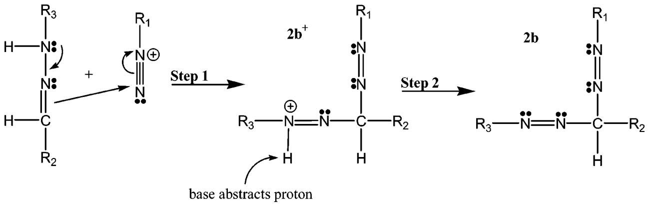
SCHEME 1

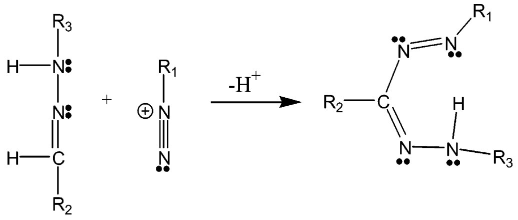


SCHEME 2



least 10^3 s^{-1}. In this paper, we report the low-energy minima of 1,3,5-triphenylformazan with their relative energies, as well as the existence and height of the energy barrier between these tautomers.

A general synthetic method for formazans was discovered by von Pechmann.[11] Formazans are usually produced by the reaction of an aldehyde arylhydrazone with a diazonium salt in slightly basic solution, as follows:

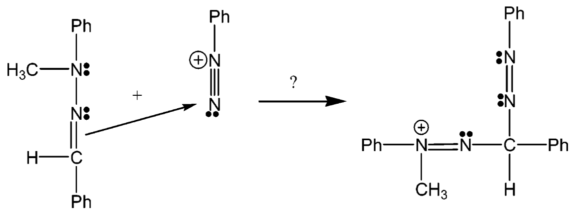


Secondary hydrazones where the amino H is replaced by an alkyl group do not react to produce formazans.[8,12] Because this hydrogen atom appears to be involved in the reaction mechanism, Busch and Pfeiffer[13] proposed that the first step in the reaction mechanism was addition of the diazonium ion to the amino nitrogen, leading to a tetrazene (Scheme 1).

The researchers experimentally isolated a yellow intermediate which could easily rearrange to a formazan and claimed that the intermediate was **2a**, a tetrazene, since some tetrazenes are known to isomerize into formazans. Intermediate **2a** is consistent with the known results of the reaction of diazonium with primary phenylhydrazines.[1]

However, in 1967, Hegarty and Scott[14] isolated the intermediate and examined its UV, IR, and NMR spectra. The authors concluded that the actual structure of the intermediate is **2b**, created by initial attack on the carbon atom, followed by abstraction of a proton from the nitrogen atom (Scheme 2).

The formazan then forms via a hydrogen shift. If Hegarty and Scott are correct, the importance of having a primary nitrogen atom is unclear. When an alkyl group replaces the hydrogen as in the following reaction, no formazan is produced:[8,12]



Hegarty and Scott confirmed that this *N*-methyl compound reacts at least 1000 times more slowly and no more quickly than it naturally decays in the solvent. The authors speculated that the methyl group might cause a conformational change in the phenylhydrazone which prevents initial coupling with the diazonium. Alternatively, direct deprotonation of the carbon is too difficult. Our results suggest that the former reason is sufficient to explain the experimental observations. In this paper, we investigate the possible transition states corresponding to initial coupling of the benzenediazonium ion to the amino nitrogen and to the central carbon of benzaldehyde *N*-phenylhydrazone. We have also examined the effects of the presence of an *N*-methyl group on this coupling.

II. Methods

All minima have been fully optimized using the B3LYP method, a Hartree–Fock/density functional theory (DFT) hybrid method including Becke's semiempirical three-parameter exchange functional[15] with the LYP correlation functional.[16] A standard 6-31G(d)[17,18] basis set was used. All stationary points were characterized by the evaluation of their harmonic vibrational frequencies. When a solvent model was included, the integral equation formalism–polarizable continuum model (IEF–PCM)[19,20] for ethanol ($\epsilon = 24.55$) was used, and the nonelectrostatic contribution to the solvation energy was also included. Excited-state energy computations were carried out using the time-dependent DFT method.[21–23] All computations were carried out with the Gaussian03 program package.[24]

III. Results

A. Formazan Structure and Tautomerism. An extensive search was made of the potential energy surface of 1,3,5-triphenylformazan using the 6-31G(d) B3LYP level of theory to find all low-energy structures. Three structural minima were found and are illustrated in Figure 1. All three keep the Ph–N=N–C=N–NH–Ph backbone of the formazan essentially planar. The global minimum **1a** is very nearly planar and benefits the most from conjugation, with a pseudo-six-membered ring completed by a strong (1.831 Å) intramolecular hydrogen bond. The amount of delocalization within the backbone is of course significant; the two central C–N bonds have somewhat similar bond lengths of 1.321 and 1.389 Å. Structure **1b** is formed beginning from **1a** and rotating around the central C–N bond, producing a pseudo-five-membered ring containing a weak (2.186 Å) hydrogen bond. Structure **1c** is formed beginning from **1a** and rotating around the C=N bond. Structure **1c** has no hydrogen bonds, and steric repulsion causes the center phenyl group to twist so it is about halfway perpendicular to the rest of the molecule.

