Table VI. Inhibitor Interaction Energies from Time Series Averages (kcal/mol)[a]

system	sets of interactions evaluated						
	pyr-protein	benzyl-protein	pyr-water	benzyl-water	inh-protein	inh-water	inh-all
trimethoprim	−110.8 ± 4.5	−17.6 ± 1.8	1.2 ± 3.6	−16.0 ± 2.3	−129.9 ± 4.7	−15.1 ± 4.2	−145.1 ± 6.1
3′-ethyl	−104.3 ± 4.4	−22.6 ± 1.7	−5.2 ± 4.7	−5.0 ± 2.0	−127.6 ± 4.2	−11.9 ± 5.0	−139.5 ± 5.6
4′-ethyl	−109.2 ± 4.2	−19.8 ± 1.9	−3.6 ± 2.9	−8.5 ± 1.9	−129.6 ± 5.0	−12.3 ± 3.7	−141.9 ± 5.3
5′-ethyl	−109.3 ± 3.9	−19.0 ± 1.8	−2.8 ± 3.8	−9.0 ± 2.2	−128.8 ± 4.2	−12.0 ± 4.8	−140.7 ± 5.6
3′,4′-ethyl	−99.9 ± 4.7	−18.7 ± 2.0	−5.3 ± 3.7	−10.9 ± 1.9	−120.2 ± 5.4	−16.4 ± 4.4	−136.6 ± 6.4
4′,5′-ethyl	−101.3 - 4.1	−18.4 ± 1.6	−8.3 ± 4.7	−8.8 ± 2.1	−120.3 ± 4.3	−17.3 ± 5.1	−137.6 ± 5.8
3′,5′-diethyl	−102.4 ± 4.5	−18.3 ± 1.5	−4.1 ± 3.8	−6.2 ± 2.0	−121.3 ± 4.5	−10.5 ± 4.2	−131.8 ± 5.7
3′,4′,5′-triethyl	−99.4 ± 4.6	−18.2 ± 1.4	−5.0 ± 1.4	−14.8 ± 2.5	−119.5 ± 4.9	−20.1 ± 5.5	−139.7 ± 5.6

[a] Pyr corresponds to pyrimidine portion of the inhibitor. Protein includes all protein and cofactor atoms. Benzyl refers to the benzyl portion of inhibitor. Inhibitor includes all inhibitor atoms.

Table VII. Comparison of Potential Energy of Inhibitor-Protein Interaction and Relative Free Energies of Binding (kcal/mol)

source of data set	model complex	inhib interactn energies	rel interactn energies[a]	rel free energies[b]
averaged, minimized	3′-ethyl	−158.9	−3.2	−2.8
	4′-ethyl	−155.5	0.2	0.4
	5′-ethyl	−155.1	0.6	0.4
	3′,4′-diethyl	−151.1	4.6	−0.8
	4′,5′-diethyl	−155.2	0.5	−2.7
	3′,5′-diethyl	−145.5	10.2	−2.2
	3′,4′,5′-triethyl	−144.3	11.4	−1.4
time series averages	3′-ethyl	−139.5	5.6	−2.8
	4′-ethyl	−141.9	3.2	0.4
	5′-ethyl	−140.7	4.4	0.4
	3′,4′-diethyl	−136.6	8.5	−0.8
	4′,5′-diethyl	−137.6	7.5	−2.7
	3′,5′-diethyl	−131.8	13.3	−2.2
	3′,4′,5′-triethyl	−139.7	5.4	−1.4

[a] Relative interaction energies were obtained by calculating the difference in interaction energy relative to the trimethoprim complex. Interaction energies for the reference complex were −155.7 kcal/mol for the averaged, minimized structure and −145.1 kcal/mol for the time series average. [b] Taken from Table I.

the enzyme active site and solvation thermodynamics. A case in point is the reversal of the preference of the enzyme for ethylation of the 3′- or 5′-position, depending on the presence or absence of the 4′-ethyl group. We observed the 3′-ethyl derivative to be preferred over the 5′-ethyl derivative. However, the opposite trend was observed for the disubstituted 3′,4′- and 4′,5′-diethyl derivatives. While the 3′-ethyl and 3′,4′-diethyl derivatives demonstrated similar trends in terms of the contribution of protein or solvation components to the thermodynamics, the 5′-ethyl and 4′,5′-diethyl derivatives exhibited different thermodynamics, both in terms of the relative dominance of energetic and entropic components and the thermodynamic contribution from protein or solvent. The results appear to demonstrate a complex relationship between the contribution of protein and solvent effects to the thermodynamics of the inhibitor binding. Energetic analysis alone, by calculating the potential energies of inhibitor interaction with its environment, did not correlate with the relative thermodynamics calculations by the free energy simulation technique.

