Solvent Effects on the Equilibrium between Localized and Delocalized States of Thermochromic Semibullvalenes and Barbaralanes

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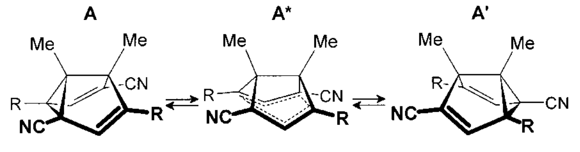
Dedicated to Professor Matthias Seefelder

Thermochromic semibullvalenes **1** and barbaralanes **2** undergo extremely rapid degenerate Cope rearrangements and, therefore, provide an opportunity to study equilibria between the two degenerate, localized ground states **A**, **A′** and the delocalized higher states **A*** that correspond to the transition states. The analysis of variable-temperature UV/Vis spectra with the help of Equation (1) showed that considerable fractions f^* exist in the higher states **A*** and disclosed enthalpy differences ΔH^0 of 1–11 kJ mol^{-1} for solutions in butyronitrile (A_{int} and $\varepsilon^*_{\text{int}}$ = integrated absorbance and integrated extinction coefficient [L mol^{-1}cm^{-2}] of the temperature-dependent long-wavelength band; c = total concentration [mol L^{-1}]; d = path length [cm]). These enthalpy differences comprise the gas-phase enthalpy differences $\Delta H^0_{\mathbf{A},\mathbf{A}*}$ between **A**, **A′** and **A*** and the solvation terms $(\Delta H_{\mathbf{A}})_{\text{L}}$ and $(\Delta H_{\mathbf{A}*})_{\text{L}}$ for the transfer from the gas phase to solution [Eq. (2)].[1]

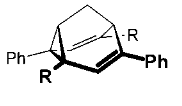
$$A_{\text{int}} \approx \varepsilon^*_{\text{int}}\, c\, d \left(1 + 2\exp\frac{\Delta H^0}{RT}\right)^{-1} \qquad (1)$$

$$\Delta H^0 = \Delta H^0_{\mathbf{A}/\mathbf{A}*} + (\Delta H_{\mathbf{A}*})_{\text{L}} - (\Delta H_{\mathbf{A}})_{\text{L}} \qquad (2)$$

Here we report the surprising influence of solvents on the relative stabilities. In fact, we have uncovered solvents that reverse the usual order of **A**, **A′** and **A***: In such solutions, the delocalized states **A*** which absorb at long wavelengths are more stable than the classical localized structures **A**, **A′**!



1a R = H; **1b** R = Ph



2a R = CN; **2b** R = Ph

UV/Vis spectra were recorded at different temperatures for degassed and subsequently with argon-saturated solutions of **1** and **2** in different solvents and corrected for the temperature-driven change of the volume with the help of density data (reference temperature 298 K). The temperature ranges covered were dictated by the limited stability of the semibullvalenes **1**, in particular **1b**, at higher temperatures[2] and, of course, the freezing point of the solvents.

Selected UV/Vis spectra of solutions of the barbaralanedicarbonitrile **2a** recorded at the lowest and highest temperatures in different solvents are displayed in Figure 1. The extinction coefficients ε of the long-wavelength band may be considered as an approximate measure of the concentration of the delocalized spezies **2a***. A cursory inspection of Figure 1 immediately reveals the enormous influence of the solvent. The exchange of cyclohexane for *N*,*N′*-dimethylpropylene urea (DMPU) not only shifts the maximum of the band in the visible region toward longer wavelengths but increases ε and hence the concentration of **2a*** by one order of magnitude. We note that the deconvolution of the near-UV/Vis spectra of **1b**, **2a** and **b** (butyronitrile solution) with Gauss curves disclosed the presence of a second temperature-dependent band at 374, 403, and 411 nm, respectively.[1] This explains why the near-UV part of the spectra is influenced not only by the Doppler broadening of the strong UV bands but also by the variable absorbance of this second band.

