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THE STABILIZATION OF THIEPIN BY SUBSTITUTION

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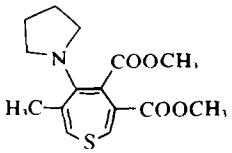
Abstract—Resonance energies of 430 substituted thiepins have been calculated using a simple Hückel method described before. The results predict that thiepins substituted with electron-withdrawing groups (methoxycarbonyl and fluorine) will be less antiaromatic than the parent thiepin. Thus the calculated REPE of the only known type of monocyclic thiepin *viz.* 3,4 - bis(methoxycarbonyl) - 5 - pyrrolidinothiepin (-0.007β) is less negative than that of the parent thiepin.

The question of the antiaromaticity of thiepin has been of interest to both synthetic and theoretical chemists in recent years. Unsubstituted thiepin has never been isolated[1] but 1-benzothiepin has been prepared[2,3] although it was found to be thermally unstable. Several derivatives of 1-benzothiepin have been prepared and found to be more stable than the parent system.[4,5] The apparent instability of the thiepin ring system is in agreement with recent theoretical predictions. Dewar and Trinajstić have found it to be weakly antiaromatic based on their Pariser–Parr–Pople calculations[6] and Hess and Schaad using the Hückel method have found it to be substantially antiaromatic (REPE = -0.029β).[7] A graph theoretical treatment of thiepin is in close agreement with the Hückel results.[8]

Recently Reinhoudt and Kouwenhoven have reported the first synthesis of substituted thiepins, e.g. 3,4 - bis(methoxycarbonyl) - 6 - methyl - 5 - pyrrolidinothiepin (**1**), although it did undergo ready desulfurization at room temperature.[9]



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We have shown that resonance energy calculations[10] on substituted derivatives of the highly antiaromatic cyclobutadiene predict that a substantial portion of the antiaromaticity of the parent compound may be removed by substitution.[11] In this paper we will describe a similar treatment of thiepin. Our goal will be to search for substituted thiepins which, because of lowered antiaromatic character, will be good candidates for synthesis and isolation.

We have examined three principal kinds of substituents, the carboxy and amino groups and fluorine. Although there are potentially six points of substitution on the thiepin ring we have performed calculations only on compounds which contain one, two, three or four substituents. All of the calculations were performed with the simple Hückel method as described previously.[7,10,11]

RESULTS AND DISCUSSION

A total of 430 compounds was examined. Since the goal of this work was to establish those compounds which would be best for possible synthesis we have listed in Table 1 only the five best (highest REPE) compounds for each grouping of substituents considered.

In the case of a single kind of substituent it is apparent from the Table that substitution of the thiepin ring with

Table 1. Resonance energies of selected substituted thiepins

Type and point of substitution			RE	REPE
COOR	NH_2	F	(β)	(β)
		four carboxy groups		
2,3,4,6	—	—	−0.09	−0.004
2,3,5,7	—	—	−0.09	−0.004
2,4,5,6	—	—	−0.09	−0.004
2,4,5,7	—	—	−0.09	−0.004
3,4,5,6	—	—	−0.09	−0.004
		two carboxy groups		
2,4	—	—	−0.13	−0.008
3,5	—	—	−0.13	−0.008
3,6	—	—	−0.13	−0.008
4,5	—	—	−0.13	−0.008
2,5	—	—	−0.14	−0.009
		one carboxy group		
4	—	—	−0.17	−0.014
3	—	—	−0.18	−0.015
2	—	—	−0.19	−0.016
		four amino groups		
—	2,4,5,7	—	−0.40	−0.025
—	2,3,5,7	—	−0.42	−0.026
—	2,4,5,6	—	−0.43	−0.027
—	2,3,4,6	—	−0.44	−0.028
—	2,3,4,7	—	−0.46	−0.029
		two amino groups		
—	2,4	—	−0.22	−0.018
—	2,7	—	−0.25	−0.021
—	2,6	—	−0.27	−0.023
—	2,5	—	−0.28	−0.023
—	3,5	—	−0.28	−0.024
		one amino group		
—	2	—	−0.22	−0.022
—	4	—	−0.24	−0.024
—	3	—	−0.29	−0.029
		four fluorines		
—	—	2,5,5,7	−0.54	−0.034
—	—	2,3,4,6	−0.54	−0.034
—	—	2,4,5,7	−0.54	−0.034