The models of the complexes obtained after averaging the coordinates over MD simulations at the thermodynamic end points, and energy minimizing to remove short contacts, revealed very few structural differences with reference to the crystal structure or each other. One feature of note, however, was the observation of hydrogen bonds between the carbonyl oxygen of Val115 and the N4 group in the inhibitor pyrimidine ring in six of eight complexes. The presence of this hydrogen bond in the *Escherichia coli* species of the enzyme and its absence in the vertebrate species has been linked to the source of inhibitor specificity for the bacterial enzyme. However, no correlation was observed between the existence of this hydrogen bond and the relative free energies of inhibitor binding, leading us to speculate about a reduced importance of this interaction in conferring stability to the bacterial species. The results of similar inhibitor transformations on the bacterial enzyme will be reported shortly.

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Registry No. DHFR, 9002-03-3; trimethoprim, 738-70-5; 3′-ethyltrimethoprim, 131618-99-0; 4′-ethyltrimethoprim, 78026-01-4; 3′,4′-diethyltrimethoprim, 131619-00-6; 3′,5′-diethyltrimethoprim, 36821-88-2; 3′,4′,5′-triethyltrimethoprim, 36821-85-9.

Communications to the Editor

The Condensation of Dicarbonyl Compounds with *N*-Phenyltriazolinedione-Dienone Ylides Derived from Phenols: The Facile Preparation of Novel Quinone Methides

R. Marshall Wilson* and Nuanphun Chantarasiri

Department of Chemistry, University of Cincinnati Cincinnati, Ohio 45221-0172

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Alkylated urazoles have been observed to undergo oxidation to *N*-phenyltriazolinedione (PTAD) ylides and these ylides to serve as highly activated carbonyl equivalents in condensations with enolates and other nucleophiles.[1] In addition, *N*-phenyltriazolinedione is known to add to a variety of aromatic molecules to form the corresponding arylated urazoles (Scheme I).[2,3]

(1) (a) Wilson, R. M.; Hengge, A. C. *Tetrahedron Lett.* **1985**, *26*, 3673. (b) Wilson, R. M.; Hengge, A. *J. Org. Chem.* **1987**, *52*, 2699. (c) Wilson, R. M.; Hengge, A. C. *J. Org. Chem.* **1990**, *55*, 197. (d) Wilson, R. M.; Hengge, A. C.; Ataei, A.; Ho, D. M. *J. Am. Chem. Soc.*, in press.

(2) (a) Wamhoff, H.; Wald, K. *Chem. Ber.* **1977**, *110*, 1699. (b) Hall, J. H. *J. Org. Chem.* **1983**, *48*, 1708. (c) Hall, J. H.; Kaler, L.; Herring, R. *J. Org. Chem.* **1984**, *49*, 2579.

(3) Electrophilic aromatic substitution reactions of PTAD frequently can be greatly facilitated by acid catalysis with trifluoroacetic acid: Wilson, R. M.; Hengge, A. C.; Ataei, A.; Chantarasiri, N. *J. Org. Chem.* **1990**, *55*, 193.

0002-7863/91/1513-2301$02.50/0

Scheme I

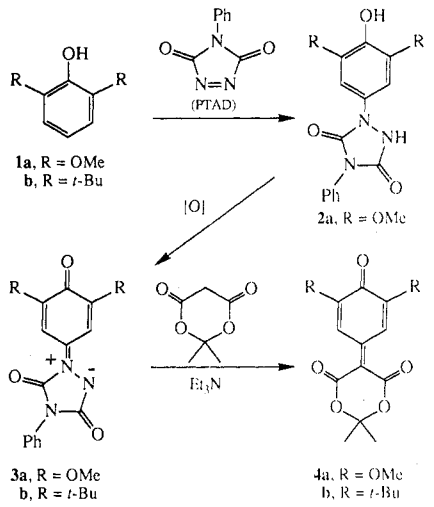
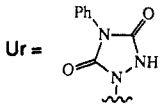
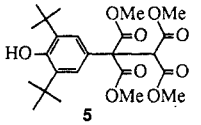
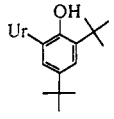
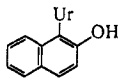


Table I. PTAD–Dienone Ylide Condensations with Enolates



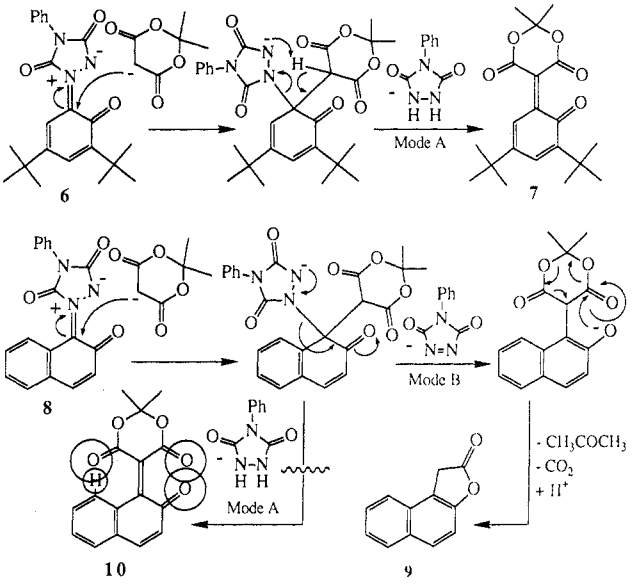
starting materials	product[a]	mp (°C)	yield (%)[b]
1a	**4a**	197.8 (dec)	37[c]
1b	**4b**	153.3-154.3	73[c]
1b	 **5**	174.2-174.5	45[c]
	**7**	147.5 (dec)	37
	**9**	102.8-103.8	10