The relative free energies of the formazan structures are reported in Table 1. The first column of data in this table are the relative gas-phase free energies at 298 K. In the second column are the relative energies that result from adding the solvation energies of the gas-phase geometries calculated with the IEF–PCM model for ethanol to the gas-phase free energies. In the final column, a complete reoptimization and vibrational frequency calculation has been performed while including the IEF–PCM solvent model throughout. In all of our reported results, reoptimization of the geometric structures and recomputation of the vibrations including solvent effects had little impact on the resulting energy differences. Isomer **1a** is found to be lower in energy than **1b** by 1.5 kcal mol^{-1} and lower than **1c** by 7.4 kcal mol^{-1}. Thus, the relative energies appear

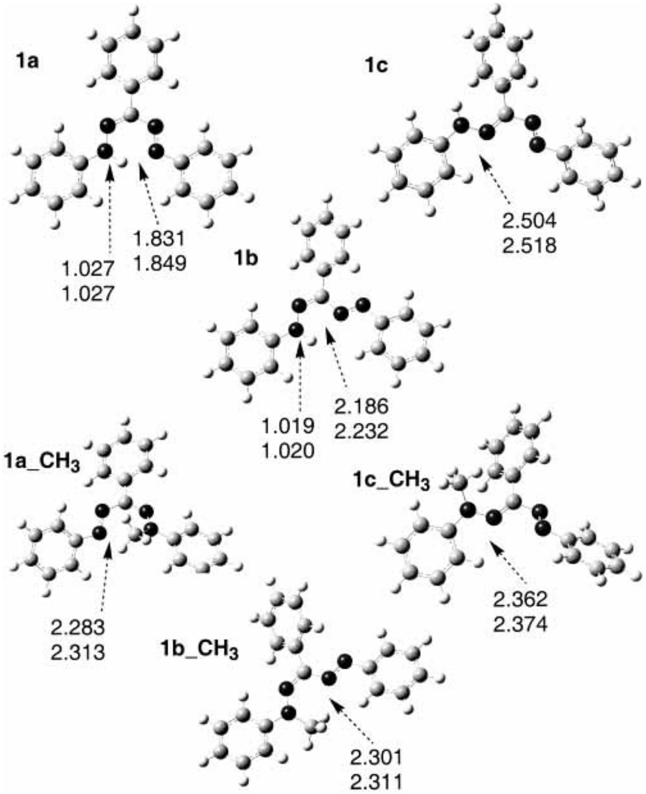


Figure 1. Minima on the potential energy surface of 1,3,5-triphenylformazan (**1a**, **1b**, and **1c**) and of 1-methyl-1,3,5-triphenylformazan (**1a_CH$_3$**, **1b_CH$_3$**, and **1c_CH$_3$**). The global minima are **1a** and **1a_CH$_3$**, respectively.

TABLE 1: Gibbs Energies (kcal mol^{-1}) for the Structures of 1,3,5-Triphenylformazan Shown in Figure 1, Relative to That of the Global Minimum 1a

	$\Delta G_{298K,gas}$	$\Delta G_{298K,gas} + \Delta E_{solv}{}^{a}$	$\Delta G_{298K,solv}{}^{b}$
1a	0.0	0.0	0.0
1b	3.5	2.2	1.5
1c	9.0	6.3	7.4
1a ↔ **1a′** transition state	4.1	4.2	

[a] The computed IEF−PCM solvation energies in ethanol of the gas-phase structures were added to the gas-phase free energies. [b] The structures were optimized and vibrational frequencies determined including the solvent model throughout.

almost entirely accounted for by the presence and strength of their hydrogen bonds.