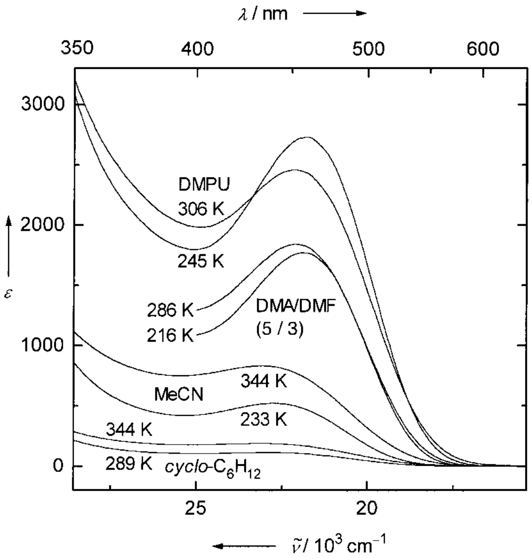


Figure 1. Near-UV/Vis spectra (ε[L mol^{-1}cm^{-1}]) taken from solutions of the barbaralanedicarbonitrile $\mathbf{2a} \rightleftharpoons \mathbf{2a}^* \rightleftharpoons \mathbf{2a}'$ in different solvents at the highest and lowest temperature.

The second intriguing result associated with the variation of the solvent is the reversal of the temperature dependence of the extinction coefficients. While they increase with rising temperatures for the solutions of **2a** in cyclohexane, acetonitrile, and most of the other solvents, they are temperature-invariant for a mixture of *N*,*N*-dimethylacetamide (DMA) and *N*,*N*-dimethylformamide (DMF) (5:3), and decrease for solutions in *N*,*N′*-dimethylpropylene urea and similar solvents, such as *N*-methylpyrrolidin-2-one, hexamethylphosphoric triamide (HMPA) and pure *N*,*N*-dimethylacetamide. This demonstrates the dominance of the solvation terms over the gas-phase enthalpy difference $\Delta H^0_{\mathbf{2a}/\mathbf{2a}*}$ in these cases [Eq. (2)]: The two degenerate, localized states **2a**, **2a′** are more stable than the delocalized state **2a*** in the former solvents, while the opposite is true for solutions in the latter.

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Table 1. Enthalpy differences ΔH^0 [kJ mol^{-1}] calculated from Equation (1), as well as the solvents and temperature ranges T [K], in which the given number n of UV/Vis spectra were recorded.

Compound	No.	Solvent	ΔH^0[a]	T	n	r^2[b]
1a	1	DMF	9.42 ± 0.25	236–322	7	0.9973
	2	butyronitrile[1]	11.06 ± 0.04	215–383	11	1.0000
1b	3	DMA/DMF (5/3)	< 0	218–250	8	
	1	DMF	≈ 0	219–251	8	
	2	butyronitrile[1]	0.82 ± 0.05	176–236	8	0.9997
2a	4	DMPU	< 0	245–306	7	
	5	1-methylpyrrolidin-2-one	< 0	309–364	4	
	6	DMA	< 0	255–400	9	
	7	HMPA	< 0	308–363	4	
	3	DMA/DMF (5/3)	≈ 0	216–286	6	
	8	dimethyl sulfoxide	0.43 ± 0.09	308–363	4	0.9083
	1	DMF	1.80 ± 0.06	218–364	10	0.9999
	9	diiodomethane	2.15 ± 0.25	308–364	4	0.9659
	10	tetrahydrofuran	2.20 ± 0.14	225–287	4	0.9893
	11	acetone	2.82 ± 0.04	217–291	5	0.9993
	12	1,4-dioxane	3.23 ± 0.28	288–363	5	0.9718
	2	butyronitrile[1]	3.30 ± 0.03	165–382	13	0.9991
	13	acetonitrile	3.36 ± 0.02	233–344	10	0.9997
	14	pyridine	3.36 ± 0.04	236–290	4	0.9996
	15	ethyl acetate	3.49 ± 0.07	217–291	5	0.9984
	16	benzonitrile	3.80 ± 0.04	263–420	9	0.9992
	17	benzene	3.90 ± 0.04	307–345	5	0.9996
	18	methanol	3.95 ± 0.05	221–325	8	0.9990
	19	1,2-dichlorobenzene	3.99 ± 0.01	307–344	5	1.0000
	20	nitromethane	4.02 ± 0.06	308–363	4	0.9994
	21	toluene	4.08 ± 0.06	220–381	11	0.9979
	22	ethanol	4.38 ± 0.05	225–288	4	0.9996
	23	[D]trichloromethane	4.41 ± 0.09	308–332	4	0.9988
	24	dibutyl ether	4.72 ± 0.19	307–400	7	0.9901
	25	tetrachloromethane	5.52 ± 0.01	308–332	4	1.0000
	26	cyclohexane	7.93 ± 0.26	289–344	4	0.9978
2b	1	DMF	1.82 ± 0.13	217–323	8	0.9646
	4	DMPU	1.92 ± 0.22	248–320	9	0.8955
	2	butyronitrile[1]	5.51 ± 0.06	175–382	14	0.9989
	27	methylcyclohexane	7.49 ± 0.44	221–323	8	0.9821

[a] With the statistical error for the least-squares fit of Equation (1) to the A_{int} versus T data. [b] Square of the regression coefficient.