[a] Reaction conditions for the formation of **4a**, **4b**, **5**, **7**, and **9**: **4a**, (1) *t*-BuOK, THF, 30 min, (2) PTAD, THF, 5 min, (3) *t*-BuOCl, 5 min, (4) Meldrum's acid, Et_3N, THF, room temperature, 12 h; **4b**, (1) 3 equiv of PTAD, THF, 12 h, (2) Meldrum's acid, Et_3N, THF, 0 °C to room temperature, 2 h; **5**, (1) 3 equiv of PTAD, THF, 12 h, (2) $CH_2(CO_2Me)_2$, *t*-BuOK, THF, 0 °C to room temperature, 12 h; **7**, (1) LTA, THF, −78 °C, 1 h, (2) Meldrum's acid, Et_3N, THF, 0 °C, 15 min; **9**, (1) *t*-BuOCl, THF, 0 °C, 2 min, (2) Meldrum's acid, Et_3N, THF, 60 °C, 7 h. [b] All yields are based upon isolated products. [c] Yields based upon starting phenols for reactions conducted by sequential addition of the reagents as specified in footnote *a*, and without isolation of the intermediate arylurazoles or ylides.

Therefore, it was of interest to investigate the chemistry of these arylated urazoles to see if they might be induced to form novel quinone methides via the corresponding PTAD–dienone ylides (**3** in Scheme I).

Two of the mechanistically more informative examples of this general strategy are shown in Scheme I. Reaction 2,6-dimethoxyphenol (**1a**) with PTAD produces the arylated urazole **2a**,[4] which can be oxidized to the stable dienone ylide **3a** upon treatment with either *tert*-butyl hypochlorite or excess PTAD. This ylide can be isolated as a purple solid in 72% yield: mp 168.2–168.7 °C; λ_{max} = 576 nm (ϵ = 30 600); ^{1}H NMR δ 3.92 (s, 3 H), 3.98 (s, 3 H), 7.36 (s, 1 H), 8.07 (s, 1 H). When ylide **3a** is formed in situ and treated with Meldrum's acid and triethylamine, the orange *p*-quinone methide **4a** is obtained (Table I). Similar behavior is exhibited by 2,6-di-*tert*-butylphenol (**1b**). In this case the bright red dienone ylide **3b** was less stable and was not characterized.[5] However, it too undergoes smooth condensations when generated in the presence of a variety of enolates. The reaction conditions and yields for several of these condensation reactions are listed in Table I. In only one case, that of the reaction of **3b** with dimethyl malonate, did the initially formed *p*-quinone methide undergo subsequent conjugate addition of a second molecule of the enolate to form 2:1 adduct **5**.

Scheme II



o-Quinone methides can also be prepared via the corresponding *o*-dienone ylides as shown in Table I and Scheme II for the conversion of ylide **6** to **7**. However, β-naphthol affords the *o*-dienone ylide **8**, which undergoes alternative condensations with enolates to afford substituted phenols such as **9**[6] rather than the expected quinone methides such as **10**.

Thus, two modes of ylide condensation are possible, modes A and B in Scheme II. In both cases, the initial attack of the enolate is rapid, as the ylide color is quenched immediately upon addition of the enolate. The subsequent collapse of the ylide adducts is much slower, requiring an hour or more for the complete formation of the final product. In the quinone methide formation (Scheme II, mode A), *N*-phenylurazole is generated, and in the phenolic substitution (Scheme II, mode B), PTAD is generated as demonstrated by its trapping with cyclopentadiene. This latter mode may be the favored pathway when planarity of the quinone methide is inhibited by the presence of flanking substituents as indicated for **10** in Scheme II.

The results described here show that PTAD–dienone ylides can be surprisingly stable species that undergo a variety of novel chemistry which includes a facile entry to unique quinone methides.

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Supplementary Material Available: Spectroscopic properties and reaction conditions for the formation of all materials described in this paper as well as for the condensations of **1a** with dibenzoylmethane, **1b** with dimedone, and **8** with dimedone (8 pages). Ordering information is given on any current masthead page.

(4) All new compounds reported here have spectroscopic properties consistent with the structures proposed. For experimental details of the syntheses of these materials, see the supplementary material paragraph at the end of this paper.

(5) The efficiency with which these dienone ylides are generated from the phenols can be evaluated by their immediate hydrolysis to the quinones through the addition of water.[1c] This procedure indicates that the efficiency of formation for the di-*tert*-butyl dienone ylide **3b** is about 78%.

(6) Laws, W. R.; Posner, G. H.; Brand, L. *Arch. Biochem. Biophys.* **1979**, *193*, 88.