The minima **1a**, **1b**, and **1c** are analogous to the minima of unsubstituted formazan called by Buemi et al. "TSSC", "TSST", and "TASC", respectively.[7] These authors reported (using 6-31G** B3LYP ZPVE-corrected energies) that the unsubstituted analogue of **1b** lies only 0.2 kcal mol^{-1} above **1a** and that the unsubstituted analogue of **1c** lies 7.3 kcal mol^{-1} above **1a**. Of the unsubstituted structures, only **1a** is able to remain essentially planar upon addition of the bulky phenyl groups. Comparing their gas-phase results to ours, the addition of the phenyl groups stabilizes the global minimum **1a** by about 3 kcal mol^{-1} relative to the next lowest conformation. Several additional minima located for unsubstituted formazan are severely destabilized by steric effects upon the addition of the phenyl groups and were not found to be minima for 1,3,5-triphenylformazan.

For some formazans, the presence of multiple conformations has been inferred from the time evolution of UV−vis spectra of freshly prepared formazans in CCl$_4$. However, no time dependence (and only the "red II" form, analogous to **1a**) is observed in the spectra of 3-isopropyl- and 3-*tert*-butyl-1,5-diphenylformazan.[25−28] Thus, our finding of **1a** as the global minimum of 1,3,5-triphenylformazan is consistent with the conclusions of Buemi et al.[7] that bulky substituents at the 3-position will result in only this conformation at equilibrium.

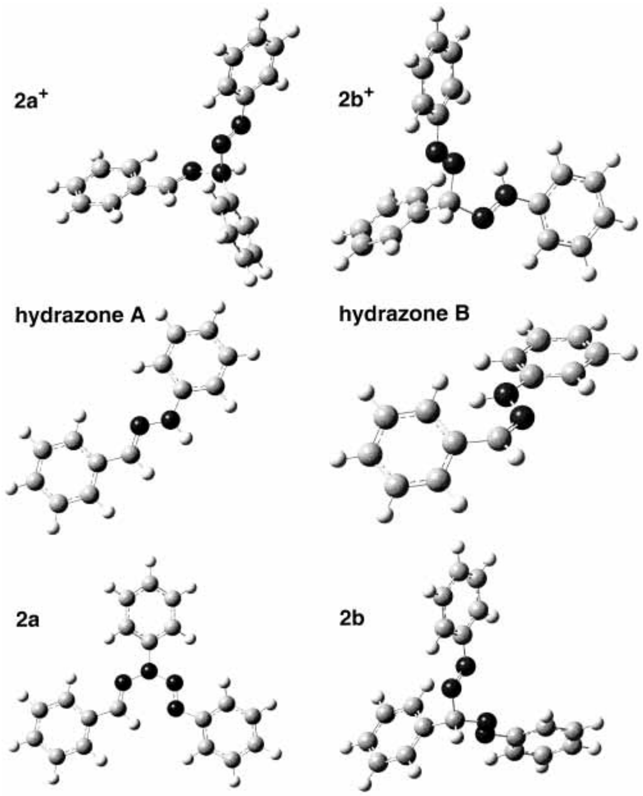


Figure 2. (Top) Charged minima resulting from diazonium coupling to the amino nitrogen (**2a**$^+$) and the central carbon atom (**2b**$^+$) of the benzaldehyde *N*-phenylhydrazone. (Middle) Two minima of the phenylhydrazone. The global minimum is hydrazone A. (Bottom) Intermediates that may result from diazonium coupling at the amino nitrogen (**2a**) and the central carbon atom (**2b**) of the phenylhydrazone followed by abstraction of a proton.

The global minimum **1a** is clearly in a position to easily tautomerize with little structural change beyond the motion of the involved hydrogen atom. This transition state was located and found to lie 4.2 kcal mol^{-1} above the two equivalent **1a** structures. This barrier height compares to computed tautomerization barriers of 3.6 kcal mol^{-1} for malondialdehyde[29] and 6.4 kcal mol^{-1} for the unsubstituted formazan.[7] Proton tunneling may obviate the need for even this much energy for the interconversion between the tautomers.

B. Formazan Synthesis from Benzaldehyde *N*-Phenylhydrazone and Benzenediazonium Ion. The diazonium may couple with the phenylhydrazone at either the central carbon atom or the amino nitrogen, resulting in the structures labeled **2a**$^+$ and **2b**$^+$ in Figure 2. The transition states for these two couplings were also located, and the relative energies of these stationary points are reported in Table 2. The transition-state structures leading to **2a**$^+$ and **2b**$^+$ do not differ substantially from those of the minima except the N−N bond length for **2a**$^+$, which lengthens to 1.836 Å, and the C−N bond length for **2b**$^+$, which lengthens to 2.001 Å. Both types of addition decidedly break the planarity of the phenylhydrazone. The relative energies of the minima and transition states are shown in Figure 3.