The quantitative exploitation of the thermochromism through the calculation of the integrated absorbance of the long-wavelength band after deconvolution with Gauss curves, and the determination of ΔH^0 and $\varepsilon^*_{\text{int}}$ by a least-squares fitting of Equation (1) to the A_{int} versus T data has been detailed in the preceding paper.[1] The results obtained in this way for a variety of different solvents are listed in Table 1 and are displayed in part in Figures 2 and 3, where the fractions of **A***, calculated according to Equation (3), are plotted against the temperature.

$$f^* = \frac{A_{\text{int}}}{\varepsilon^*_{\text{int}}\, c\, d} = \left(1 + 2\exp\frac{\Delta H^0}{RT}\right)^{-1} \qquad (3)$$

The spectra obtained for solutions of **2a** in *N,N'*-dimethylpropylene urea (Figure 1) can be used to define the limits for the calculation of A_{int}. Since the strong near-UV absorptions are subject to particularly strong Doppler broadening while the (relatively weak) band in the visible region simultaneously broadens *and decreases* with rising temperature, overlap becomes deleterious and thus the calculated A_{int} data are no longer sufficiently accurate for a good least-squares fitting of Equation (1). One can only state with confidence that ΔH^0 is negative in these cases. Attempts to fit Equation (1) to A_{int} versus T data are not meaningful, of course, if the UV/Vis spectra are virtually temperature-invariant and, accordingly, ΔH^0 is very close to zero (Figures 2 and 3, Table 1).

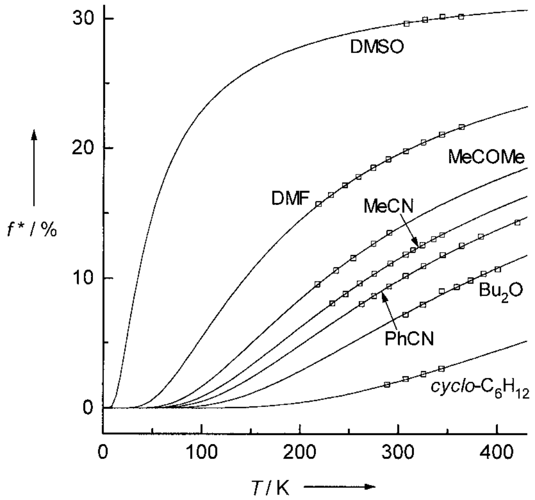

Figure 2. Temperature dependence of the fractions f^* [Eq. (3)] of the barbaralanedicarbonitrile **2a*** in various solvents. Filled squares correspond to the UV/Vis spectra displayed in Figure 1.

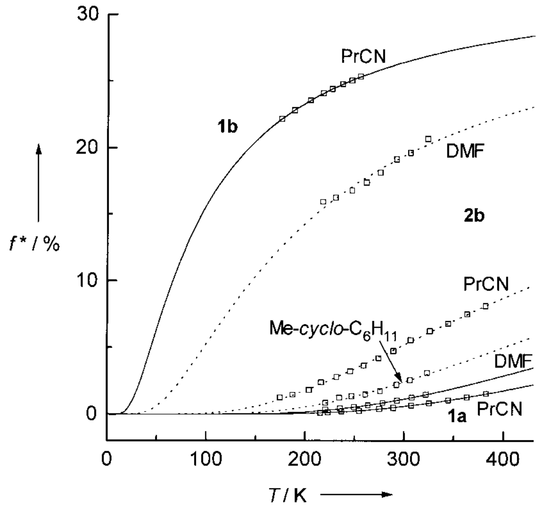

Figure 3. Temperature dependence of the fractions f^* of the semibullvalenedicarbonitriles **1a***, **b*** and tetraphenylbarbaralane **2b*** in various solvents as calculated from Equation (3).