Table 1. *Contd.*

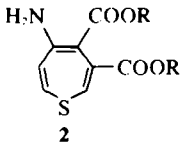
Type and point of substitution COOR	NH_2	F	RE (β)	REPE (β)	Type and point of substitution COOR	NH_2	F	RE (β)	REPE (β)
		four fluorines				three carboxy and one amino group			
—	—	2,4,5,6	−0.55	−0.035	3,5,7	2	—	−0.02	−0.001
—	—	2,3,4,7	−0.61	−0.038	3,5,6	2	—	−0.05	−0.002
					3,6,7	2	—	−0.07	−0.003
		two fluorines			3,4,7	2	—	−0.07	−0.003
—	—	2,4	−0.10	−0.008	3,4,5	2	—	−0.07	−0.003
—	—	2,7	−0.15	−0.012					
—	—	2,6	−0.20	−0.017		one carboxy and one fluorine			
—	—	3,5	−0.27	−0.022	5	—	2	0.00	0.000
—	—	2,5	−0.27	−0.023	3	—	2	−0.01	0.000
					2	—	7	−0.03	−0.002
		one fluorine			4	—	5	−0.06	−0.004
—	—	2	−0.13	−0.013	2	—	5	−0.08	−0.006
—	—	4	−0.21	−0.021					
—	—	3	−0.32	−0.032		one carboxy group and two fluorines			
	one carboxy and one amino group				5	—	2,4	+0.07	+0.004
5	2	—	−0.12	−0.009	7	—	2,4	+0.04	+0.003
4	5	—	−0.14	−0.010	3	—	2,7	0.00	0.000
3	2	—	−0.14	−0.010	3	—	2,4	−0.01	0.000
2	7	—	−0.14	−0.011	2	—	3,7	−0.02	−0.001
2	5	—	−0.15	−0.011					
						one carboxy group and three fluorines			
	one carboxy and two amino groups				2	—	3,5,7	+0.05	+0.003
5	2,4	—	−0.10	−0.006	4	—	2,5,7	−0.02	−0.001
7	2,4	—	−0.11	−0.007	5	—	2,4,6	−0.03	−0.002
3	2,4	—	−0.16	−0.010	3	—	2,5,7	−0.07	−0.004
2	3,5	—	−0.16	−0.010	3	—	2,4,6	−0.08	−0.004
2	3,7	—	−0.16	−0.010					
						two carboxy groups and one fluorine			
	one carboxy and three amino groups				3,5	—	2	+0.08	+0.005
2	3,5,7	—	−0.12	−0.007	2,4	—	7	+0.06	+0.003
4	2,5,7	—	−0.16	−0.009	3,7	—	2	+0.06	+0.003
5	2,4,6	—	−0.17	−0.009	3,6	—	2	+0.03	+0.001
3	2,5,7	—	−0.20	−0.011	5,6	—	2	+0.01	+0.001
3	2,4,6	—	−0.21	−0.012					
						two carboxy groups and two fluorines			
	two carboxy and one amino group				2,4	—	5,7	+0.15	+0.008
3,5	2	—	−0.06	−0.004	3,5	—	2,4	+0.13	+0.007
2,4	7	—	−0.07	−0.004	3,6	—	2,7	+0.12	+0.006
2,4	5	—	−0.08	−0.005	3,7	—	2,4	+0.11	+0.006
3,7	2	—	−0.08	−0.005	3,4	—	2,7	+0.09	+0.005
5,6	2	—	−0.10	−0.006					
						three carboxy groups and one fluorine			
	two carboxy and two amino groups				3,5,7	—	2	+0.13	+0.006
2,4	5,7	—	−0.03	−0.001	3,5,6	—	2	+0.09	+0.004
3,5	2,4	—	−0.07	−0.003	3,4,5	—	2	+0.07	+0.003
3,7	2,4	—	−0.07	−0.004	3,6,7	—	2	+0.06	+0.003
5,6	2,4	—	−0.08	−0.004	3,4,7	—	2	+0.06	+0.003
3,6	2,7	—	−0.09	−0.005					

only amino groups has very little effect on the antiaromatic character of thiepin. On the other hand, carboxy groups in all cases appear to stabilize the thiepin. It was generally found that the point of placement of the carboxy groups on the ring made little difference. This can be seen especially by examining three possible monocarboxy derivatives, all of which have essentially the same REPE value. In the case of fluoro-derivatives, with the exception of several mono- and difluorothiepins, substitution leads either to a decrease in stability or to no change.

There are a number of compounds containing both amino and carboxy groups in which the antiaromaticity has been considerably lowered from that of thiepin. However, it is readily seen that the dominant effect appears to be that of the carboxy groups rather than the amino group. A different behavior is found in the thiepins containing both fluorine and carboxy groups. We have found a large number of carboxy derivatives of thiepin in which the addition of a fluorine yields a moderately positive REPE. For example, in 3,5 - dicarboxy - 2 - fluorothiepin in the REPE is $+0.005\beta$ a substantial increase over that of 3,5 - dicarboxythiepin (REPE = -0.008β). Similar results have been obtained in substituted cyclobutadienes.[11] There also it was found that while the addition of an amino group to carboxylic acid derivatives of cyclobutadiene did increase the stability, it did not do so nearly as much as a fluorine.

Finally let us consider the REPE of compound **1**. We find that the REPE of 3,4 - dicarboxy - 5 - aminothiepin

(2) is -0.007β. While 2 does not have the 6-Me group it is felt that this will have only a very minor influence and that 1 and 2 should be quite similar in stability. This result is encouraging and suggests along with our calculated REPE of other systems that some will be stable thiepins. For example, 2 - amino - 3,5,7 - tricar-



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boxythiepin and 5,7 - diamino - 2,4 - dicarboxythiepin both have an REPE of -0.001β which is substantially lower than that of 2. Furthermore, many of the fluoro derivatives have positive REPE.

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