TABLE 2: Relative Energies (kcal mol^{-1}) for the Coupling of Benzenediazonium Ion to Benzaldehyde *N*-Phenylhydrazone To Form 1,3,5-Triphenylformazan[a]

	$\Delta G_{298K,gas}$	$\Delta G_{298K,gas} + \Delta E_{solv}$	$\Delta G_{298K,solv}$
diazonium + phenylhydrazone + NEt$_3$	0.0	0.0	0.0
transition state to **2a**$^+$ + NEt$_3$	10.5	32.6	
2a$^+$ + NEt$_3$	10.5	32.2	30.4
transition state to **2b**$^+$ + NEt$_3$	9.5	35.5	
2b$^+$ + NEt$_3$	1.1	24.4	20.4
2a + NEt$_3^+$	−4.8	8.4	5.8
2b + NEt$_3^+$	−1.3	10.2	7.6
1a + Et$_3^+$	−21.6	−8.6	−10.7
With an *N*-Methyl Group[b]			
2b$^+$_CH$_3$ + NEt$_3$	11.2	34.1	33.4
1a_CH$_3$ + NEt$_3^+$	−3.2	6.6	4.7
1b_CH$_3$ + NEt$_3^+$	−6.6	3.1	1.3
1c_CH$_3$ + NEt$_3^+$	−1.7	6.8	4.5

[a] NEt$_3$ = Triethylamine. Also shown are the relative energies with an added *N*-methyl group. See Table 1 for an explanation of the columns. [b] These energies are relative to the reactants including the *N*-methyl-*N*-phenylhydrazone.

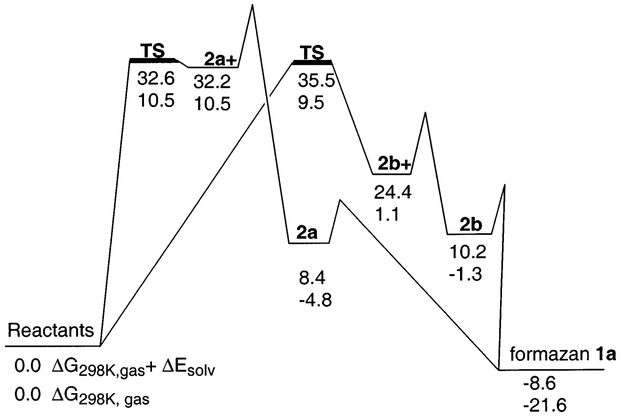


Figure 3. 6-31G(d) B3LYP gas-phase and solvent-corrected free energy profiles for the reaction of diazonium with benzaldehyde *N*-phenylhydrazone showing the location of the computed stationary points.

The **2a**$^+$ structure is bound relative to the transition state for its formation by only 1.2 kcal mol^{-1} of gas-phase potential energy. The vibrational contributions to the free energy reduce this binding value even further, and the solvent makes no significant difference. The computed solvent-corrected barrier heights are similar (32.6 and 35.5 kcal mol^{-1} for **2a**$^+$ and **2b**$^+$, respectively) and large, but still within the range for common, spontaneous organic reactions.[30] Although the formation of **2b**$^+$ has a slightly larger transition-state barrier, the resulting **2b**$^+$ minimum is 10.0 kcal mol^{-1} more stable than **2a**$^+$, and also has a significant barrier (11.1 kcal mol^{-1}) to redissociation. Thus, **2b**$^+$ is predicted to have a much longer lifetime in solution than **2a**$^+$. Thus, the reaction appears thermodynamically, and not kinetically, controlled.

The ethanol solvent correction is seen to have little effect on the relative energies of the stationary points, except in comparison to the reactants. For example, relative to the reactants, the free energies of **2a**$^+$ and **2b**$^+$ are shifted upward by 19.9 and 19.3 kcal mol^{-1}, respectively, by the inclusion of the solvent.

Two low-energy minima of the hydrazone are shown in Figure 2. "Hydrazone A" is the global minimum, and "hydrazone B" is another minimum that lies 6.5 kcal mol^{-1} higher in energy ($\Delta G_{298K,solv}$, 6-31G(d) B3LYP). Comparing the structures shown in Figure 2, it is seen that the transition-state structures **2a**$^+$ and **2b**$^+$ correspond to hydrazone B and *not* to the global minimum hydrazone A. The intrinsic reaction coordinates of the transition states to **2a**$^+$ and **2b**$^+$ were mapped to confirm this connection. The energy necessary to rearrange the hydrazone to the higher energy conformer is thus part of the energy needed for reaction. Repeated attempts to find other transition states (to possibly other minima) for coupling directly to the global minimum hydrazone A failed.