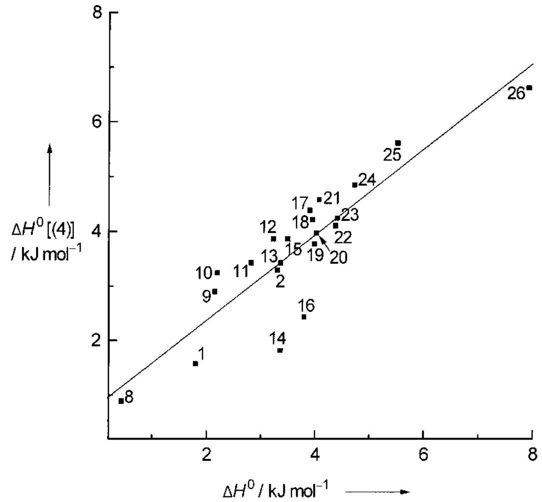

Figure 4. Calculated [Eq. (4)] versus experimental enthalpy differences [Eq. (1)] for all 21 solvents that afforded positive ΔH^0 values. The key to the solvent numbers is given in Table 1. The linear least-squares fit of the data has the same correlation coefficient as Equation (4).

Table 1 shows that the experimentally accessible enthalpy differences ΔH^0, which are composed of the gas-phase enthalpy differences and the solvation terms [Eq. (2)], are very small indeed and actually in the range of van der Waals interactions, potential barriers toward conformational changes, and enthalpy differences between cyclohexane conformations.[3] In view of the large data set obtained for **2a**, it appeared promising to correlate ΔH^0 with solvent properties. Thus one could hope to recognize the predominant solvent contributions to the stabilization of **2a*** in solution and extrapolate the gas-phase term $\Delta H^0_{2a/2a^*}$ from the solution ΔH^0 data. Toward this end, a number of multiparameter equations for the correlation of solute–solvent interactions were tried.[4] Reasonable results were obtained with the equation from Abraham, Kamlet, and Taft.[5] The omission of the fourth parameter, namely, the cohesive energy density, in their equation does not change the correlation coefficient and therefore need not be included.[6] The coefficients of the resulting three-parameter Equation (4; π^* = solvatochromic parameter which describes a combination of dipolarity and polarizability (0.00 for cyclohexane, 1.00 for dimethyl sulfoxide);[7a] α = hydrogen bond donation ability (0.00 for hexane, 1.96 for hexafluoroisopropanol);[7b] β = hydrogen bond acceptance or electron pair donation ability to form a coordinative bond (0.00 for hexane, 1.43 for 1,2-diaminoethane))[7b] are small and interestingly resemble those

$$\Delta H^0 = (6.69 \pm 0.45) - (3.79 \pm 0.67)\pi^* + (1.53 \pm 0.66)\alpha - (2.55 \pm 0.72)\beta \quad (4)$$

that are obtained when this equation is applied to the solvent dependence of the rate constants of the two irreversible Cope rearrangements reported by Mitsuhashi et al.[8] Figure 4 shows a good correlation between the experimental [Eq. (1)] and calculated enthalpy differences [Eq. (4)] for all 21 solvents that afforded positive ΔH^0 values. The correlation coefficient ($r^2 = 0.782$) might be improved by a more even distribution of the solvents over the whole range.

Equation (4) shows that dipolarity and polarizability (π^*) and the electron pair donation ability (β) of the solvents play the predominant role. The negative sign of both coefficients signifies that an increase of these solvent properties will lower ΔH^0. This is in good accord with the expectation that the delocalized species **2a*** is more polarizable than the classical, localized structures **2a**, **2a′**. Neither **2a**, **2a′** nor **2a*** possess sizeable dipole moments, but they are certainly expected to have different quadrupole moments. That of **2a*** is most probably larger, because the donor (=phenyl) and the acceptor (=cyano) groups interact more effectively in the delocalized system. Of two equilibrating molecules devoid of a dipole moment, dipolar solvents favor the one with the larger quadrupole moment.[3]

The first term in Equation (4) is the statistically defined enthalpy difference between **2a**, **2a′** and **2a*** for solutions in saturated hydrocarbons. Its value agrees reasonably well with the experimental one (Table 1) and represents the closest possible approximation to the gas-phase enthalpy difference $\Delta H^0_{2a/2a^*}$ of Equation (2).

Although such an extended series of solvents have not been employed in the study of the other compounds, it is evident from Figure 3 that only the influence of dipolar solvents confers higher stability to the delocalized species **A***, that is, none of these compounds prefers the delocalized structure in the gas phase.