TABLE 3: Lowest Excitation Energies of Proposed Intermediates 2a and 2b in the Gas Pase (nm)[a]

excited state	2a	2b
first singlet	396 (0.4135)	450 (0.0011)
second singlet	385 (0.1874)	440 (0.0017)
third singlet	312 (0.2348)	345 (0.0237)

[a] Oscillator strengths are in parentheses.

Potential intermediates **2a** and **2b**, formed by the extraction of a proton from **2a**$^+$ and **2b**$^+$, respectively, are shown in Figure 2. The intermediates **2a** and **2b** are computed to be within 2 kcal mol^{-1} in energy. The overall reaction is computed to have $\Delta G_{298K,solv} = -10.7$ kcal mol^{-1}.

C. *N*-Methyl Substitution of the Phenylhydrazone. For several reasons, we support the identification of the intermediate isolated by Hegarty and Scott as **2b**. First, as shown earlier, **2b**$^+$ will have a much longer lifetime than **2a**$^+$. Second, experiments have shown that the formazan reaction does not proceed in the presence of an *N*-methyl group in place of the hydrogen on the phenylhydrazone. We have attempted to optimize the molecular structures of the *N*-methyl analogues of **2a**$^+$, **2b**$^+$, **2a**, and **2b**. In this case, the analogue of **2a**$^+$ is unbound and is not a minimum. The substituted analogue of **2b**$^+$ has an energy relative to those of the reactants of $\Delta G_{298K,solv} = 33.4$ kcal mol^{-1}, an increase from 20.4 kcal mol^{-1} from the unsubstituted case. It is reasonable to assume that the transition state (which has a very similar structure in the unmethylated case) is increased by a similar magnitude. Thus, the overall barrier to reaction is increased by the methyl substitution by ~13 kcal mol^{-1}. The energies of all of the succeeding structures, including the products, are raised by a similar amount.

If the substituted analogues of the hydrazone minima shown in Figure 2 are examined, it is found that hydrazone A is still the global minimum, but that hydrazone B now lies 15.8 kcal mol^{-1} higher in energy ($\Delta G_{298K,solv}$), which is increased from 6.5 kcal mol^{-1} for the unsubstituted case. Thus, the speculation made by Hegarty and Scott is correct. The substitution of a methyl group raises the energy of the active hydrazone conformation by 9.3 kcal mol^{-1}.

For the potential methylated formazan, the three analogous minima are shown in Figure 1. The methyl group substitution prevents the previously present internal hydrogen bonding. As shown in Table 2, **1b_CH$_3$** is now the global minimum of the formazan and lies below **1a_CH$_3$** and **1c_CH$_3$** by 3−4 kcal mol^{-1}. The addition of the methyl group raises the free energy change for the entire reaction from $\Delta G_{298K,solv} = -10.7$ kcal mol^{-1} to $\Delta G_{298K,solv} = +1.3$ kcal mol^{-1}. The reaction may no longer be exergonic.

Finally, we have computed the UV−vis spectra of intermediates **2a** and **2b** using linear-response DFT. The three lowest excited-state energies and oscillator strengths are shown in Table 3. Compound **2b** is seen to have absorptions (admittedly with low oscillator strength) more clearly in the visible spectrum, consistent with an intermediate of yellow color.

IV. Conclusion

The reaction of benzenediazonium with benzaldehyde *N*-phenylhydrazone to form 1,3,5-triphenylhydrazone begins with coupling to the central carbon atom and not to the nitrogen (to form a tetrazene). Although the initial transition-state energies are similar, the intermediate produced by coupling to the carbon atom is more stable (lower in energy) and bound (higher transition state back to dissociation) than that formed by addition to the nitrogen. The energy of the overall reaction is computed to be $\Delta G_{298\mathrm{K,solv}} = -10.7$ kcal mol^{-1}.

Computations of the analogous stationary points for benzaldehyde *N*-methyl-*N*-phenylhydrazone show that, compared to the unsubstituted case, the energies of the intermediates and products are raised, and the overall reaction becomes slightly endergonic, $\Delta G_{298\mathrm{K,solv}} = +1.3$ kcal mol^{-1}.

The phenylhydrazone must change conformation for the initial coupling at the carbon atom to occur. For the primary phenylhydrazone, this higher energy conformer lies 6.5 kcal mol^{-1} above the global minimum. However, for the methyl-substituted case, this minimum is 15.8 kcal mol^{-1} higher in energy [6-31G(d) B3LYP, including solvent]. Thus, the methyl substitution acts to lock the phenylhydrazone in a conformation unsuitable for the initial coupling to occur.

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