Finally, we emphasize that the conventional cross section along the Cope reaction coordinate through the adiabatic energy hypersurfaces of the ground and excited state, which is useful for a simple pictorial description of the relative enthalpies of **A**, **A′** and **A*** in the gas phase,[1] cannot be employed for solutions. This is because it does not involve the solute–solvent interactions, which are indeed of the same order of magnitude or even greater than the gas-phase enthalpy differences. Though *solvated*, bishomoaromatic semibullvalenes and barbaralanes may be more stable than their classical, localized isomers, provided that the former enjoy stronger stabilization by the surrounding solvent molecules, single-minimum systems of this sort, which consist exclusively of a *single*, delocalized, bishomoaromatic species in the gas phase, remain as yet an intriguing myth.

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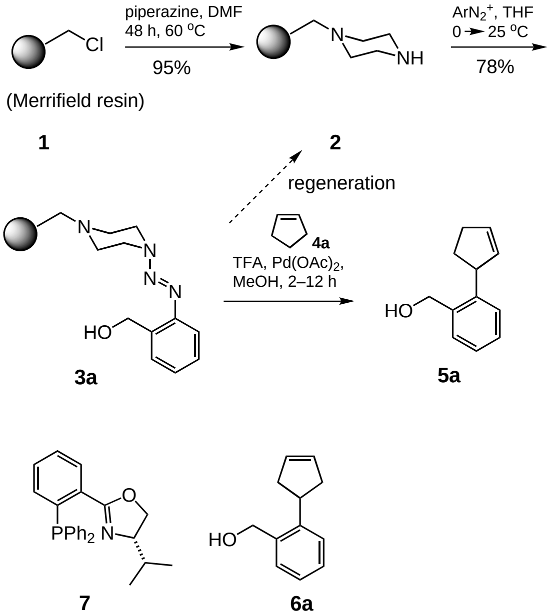
Efficient Cleavage–Cross-Coupling Strategy for Solid-Phase Synthesis—A Modular Building System for Combinatorial Chemistry**

Stefan Bräse* and Maarten Schroen

Dedicated to Professor Armin de Meijere on the occasion of his 60th birthday

Solid-phase reactions play an important role in parallel synthesis and combinatorial chemistry, particularly in the area of medicinal chemistry, where its potential has emerged due to the possibility of automation.[1] Research has focused on the synthesis of small, nonpeptidic molecules, because they are applicable systemically and their properties can be modified so that they can cross the blood–brain barrier more easily.[2] Cross-coupling reactions serve as efficient methods for their synthesis because they proceed under mild conditions with the formation of C–C bonds.[3, 4] Recently, we have shown that triazenes are suitable for the linkage of anilines to solid supports and that they may be cleaved to form hydrocarbons.[4] An advantage of this linker type is its accessibility from a pool of aminoarenes. The cleavage of this traceless linker proceeds via arene diazonium ions. We report herein on the possibilities of a cleavage–cross-coupling strategy starting from these diazonium ions.

The Heck reaction[5] of arene diazonium salts bearing little or no functionalization or triazenes, cleaved by acids, with simple olefins proceeds in general under mild thermal conditions to give the expected products in moderate to good yields.[5, 6] Preliminary experiments with triazenes in methanol as the solvent showed that the reduction products are formed in various amounts together with aryl ether by-products through reaction with the solvent.



Scheme 1. Synthesis and cleavage–cross-coupling reactions on the triazene resin **3a**.

The reactions on solid supports were conducted with the known amine resin **2**[4] (Scheme 1). Benzyl alcohol **3** bound through the triazene system initially served as a test system. The one-pot cleavage–cross-coupling reaction was conducted with cyclopentene (**4a**), a moderately reactive alkene for the Heck reaction. The resin was cleaved with two equivalents of trifluoracetic acid (TFA) in MeOH at 0 °C to give the diazonium ion. In situ coupling with the alkene in the presence of catalytic amounts (5 mol%) of palladium(II) acetate furnished 2-cyclopent-2-eneylbenzyl alcohol (**5a**) in over 92% purity (HPLC, GC, and NMR) and up to 95% yields after 12 h at 40 °C in MeOH, filtration to remove the resin, and removal of the solvent with a rotary evaporator. The regioisomeric, achiral cyclopentene derivative **6a** was isolated as a by-product in 5% yield. An examination of the use of various phosphane types as ligands gave the following result: addition of triphenylphosphane lowered the purity

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